charles river

FINAL REPORT

Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats Followed by a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
200 Technology Square, Third Floor
Cambridge, MA 02139
USA

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
1580 Ida-Metivier
Sherbrooke, QC J1E 0B5
Canada

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QUALITY ASSURANCE STATEMENT

Study Number: 5002034

This Study has been audited by Quality Assurance in accordance with the applicable Good Laboratory Practice regulations. Reports were submitted in accordance with SOPs as follows:

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
09-Mar-2017	Final Study Plan	10-Mar-2017	10-Mar-2017
20-Mar-2017	Study Plan Amendment 1	20-Mar-2017	20-Mar-2017
23-Mar-2017	Addition of Study Plan to Provantis	23-Mar-2017	23-Mar-2017
23-Mar-2017	Study Plan Amendment 2	23-Mar-2017	23-Mar-2017
05-Apr-2017	Dose Preparation	05-Apr-2017	05-Apr-2017
06-Apr-2017	Draize Evaluation	06-Apr-2017	06-Apr-2017
18-Apr-2017	Study Plan Amendment 3	18-Apr-2017	18-Apr-2017
04-May-2017	Necropsy	04-May-2017	04-May-2017
05-May-2017	Study Plan Amendment 4	05-May-2017	05-May-2017
11-May-2017	Biochemistry	11-May-2017	11-May-2017
22-Jun-2017	Data Review - Veterinary Services	30-Jun-2017	30-Jun-2017
23-Jun-2017	Data Review - Animal Care	30-Jun-2017	30-Jun-2017
23-Jun-2017 - 27-Jun-2017	Data Review - Technical Operations	30-Jun-2017	30-Jun-2017
27-Jun-2017	Data Review - Formulations	30-Jun-2017	30-Jun-2017
27-Jun-2017 - 28-Jun-2017	Data Review - Clinical Pathology	30-Jun-2017	30-Jun-2017
27-Jun-2017	Data Review - Technical Operations	30-Jun-2017	30-Jun-2017
28-Jun-2017	Study Plan Amendment 5	28-Jun-2017	28-Jun-2017
28-Jun-2017	Data Review - Shipping/Receiving	30-Jun-2017	30-Jun-2017
28-Jun-2017	Report Preparation	30-Jun-2017	30-Jun-2017
28-Jun-2017	Data Review - Necropsy	30-Jun-2017	30-Jun-2017
28-Jun-2017 - 29-Jun-2017	Data Review - Histology	30-Jun-2017	30-Jun-2017
29-Jun-2017	Draft Phase Report - Ophthalmology	30-Jun-2017	30-Jun-2017
29-Jun-2017 - 30-Jun-2017	Draft Report - Materials and Methods	30-Jun-2017	30-Jun-2017
29-Jun-2017	Report Preparation	30-Jun-2017	30-Jun-2017
29-Jun-2017	Data Review - Shipping/Receiving	30-Jun-2017	30-Jun-2017
25-Aug-2017 - 26-Aug-2017	Final Report	28-Aug-2017	28-Aug-2017
29-Aug-2017 31-Aug-2017 - 01-Sep-2017	Data Review - Analytical Chemistry	01-Sep-2017	01-Sep-2017
29-Aug-2017 31-Aug-2017 - 01-Sep-2017	Draft Phase Report - Dose Formulation Analysis	01-Sep-2017	01-Sep-2017
18-Sep-2017	Study Plan Amendment 6	18-Sep-2017	18-Sep-2017

QUALITY ASSURANCE STATEMENT - Study Number: 5002034

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
25-Sep-2017	Final Report	26-Sep-2017	26-Sep-2017

In addition to the above-mentioned audits, process-based and/or routine facility inspections were also conducted during the course of this study. Inspection findings, if any, specific to this study were reported by Quality Assurance to the Study Director and Management and listed as a Phase Audit on this Quality Assurance Statement.

The Final Report has been reviewed to assure that it accurately describes the materials and methods, and that the reported results accurately reflect the raw data.

(b) (6)

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03 - OCT - 2017
Date

COMPLIANCE STATEMENT

The study was performed in accordance with the OECD Principles of Good Laboratory Practice and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in the USA was performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration. United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions from the above regulations are listed below.

- Characterization of the Test Item was performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses were not conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines, α2-macroglobulin, α1-acid glycoprotein, anti-therapeutic antibody and PBMCs were conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- The purity analysis of the bulk test item was conducted using a scientifically qualified methods and in accordance with applicable analytical procedures.
- Pathology peer review.

This study was conducted in accordance with the procedures described herein. All deviations authorized/acknowledged by the Study Director are documented in the Study Records. The report represents an accurate and complete record of the results obtained.

There were no deviations from the above regulations that affected the overall integrity of the study or the interpretation of the study results and conclusions.

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Date: 03Oct 2017

1. RESPONSIBLE PERSONNEL

1.1. Test Facility

Study Director	(b) (6)
Test Facility Management	(b) (6)

1.2. Individual Scientists (IS) at Test Facility

Ophthalmology	(b) (6) Senneville, QC, Canada
Analytical Chemistry (Concentration, and Particle size and Purity Analysis)	(b) (6) Charles River Laboratories Montreal ULC Senneville, QC, Canada
Immunology (Cytokine, Alpha-2 Macroglobulin and Alpha-1 Glycoprotein Analysis)	(b) (6) Charles River Laboratories Montreal ULC Sherbooke, QC, Canada

1.3. Principal Investigators (PI) at Test Facility-designated Test Site(s)

Pathology	(b) (6) Charles River Laboratories, Inc. Durham, NC, USA

1.4. PIs at Sponsor or Sponsor-designated Test Site(s)

Anti-Therapeutic Antibody Analysis	(b) (6) Integrated BioTherapeutics, Inc. Rockville, MD, USA
PBMC Analysis	(b) (6) Southern Research Birmingham, AL, USA

2. SUMMARY

The objectives of this study were to determine the potential toxicity of mRNA 1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

The study design was as follows:

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10/8.9	200	0.05/0.045	10	10	-	-
3	mRNA-1647	30/27	200	0.15/0.14	10	10	-	-
4	mRNA-1647	100/89	200	0.5/0.45	10	10	5	5

- : Not applicable
[a] Values based on Summary of Analysis (SoA) issued on 16 Mar 2017 / Values based on SoA issued on 31 May 2017 (Refer to memorandum in Appendix 2).

The following parameters and endpoints were evaluated in this study: clinical observations consisting of twice daily examinations for mortality/moribundity and weekly detailed examinations; local irritation assessment at least 24- and 72-hour postdose on dosing days and weekly when there were no dosing and during the recovery period; weekly body weights and food consumption measurements; ophthalmic examinations once prior to dosing initiation and during Day 40 (males) or Day 39 (females) of the dosing period; body temperature on Days 1 and 43 at predose and 6 and 24 hours postdose (end of each group); clinical pathology assessment (hematology, coagulation, clinical chemistry, α1-acid glycoprotein and α2-macroglobulin) at termination; cytokine analysis (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) on Days 1, 15, 29 and 43 at 6 hours postdose and on Day 57; Anti-Therapeutic Antibody (ATA) analysis prior to dosing initiation, on Day 29 (predose), on Day 43 (postdose) and on Day 57; PBMC analysis on Day 44; gross necropsy findings, organ weights, and histopathologic examinations.

There were no mRNA-1647-related changes in food consumption and ophthalmology.

There were no mRNA-1647-related mortalities during the course of the study. One male given the Reference Item (PBS) was found dead on Day 43. The pathological evaluation revealed gross abnormal findings in the adrenal gland , kidneys , thymus; and lungs. Histopathology findings for this control male were incidental and did not explain the cause of death.

mRNA-1647-treated main study and recovery animals had significant detectable antibody responses against CMV gB protein and CMV gH pentamer complex.

mRNA-1647 elicited both CD4 and CD8 T cell responses to both CMV Pentamer and gB. T cell response (PBMC analysis) were significantly variable within each test group with data trending towards higher T cells responses at higher doses of mRNA-1647.

The primary mRNA-1647-related findings were observed at the site of injection. At all doses, increase in incidence and/or severity with dose of very slight to severe edema was noted at the injection site, following dosing of males and females (peaking 24 hours postdose, generally decreasing by 72 hours postdose). Although sporadic in occurrences, slight to moderately severe erythema was noted as well, but was only considered mRNA-1647-related at 89 µg/dose. Swelling (soft or firm), noted on the injection site following the third and/or fourth doses, together with localized skin redness at the injection site noted throughout the dosing period, were consistent with the edema and erythema findings. Macroscopically, dose-dependent firm abnormal consistency, dark foci and/or swelling at the injection site correlated with microscopic changes observed at all doses that included minimal to moderate mixed cell inflammation involving the subcutaneous tissues, skeletal muscle, and to a lesser extent the dermis, as well as minimal to moderate subcutaneous edema. Increased incidence and/or severity of minimal to marked mixed cell inflammation was seen in the popliteal and/or inguinal lymph nodes (draining) of all animals at ≥ 8.9 µg/dose which correlated macroscopically with enlargement; minimal to marked mixed cell inflammation was frequently observed in the perineurial tissue surrounding the sciatic nerve of animals given ≥ 8.9 µg/dose. Sciatic nerve and lymph node inflammatory changes were regarded as secondary to the injection site inflammation. mRNA-1647-related microscopic findings were still noted at the injection site and sciatic nerve of recovery animals; minimal to mild mononuclear cell infiltration and minimal mixed cell inflammation were seen respectively in the injection site and on the sciatic nerves of males and/or females given 89 µg/dose. The absence of mixed cell inflammation and edema, with a shift to minimal to mild mononuclear cell infiltration, at the intramuscular injections sites and a reduced incidence and/or severity of perineurial mixed cell inflammation associated with the sciatic nerves were however all indicative of a partial recovery. Clinical signs (i.e. edema, swelling, erythema and reddening of the skin) observed at the injection site and gross pathology findings as well as microscopic findings observed at the inguinal and popliteal lymph nodes were no longer observed in recovery animals, indicating a complete recovery for these changes.

mRNA-1647-related systemic changes associated with inflammation were also observed in animals given ≥ 27 µg/dose and included minimally increased hematopoiesis of the myeloid lineage in the bone marrow. This change was likely a reactive response to the pronounced inflammation observed at the injection site. Other systemic findings included increases in absolute and/or relative spleen weights without correlating histopathology, and minimal to mild decreased cellularity of the splenic periarteriolar lymphoid sheath. Clinical pathology changes suggestive of inflammation were also observed in males and/or females given mRNA-1647 at all doses (unless noted otherwise) and included: minimal to moderate increases in neutrophil, eosinophil and large unstained cell counts with concomitant increases in white blood cell counts, minimal decreases in lymphocyte counts and platelet counts (females at 89 µg/dose), minimal increases in activated partial thromboplastin time and mild increases in fibrinogen, minimal increases in globulin, minimal decreases in albumin, with concomitant decreases in A/G ratio. Increase in body temperature postdose (89 µg/dose), along with increases in acute phase protein Alpha-1-Glycoprotein and Alpha-2-Macroglobulin and elevations of cytokine levels IP-10

(89 µg/dose) and MCP-1, were all suggestive of inflammation. At the end of the 2-week recovery period, Alpha-2-Macroglobulin levels were still higher than controls, but to a lesser extent, the incidence and severity of increased absolute and/or relative spleen weights was reduced, as well as the decrease in cellularity of the periarteriolar lymphoid sheath in the spleen, suggesting only a partial recovery for these aforementioned findings. All other mRNA-1647-related systemic changes returned close to control values and, as such, were considered fully recovered.

When compared to controls, following each dose, a tendency towards lower mean body weight gains was noted in males given ≥ 8.9 µg/dose and in females given 89 µg/dose; these changes sometimes reached statistical significance. The changes were only cumulative in males. There were no clear association of the body weight changes with food consumption or clinical observations. The body weight changes were generally comparable or rebounded during the 2-week recovery period.

In conclusion, administration of mRNA-1647 by intramuscular injection for 6 weeks (4 doses) was clinically well tolerated (no mortality, major decreases in body weight and no changes in food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 89 µg/dose. Starting at 8.9 µg/dose, generally dose-dependent changes in clinical signs at the injection site, clinical pathology parameters, cytokines and acute protein levels were consistent with an inflammatory response at the injection site. Dose-related target organ effects were limited to the injection site, the bone marrow, the inguinal and popliteal lymph nodes, the connective tissue surrounding the sciatic nerve and the spleen of animals given mRNA-1647. At the end of the 2-week recovery period, all changes were partially or fully recovered.

3. INTRODUCTION

The objectives of this study were to determine the potential toxicity of mRNA 1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

The design of this study is based on the study objectives, the overall product development strategy for the Test Item, and the following study design guidelines:

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.
- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 Nov 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

The Study Director signed the study plan on 08 Mar 2017, and dosing was initiated on 22 Mar 2017 (males) and on 23 Mar 2017 (females). The in-life phase of the study was completed on 05 May 2017 (main study animals) and on 18 May 2017 (recovery study animals), the date of the last necropsy. The experimental start date was 08 Mar 2017, and the experimental completion date is 20 Sep 2017 (signature of the pathology report). The study plan, study plan amendments, and deviations are presented in Appendix 1.

4. MATERIALS AND METHODS

4.1. Test Item

Identification:	mRNA-1647
Batch (Lot) No.:	MTDP17015
Retest Date:	An end-of-use analysis of the bulk Test Item was performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanoparticle dispersion
Concentration:	2.7 / 2.4*mg/mL
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc

* Concentration based on SoA released on 16 Mar 2017 /Concentration based on SoA released on 31 May 2017

4.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Batch (Lot) No.:	1809319 1854892 1759866 1830677
Expiration Date:	Jul 2018 Dec 2018 Feb 2018 Sep 2018
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

4.3. Test and Reference Item Characterization

The Sponsor provided to the Test Facility documentation of the identity, strength, purity, composition, and stability for the Test Item. A Summary of Analysis was provided to the Test Facility and is presented in Appendix 2.

4.4. Analysis of Test Item

A sample (2 vials) of the Test Item were taken on the completion of the dosing period. Analysis of bulk Test Item for concentration, particle size and purity were performed.

The first vial was transferred (on dry ice) to the analytical laboratory at the Test Facility for concentration and particle size analysis.

The second vial was transferred (on dry ice) to the analytical laboratory at the Test Facility for purity analysis.

Concentration, Purity and Particle size analysis were performed by IEX- HPLC, Differential Light Scattering (DLS) and rHPLC using validated or qualified analytical procedures.

4.5. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 mL or 1 vial) was collected and maintained under the appropriate storage conditions by the Test Facility (refer to Appendix 1 for one exception).

4.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, and storage and disposition of Test and Reference Items were maintained. With the exception of reserve samples, all unused Test and Reference Items were returned to the Sponsor after completion of dosing.

4.7. Dose Formulation and Analysis

(Appendix 3)

4.7.1. Preparation of Reference Item

Dose formulation preparations were performed under a laminar flow hood using clean procedures.

The Reference Item, Phosphate-buffered Saline (PBS) pH 7.2, was dispensed on days of dosing (i.e. Days 1, 15, 29 and 43) for administration to Group 1 control animals and was used as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots were stored in a refrigerator set to maintain 4°C until use. They were removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

Details of the preparation and dispensing of the Reference Item have been retained in the Study Records.

4.7.2. Preparation of Test Item

Dose formulation preparations were performed under a laminar flow hood using clean procedures.

Test Item formulations were diluted with PBS pH 7.2, as necessary for administration. The dosing formulations were prepared on each days of dosing (i.e. Days 1, 15, 29 and 43) and were stored in a refrigerator set to maintain 4°C. The dose formulations were allowed to warm to room temperature for at least 30 minutes prior to dosing. Stock vials were used only once.

Empty vials were discarded. Any residual volumes of formulated Test Item and stock Test Item were stored in a refrigerator set at 4°C and were discarded prior to report finalization.

4.7.3. Sample Collection and Analysis

Dose formulation samples were collected for analysis as indicated in Text Table 2.

Text Table 2
Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 43	N/A	All groups	Dosing container

N/A = Not applicable.
[a] The homogeneity results obtained from the top, middle and bottom preparations were averaged and utilized as the concentration results.
[b] Samples were collected on the first preparation of the study and on the last preparation of the study.

Samples to be analyzed were transferred on ice pack to the analytical laboratory.

4.7.3.1. Analytical Method

Analyses described below were performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No.1802050).

4.7.3.2. Concentration and Homogeneity Analysis

On Days 1 and 43 of the study, duplicate sets of samples (0.5 mL) were sent to the analytical laboratory; triplicate set of samples (0.5 mL) were retained at the Test Facility as backup samples. Samples were collected in an appropriate sized glass container from the top, middle and bottom strata of the dosing container for each concentration except for Group 1 dosing formulation and on day 43 where only concentration analysis were required; the formulation was then only sampled from the middle stratum.

Concentration results were considered acceptable if mean sample concentration results were within or equal to ± 15% of theoretical concentration. Each individual sample concentration result was considered acceptable if it was within or equal to ± 20%. After acceptance of the analytical results, backup samples were discarded.

Homogeneity results were considered acceptable if the relative standard deviation (RSD) of the mean value at each sampling location was ≤ 5%.

After acceptance of the analytical results, backup samples were discarded.

4.7.3.3. Stability Analysis

There was no stability analysis performed for concentration used on this study however, end of use stability analysis of the bulk test item was performed at the end of the dosing period.

4.8. Test System

4.8.1. Receipt

On 08 March 2017, one hundred and twenty Crl:CD(SD) Sprague-Dawley rat (60 males and 60 females) were received from Charles River Canada Inc., St. Constant, QC, Canada. The animals were 08 weeks old and males weighed between 235 and 297 grams and females weighed between 195 and 248 grams at initiation of dosing.

4.8.2. Justification for Test System and Number of Animals

The Sprague Dawley rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies.

The total number of animals to be used in this study was considered to be the minimum required to properly characterize the effects of the Test Item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

4.8.3. Animal Identification

Each animal was identified using a subcutaneously implanted electronic identification chip.

4.8.4. Environmental Acclimation

A minimum acclimation period of 14 days was allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment (refer to Appendix 1).

4.8.5. Selection, Assignment, Replacement, and Disposition of Animals

Animals were assigned to groups by a stratified randomization scheme designed to achieve similar group mean body weights. Males and females were randomized separately. Animals in poor health or at extremes of body weight range were not assigned to groups.

Before the initiation of dosing, assigned animals with compromising background ophthalmic findings, that were considered unsuitable for use in the study, were replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

The alternate animals were used as replacements on the study within approximately 4 days.

4.8.6. Husbandry

4.8.6.1. Housing

Animals were group housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions were maintained all along the study. The rooms in which the animals were kept was documented in the study records.

Animals were separated during designated procedures/activities. Each cage was clearly labeled with a color-coded cage card indicating study, group, animal number(s), and sex. Cages were arranged on the racks in group order. Control group animals were housed on a separate rack from the Test Item-dosed animals.

4.8.6.2. Environmental Conditions

Target temperatures of 19°C to 25°C with a relative target humidity of 30% to 70% were maintained. A 12-hour light/12-hour dark cycle was maintained, except when interrupted for designated procedures.

4.8.6.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 (14% protein) was provided ad libitum throughout the study, except during designated procedures. The same diet in meal form was provided to one female animal from Group 4 as warranted by clinical signs (broken/damaged incisors). On few occasions, wet pellets were also provided to Group 4 animals as warranted by clinical signs.

The feed was analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis are provided by the supplier and are on file at the Test Facility.

It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

4.8.6.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation was freely available to each animal via an automatic watering system (except during designated procedures).

Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility.

It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

4.8.6.5. Animal Enrichment

Animals were socially housed for psychological/environmental enrichment and were provided with items such as a hiding device and a chewing object, except when interrupted by study procedures/activities.

4.8.6.6. Veterinary Care

Veterinary care was available throughout the course of the study, and animals were examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations were documented in the study records. No veterinary treatments were necessary during the course of the study.

Reaction (Skin scab) to non-toxic pen used for marking the injection area was observed for control Animals Nos. 1510 and 1514 on Day 21 and 38, respectively. Consequently, no marking of the injection site was performed for these animals after that day.

4.9. Experimental Design

Text Table 3
Experimental Design

Group No.	Test Material	Dose Level[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)	Animals No.			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	1001-1010	1501-1510	1011-1015	1511, 1612, 1513-1515
2	mRNA-1647	10/8.9	200	0.05/0.045	2001, 2102, 2003-2010	2501-2510	-	-
3	mRNA-1647	30/27	200	0.15/0.14	3001, 3002, 3103, 3004-3010	3501-3503, 3604, 3505-3510	-	-
4	mRNA-1647	100/89	200	0.5/0.45	4001-4010	4501-4510	4011-4015	4511-4515

- : Not applicable
[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 31 May 2017.

Prior to the start of dosing, animals were rejected from the study due to compromising background ophthalmic findings and were replaced with spare animals. The final allocation of animals is listed under Text Table 3. All animals remaining unassigned to groups after Day 4 (males) or 3 (females) were released from the study and their disposition, documented.

4.9.1. Administration of Test Materials

The Test and Reference Items were administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, 29 and 43, the injection site was alternated on each dosing occasion (site 1= left; site 2= right). The volume for each dose was administered using a syringe/needle within the demarcated area. The first day of dosing was designated as Day 1.

The injection area was marked as frequently as required to allow appropriate visualization of administration sites (refer to Section 4.8.6.6 for exceptions). Hair may have been clipped or shaved, if required, to improve visualization of the injection sites. The injection site was documented in the raw data for each dose administered.

4.9.2. Justification of Route and Dose Levels

The intramuscular route of exposure was selected because this is the intended route of human exposure.

The dose levels for this toxicology study were chosen to approximate a substantial multiple of the anticipated clinical starting dose and top clinical dose. The highest dose to be tested was expected to represent the intended maximum human clinical dose and volume and was administered by the clinical route (intramuscular). At this dose level, minimal systemic toxicity was expected, but it was possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may have been observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound.

4.10. In-life Procedures, Observations, and Measurements

4.10.1. Mortality/Moribundity Checks

Throughout the study, animals were observed for general health/mortality and moribundity twice daily, once in the morning and once in the afternoon. Animals were not removed from cage during observation, unless necessary for identification or confirmation of possible findings.

4.10.2. Clinical Observations

4.10.2.1. Detailed Clinical Observations

The animals were removed from the cage, and a detailed clinical observation was performed weekly during the dosing and recovery periods, beginning during Week -1.

4.10.3. Local Irritation Assessment

On days of dosing and at least 24 and 72 hours postdose (end of each group), all animals had the dose injection site examined for signs of erythema/edema. Examinations were also performed weekly when there was no dosing and during the recovery period. Following Day 43 dosing, no assessment was performed on Main Study animals at 72 hours postdose as these animals were sent to necropsy on Day 44.

Observations were scored according to the Local Irritation Assessment scoring table as follows:

Erythema (Redness)	**Score**
No erythema	0
Very slight erythema (barely perceptible)	1
Mild erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness to slight eschar formation, injury in depth)	4
Notable dermal lesion (maximized)	M
Edema (Swelling)	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema	2
Moderate edema	3
Severe edema	4

4.10.4. Body Weights

Animals were weighed individually weekly, starting during Day -1. A fasted weight was recorded on the day of necropsy. Terminal body weight was not collected from animals found dead.

4.10.5. Food Consumption

Food consumption was quantitatively measured starting on Day -9 and weekly throughout the dosing and recovery periods (refer to Appendix 1 for additional details).

4.10.6. Ophthalmic Examinations

Animals had funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations once prior to dosing (all animals) and on Day 40 for males and Day 39 for females. As there were no Test Item-related ophthalmoscopic findings at the end of the dosing period, examinations were not performed during the recovery phase. The mydriatic used was atropine 0.126%.

4.10.7. Body Temperature

Rectal body temperature was recorded on un-sedated animals on Days 1 and 43 at predose and 6 and 24 hours postdose (end of each group). After first dose administration, body temperature of Group 4 female animals was monitored until 48 post dose, after which body temperature normal range (36.0°C to 38.0°C) was recovered.

4.11. Laboratory Evaluations

4.11.1. Clinical Pathology

4.11.1.1. Sample Collection

Blood was collected from the abdominal aorta following isoflurane anesthesia. After collection, samples were transferred to the appropriate laboratory for processing.

Animals were fasted overnight before blood sampling (for clinical chemistry). Samples were collected according to Text Table 4.

Text Table 4
Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	α1-acid glycoprotein/ α2-macroglobulin
1 to 4[a]	Day 44	X	X	X	X
1 and 4	Day 57	X	X	X	X

X = Sample collected
[a] Samples were only collected from those animals scheduled for euthanasia on Day 44.

4.11.1.2. Hematology

Blood samples (target volume of 0.5 mL collected in a tube containing EDTA as anticoagulant) were analyzed for the parameters specified in Text Table 5.

Text Table 5
Hematology Parameters

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red Blood Cell Distribution Width Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute) Platelet count	White blood cell count Neutrophil count (absolute) Lymphocyte count (absolute) Monocyte count (absolute) Eosinophil count (absolute) Basophil count (absolute) Large unstained cells (absolute)

A blood smear was prepared from each hematology sample. Blood smears were labeled, stained, and stored. Blood smears were read to investigate results for some animals.

4.11.1.3. Coagulation

Blood samples (target volume of 1.2 mL collected in a 1.3 mL tube containing citrate as anticoagulant) were processed for plasma, and plasma was analyzed for the parameters listed in Text Table 6.

Text Table 6
Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

4.11.1.4. Clinical Chemistry

Blood samples (target volume of 0.7 mL collected in serum separator tubes) were processed for serum, and the serum was analyzed for the parameters specified in Text Table 7.

Text Table 7
Clinical Chemistry Parameters

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine Kinase	Glucose
Total bilirubin	Cholesterol
Urea nitrogen	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphorus	Chloride
	Sample Quality

4.11.1.5. α1-acid Glycoprotein and α2-macroglobulin Analysis

Blood (target volume of 0.7 mL collected in a serum separator tube) was obtained via abdominal aorta following isoflurane anesthesia before scheduled necropsy for all animals.

Blood samples were allowed to clot at ambient room temperature, until centrifugation which was carried out as soon as practical. The samples were centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)) at (b) (4) Samples were processed to serum by the Immunology Department. Serum were aliquoted into 1 x 75 µL aliquot for α2-macroglobulin and 2 x 75 µL aliquot and a leftover (when available) for α1-acid glycoprotein. All samples were stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin was conducted using a qualified ELISA method by the Immunology Department. The procedure to be followed along with the assay acceptance criteria was detailed in the appropriate analytical procedure.

Samples were analyzed in duplicate. Any residual/retained samples were discarded prior to report finalization.

4.11.2. Laboratory Investigation (Cytokines Analysis)

Blood was collected from the jugular vein of recovery animals. After collection, blood samples for serum were allowed to clot at ambient room temperature and blood samples for plasma were transferred on wet ice to the appropriate laboratory for processing.

Text Table 8
Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)** (refer to Appendix 1 for one exception)	**EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hrs**	**Males/ Females No.**	IFN-α*	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	1011-1015, 4011-4015	X	X
15	6		X	X
29	6		X	X
43	6	1511, 1612, 1513-1515, 4511-4515	X	X
57	N / A		X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR-SHB	CR-SHB

X = Sample collected; N/A = not applicable

* The assay validation of IFN-α did not work appropriately and serum samples analysis was not conducted.

The samples were analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 were conducted using a multiplex Luminex method. The procedures to be followed during the course of this study along with the assays acceptance criteria were detailed in the appropriate analytical procedure. Samples were analyzed in duplicate.

An Immunology Report for cytokine analysis is included as an appendix to the Final Report.

4.11.3. Anti-Therapeutic Antibody (ATA) Analysis

Before the initiation of dosing, on Day 29 (before dose administration, all animals), on Day 43 (post dose administration, main animals only) and on Day 57 (recovery animals), target blood volume of 0.5 mL was collected in a serum separator tube by jugular venipuncture from the appropriate animals.

Samples were mixed gently and allowed to clot at ambient room temperature until centrifugation, which was carried out as soon as practical. The samples were centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)) at (b) (4) The resultant serum was separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C until shipment on dry ice to Integrated BioTherapeutics, Inc., Rockville, MA, USA for analysis.

The samples were analyzed for rat anti-CMV antibodies using a qualified ELISA method.

An Anti-therapeutic Antibody Report is included as an appendix to the Final Report.

4.12. PBMC Analysis

On Day 44, blood (target volume of 0.5 mL collected in a tube containing Sodium Heparin as anticoagulant) was obtained by jugular venipuncture from main animals only. Samples were shipped at controlled temperature set to maintain 21°C via overnight courier to Southern research, Birmingham, AL, for whole blood stimulation and cytokine analysis.

The PBMC samples were analyzed using a qualified method.

An Immunology Report for PBMC analysis is included as an appendix to the Final Report.

4.13. Terminal Procedures

Terminal procedures are summarized in Text Table 9.

Text Table 9
Terminal Procedures

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	44	X	X	X	Full Tissue[a]	Full Tissue[a]
2	10	10					Full Tissue[a]	Gross Lesions Target Tissues
3	10	10					Full Tissue[a]	Gross Lesions Target Tissues
4	10	10					Full Tissue[a]	Full Tissue[a]
1	5	5	57	X	X	X	Full Tissue[a]	Full Tissue[a]
4	5	5					Full Tissue[a]	Full Tissue[a]
Unscheduled Deaths				X	X	-	Full Tissue[a]	Full Tissue[a]

X = Procedure conducted; - = Not applicable.
[a] See Tissue Collection and Preservation table for listing of tissues.

4.13.1. Unscheduled Deaths

A complete necropsy was conducted for one control animal assigned to recovery study that died during dosing, and specified tissues were saved. Animal was refrigerated before necropsy to minimize autolysis.

4.13.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia had a terminal body weight recorded, samples for laboratory evaluation were collected (as appropriate), and were euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. The animals were euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, were necropsied throughout the day. Animals were fasted overnight before their scheduled necropsy.

4.13.3. Necropsy

Main study and recovery animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices;

cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Necropsy procedures were performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, was available.

4.13.4. Organ Weights

The organs identified in Text Table 10 were weighed at necropsy for all scheduled euthanasia animals. Organ weights were not recorded for animal found dead. Paired organs were weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ to body weight ratio (using the terminal body weight) and organ to brain weight ratios were calculated.

Text Table 10
Organs Weighed at Necropsy

Brain	Liver
Epididymis[a]	Lung
Gland, adrenal[a]	Ovary[a]
Gland, pituitary	Spleen
Gland, prostate	Testis[a]
Gland, thyroid[a]	Thymus
Heart	Uterus
Kidney[a]	

[a] Paired organ weight.

4.13.5. Tissue Collection and Preservation

Representative samples of the tissues identified in Text Table 11 were collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated.

Text Table 11
Tissue Collection and Preservation

Injection site[c]	Large intestine, rectum
Animal identification	Larynx
Artery, aorta	Liver
Body cavity, nasal	Lung
Bone marrow smear	Lymph node, mandibular
Bone marrow	Lymph node, mesenteric
Bone, femur	Lymph node, Inguinal[e]
Bone, sternum	Lymph node, Popliteal[e]
Brain[d]	Small intestine, duodenum
Cervix	Small intestine, ileum
Epididymis	Small intestine, jejunum
Esophagus	Muscle, skeletal
Eye[a]	Nerve, optic[a]
Gland, adrenal	Nerve, sciatic
Gland, harderian	Ovary
Gland, mammary	Pancreas
Gland, parathyroid	Skin
Gland, pituitary	Spinal cord
Gland, prostate	Spleen
Gland, salivary	Stomach
Gland, seminal vesicle	Testis[b]
Gland, thyroid	Thymus
Gross lesions/masses	Tongue
Gut-associated lymphoid tissue	Trachea
Heart	Urinary bladder
Kidney	Uterus
Large intestine, cecum	Vagina
Large intestine, colon	

[a] Preserved in Davidson's fixative.
[b] Preserved in Modified Davidson's fixative.
[c] Thigh site used for the last injection.
[d] Seven brain levels examined included olfactory bulb (Examine in Body cavity, nasal section level 4).
[e] Lymph node draining the last administration site used (unilateral examination).

4.13.6. Histology

Tissues identified in Text Table 11 (except animal identification, bone marrow smears and larynx) were embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

4.13.7. Histopathology

Histopathological evaluation was performed by a board-certified veterinary pathologist.

4.13.8. Peer Review

(Appendix 20)

A pathology peer review was conducted by a Sponsor-designated pathologist; (b) (6), (b) (6) from Experimental Pathology Laboratories, Inc., Research Triangle Park, NC 27709, USA.

The peer review statement was included as an appendix to the Final Report.

4.13.9. Bone Marrow Smear Analysis

Two bone marrow smears were prepared from each euthanized animal, air dried, stained with Wright's Giemsa stain, and not coverslipped. Bone marrow smears were not evaluated.

5. CONSTRUCTED VARIABLES

Body Weight Gains	calculated between each scheduled interval as well as between the beginning and end of each phase
Organ Weight relative to Body Weight	calculated against the Terminal body weight for scheduled intervals
Organ Weight relative to Brain Weight	calculated against the brain weight for scheduled intervals

All results presented in the tables of the report are calculated using non-rounded values as per the raw data rounding procedure and may not be exactly reproduced from the individual data presented.

6. STATISTICAL ANALYSIS

Numerical data collected on scheduled occasions for the listed variables were analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) were reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics were performed according to the matrix below when possible, but excluded semi-quantitative data, and any group with less than 3 observations.

Text Table 12
Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
α2-macroglobulin	X
α1-acid glycoprotein	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons were made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

6.1. Parametric/Non-parametric

Levene's test was used to assess the homogeneity of group variances parametric assumption at the 5% significance level. Datasets with at least 3 groups were compared using an overall one-way ANOVA *F*-test if Levene's test was not significant or the Kruskal-Wallis test if it was. If the overall *F*-test or Kruskal-Wallis test was found to be significant, then the above pairwise comparisons were conducted using Dunnett's or Dunn's test, respectively.

Datasets with 2 groups (the designated control group and 1 other group) were compared using a *t*-test if Levene's test was not significant or Wilcoxon Rank-Sum test if it was.

All significant pairwise comparisons were reported at the 0.1, 1, and 5% significance levels.

7. COMPUTERIZED SYSTEMS

Critical computerized systems used in the study are listed below or presented in the appropriate Phase Report. All computerized systems used in the conduct of this study have been validated; when a particular system has not satisfied all requirements, appropriate administrative and procedural controls were implemented to assure the quality and integrity of data.

Text Table 13
Critical Computerized Systems

System Name	Version	Description of Data Collected and/or Analyzed
Provantis	8	In-life; clinical pathology; postmortem
Dispense	8	Test Material receipt, accountability and/or formulation activities
In-house reporting software Nevis (using SAS)	Nevis 2 (SAS 9.2)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7.0 and 4.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Build 3471 SR1	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
Bio Plex Manager (Bio-Rad)	6.1	Cytokine data collection
Softmax Pro GxP	5.4.6	Cytokine data collection
Watson LIMS	7.4.2 SP1	Sample tracking/analysis/regression - biomarkers
Dynamics (Wyatt)	7.1.9.3	Data acquisition for particle size analysis for the test item using DLS

8. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, documentation, study plan, samples, specimens, and final reports from this study were archived at CRL-MTL by no later than the date of final report issue unless otherwise specified in the study plan. At least one year after issue of the draft report, the Sponsor will be contacted to determine disposition of materials associated with the study.

Electronic data generated by the Test Facility were archived as noted above, except that the data collected using Provantis 8 and reporting files stored on SDMS, which were archived at the Charles River Laboratories facility location in Wilmington, MA.

All records, retained samples and specimens, and reports generated from phases or segments performed by Test Facility-designated subcontractors were returned to the Test Facility for archiving Archival location and duration are detailed in the applicable PI report(s) or details regarding the retention of the materials were provided to the Study Director for inclusion in the Final Report.

All records, retained samples and specimens, and reports generated from phases or segments performed by Sponsor-designated subcontractors were returned to the Test Facility for archiving Archival location and duration are detailed in the applicable PI report(s) or details regarding the retention of the materials were provided to the Study Director for inclusion in the Final Report.

9. RESULTS

9.1. Dose Formulation Analyses

(Appendix 3)

Dose formulation concentration results were within specification. Homogeneity testing showed that the formulation technique used produced homogeneous preparations.

9.2. End of Use Bulk Test Item Analysis

(Appendix 3)

The bulk Test Item analysis demonstrated that the Test Item was suitable for use during the study period; the concentration, purity and particle size results obtained were consistent with the revised Summary of Analysis.

9.3. Mortality

(Appendix 4)

There were no mRNA-1647-related mortalities during the course of the study.

One male (No. 1014) given the Reference Item was found dead on Day 43. The pathological evaluation revealed a small, dark discoloration, and soft abnormal consistency of the right adrenal gland without histopathology correlates; a dark discoloration of the corticomedullary junction of the kidneys without histopathology correlates; a dark focus and dark discoloration of the thymus (incidental thymic hemorrhage); and a failure of the lungs to collapse (lung congestion). Histopathology findings for this control male were incidental and did not explain the cause of death for this animal.

9.4. Clinical Observations

(Table 1 and Appendix 5)

On the day following the last dosing occasion, a dose-related (in severity) soft swelling was noted on the last injection site (i.e. the right hindlimb). Firm swelling (severe) was also noted at the injection site of individual males and females given 89 µg/dose. The firm swelling was noted two days following the third dose and, for one male only, 1 day following the last dose. In addition, skin redness at the injection site, was noted at a higher incidence throughout the dosing period for animals given 89 µg/dose.

Given the absence of swelling or redness at the injection site 3 days following the last dose and throughout the recovery period, these clinical observations were considered fully reversed.

9.5. Local Irritation Assessment

(Appendix 5)

Slight to severe edema was noted at the injection site following dosing of males and females given ≥ 8.9 µg/dose. The incidence and severity of these findings were dose-dependent. The apex of severity was noted 24 hours postdose and generally decreased 72 hours postdose.

Sporadic, slight to (rare) moderately severe erythema, noted at the injection site, was considered mRNA-1647-related only at 89 µg/dose and occurred generally following the third and fourth (last) doses.

Edema and erythema were no longer observed one week into the recovery period, and as such, they were considered completely reversed.

9.6. Body Weights and Body Weight Gains

(Figure 1, Figure 2, Table 2, Table 3, Appendix 6 and Appendix 7)

When compared to controls, following each dose, a tendency towards lower mean body weight gains was noted in males given ≥ 8.9 µg/dose and in females given 89 µg/dose; these changes sometimes reached statistical significance. The changes were only cumulative in males and were down to 0.86X controls from Day -1 to 42. The body weight changes were generally comparable or rebounded during the 2-week recovery period.

9.7. Food Consumption

(Table 4 and Appendix 8)

Given the variability in weekly food consumption results, the occasional weekly changes, with no clear dose-relationship, were considered not mRNA-1647-related.

9.8. Opthalmology

(Appendix 15)

There were no mRNA-1647-related ocular changes observed during the course of the study. The findings noted were age-related or incidental in origin and to be expected in this population of animals.

9.9. Body Temperature

(Table 5 and Appendix 9)

In general body temperatures were within normal ranges of 36-38°C . When compared to control animals and pre-dose body temperature measurements, the mean body temperature appeared minimally increased in males and females given 89 µg/dose, 6 and/or 24 hours post Day 1 and Day 43 doses. These statistically-significant changes were considered mRNA-1647-related.

9.10. Hematology

(Table 6 and Appendix 10)

mRNA-1647-related hematology changes were noted for males and females starting at 8.9 µg/dose and included increases in neutrophil (NEUT), eosinophil (EOS) and/or large unstained cell (LUC) counts (with concomitant increases in white blood cell [WBC] counts) and decreases in lymphocyte (LYMPH) and platelet (PLT) counts. These changes are illustrated in Text Table 14.

Text Table 14
Hematology Changes

Dose (µg/dose)	8.9		27		89	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
WBC						
Day 44	**-**	1.2	1.3	**1.4**	**1.8**	**1.8**
Day 57					1.1	1.1
NEUT						
Day 44	1.8	4.6	**4.4**	**6.2**	**7.2**	**8.9**
Day 57					0.63	0.95
LYMPH						
Day 44	0.84	0.73	0.74	0.73	0.77	0.83
Day 57					1.2	1.2
EOS						
Day 44	**2.6**	**4.0**	**2.8**	**3.9**	**3.8**	**6.5**
Day 57					1.0	1.2
LUC						
Day 44	**2.2**	1.9	**2.2**	2.1	1.8	2.0
Day 57					1.1	0.81
PLT						
Day 44	-	-	-	**-**	**-**	**0.82**
Day 57					-	1.1

Changes are expressed as X Fold from mean Group 1 (control) value.
–: indicates results were considered not to be meaningfully different from mean control value.
Bolded values were statistically significant.
Shaded boxes indicate no collection at this timepoint for corresponding groups.

Mild to moderate increases in WBC counts (up to 1..8X controls for both genders) were noted in males given ≥ 27 µg/dose and females given ≥ 8.9 µg/dose, mainly due to minimal to moderate increases in NEUT, LUC (up to 7.2X and 2.2X controls for males and 8.9X and 2.1X controls for females) and/or EOS (up to 3.8X controls for males and up to 6.5X controls for females). Minimal decreases in LYMPH counts were noted for males and females at ≥ 8.9 µg/dose (down to 0.74X and 0.73X controls, respectively).

Minimal decreases in PLT were noted in females given 89 µg/dose (0.82X controls).

Of the above changes noted following the dosing period, a full recovery of the findings were noted following the 2-week recovery period.

Any other differences in hematology parameters, including those attaining statistical significance, were judged to be due to individual or biological variation or lacked true dose relationship and therefore were considered not mRNA-1647-related.

9.11. Coagulation

(Table 7 and Appendix 11)

mRNA-1647-related increases in activated partial thromboplastin time (APTT) and in fibrinogen (FIB) were noted in males and females given ≥ 8.9 µg/dose. The changes are illustrated in Text Table 15.

Text Table 15
Coagulation Changes

Dose (µg/dose)	8.9		27		89	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
APTT						
Day 44	1.1	**1.2**	**1.1**	**1.2**	**1.2**	**1.2**
Day 57					0.99	0.96
FIB						
Day 44	**1.7**	**1.7**	**1.9**	**1.9**	**2.1**	**2.1**
Day 57					0.95	1.1

Changes are expressed as X Fold from mean (Group 1) control value.
Bolded values were statistically significant.
Shaded boxes indicate no collection at this timepoint for corresponding groups.

Minimal increases in APTT were noted for males and females given ≥ 8.9 µg/dose (up to 1.2X controls for both genders). Mild increases in FIB were noted for males and females given ≥ 8.9 µg/dose (up to 2.1X controls for both genders). At the end of the 2-week recovery period, changes were fully recovered.

Any other differences in the coagulation parameters were judged to be due to individual or biological variability or lacked true dose relationship and therefore were considered not mRNA-1647-related.

9.12. Clinical Chemistry

(Table 8 and Appendix 12)

mRNA-1647-related decreases in albumin (ALB) and increases in globulin (GLOB) were noted for males and females; these changes were reflected by overall decrease in A/G ratio. The changes are illustrated in Text Table 16.

Text Table 16
Clinical Chemistry Changes

Dose (µg/dose)	8.9		27		89	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
ALB						
Day 44	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**
Day 57					1.0	**0.9**
GLOB						
Day 44	**1.2**	**1.2**	**1.2**	**1.2**	**1.3**	**1.2**
Day 57					**0.9**	1.0
A/G						
Day 44	**0.8**	**0.8**	**0.8**	**0.8**	**0.7**	**0.7**
Day 57					**1.1**	0.9

Changes are expressed as X Fold from mean Group 1 (control) value.
Bolded values were statistically significant.
Shaded boxes indicate no collection at this timepoint for corresponding groups.

Minimal decreases in ALB and minimal increases in GLOB were noted for males and females given ≥ 8.9 µg/dose (0.9X controls and up to 1.3X controls respectively) and affected the A/G ratio (down to 0.7X controls, for both genders). At the end of the 2-week recovery period, changes were fully recovered.

Any other differences in the clinical chemistry parameters, including those attaining statistical significance, were judged to be due to individual or biological variability or lacked true dose relationship and therefore were considered not mRNA-1647-related.

9.13. Alpha-1-Acid Glycoprotein

(Table 9, Appendix 13 and Appendix 18)

When compared to controls, statistically-significant dose-related increases in Alpha-1-Glycoprotein were noted in males and females, following the dosing period.

Following the 2-week recovery period, the concentrations of Alpha-1-Glycoprotein were comparable in both the controls and the males and females that were previously given 89 µg/dose, suggesting a full recovery.

9.14. Alpha-2-Macroglobulin

(Table 9, Appendix 13 and Appendix 18)

When compared to controls, dose-related increases in Alpha-2-Macroglobulin was noted in males and females, following the dosing period.

Following the 2-week recovery period, the concentrations of Alpha-2-Macroglobulin were still slightly higher than controls, suggesting only a partial recovery.

9.15. Cytokines

(Table 10, Appendix 14 and Appendix 18)

When compared to controls, statistically-significant higher concentrations of IP-10 were observed in both genders given 89 µg/dose at all timepoints, except on Day 57 (end of recovery) where the IP-10 concentrations were comparable to control levels. The highest IP-10 concentrations were generally observed 6 hours post Day 1 dose.

Higher concentrations of MCP-1 were noted in Test Item-given females on Days 1, 15 and 29, 6 hours postdose; the increases were statistically significant. MCP-1 concentrations were comparable to control levels on Day 57.

No mRNA-1647-related changes were observed in IL-1β, IL-6, MIP-1α and TNF-α levels.

9.16. Anti-Therapeutic Antibody (ATA)

(Appendix 16)

The Day 43 samples from mRNA-1647-treated Main Study animals had detectable antibody responses against CMV gB protein and CMV gH pentamer complex. The Day 57 samples from Recovery Study animals previously given 89 µg/dose had similar antibody titers compared to Day 43 titers.

9.17. PBMC

(Appendix 17)

T-cell responses were evaluated by assessment of Interferon gamma (INFγ) producing T cells. The results are detailed in the following tables.

Summary of Pentamer Specific INF γ Response

	Group	Test material	N	Dose level (µg)	Pentamer specific CD4+ T Cells Range (%)*;	Mean (%);	SD	Pentamer specific CD8+ T Cells Range (%)*;	Mean (%);	SD
Males	1	Reference	9	0	0.00-0.46;	0.03;	0.30	0.00-0.32;	0.01;	0.23
	2	mRNA-1647	10	8.9	0.00-1.20;	0.04;	0.52	0.00-2.73;	0.43;	0.88
	3	mRNA-1647	10	27	0.00-0.46;	0.08;	0.25	0.00-0.74;	0.21;	0.33
	4	mRNA-1647	10	89	0.00-6.99;	0.90;	2.19	0.00-8.96;	1.29;	2.83
Females	1	Reference	10	0	0.00-1.13;	0.02;	0.70	0.00-0.33;	0.01;	0.24
	2	mRNA-1647	10	8.9	0.00-1.39;	0.09;	0.78	0.00-3.91;	1.10;	1.61
	3	mRNA-1647	10	27	0.00-2.16;	0.34;	1.01	0.00-2.70;	0.69;	1.30
	4	mRNA-1647	10	89	0.00-3.16;	0.31;	1.42	0.00-4.35;	0.95;	1.56

Summary of Glycoprotein B Specific INF γ Response

	Group	Test material	N	Dose level (µg)	Glycoprotein specific CD4+ T Cells Range (%)*;	Mean (%);	SD	Glycoprotein specific CD8+ T Cells Range (%)*;	Mean (%);	SD
Males	1	Reference	9	0	0.00-0.57;	0.00;	0.31	0.00-0.12;	0.00;	0.17
	2	mRNA-1647	10	8.9	0.00-0.79;	0.00;	0.38	0.00-0.26;	0.00;	0.13
	3	mRNA-1647	10	27	0.00-0.91;	0.15;	0.35	0.00-0.64;	0.13;	0.28
	4	mRNA-1647	10	89	0.00-3.17;	0.53;	0.99	0.00-4.52;	0.46;	1.46
Females	1	Reference	10	0	0.00-0.79;	0.04;	0.41	0.00-0.69;	0.13;	0.36
	2	mRNA-1647	10	8.9	0.00-1.30;	0.03;	0.92	0.00-0.00;	0.00;	0.37
	3	mRNA-1647	10	27	0.00-2.15;	0.08;	1.28	0.00-4.17;	0.71;	1.62
	4	mRNA-1647	10	89	0.00-3.00;	0.00;	1.62	0.00-4.76;	0.79;	1.96

* For purpose of Range and Mean calculation, value <0.00 following unstimulated Control subtration were set to 0.00 for reporting

Maximal antigen-specific response was observed at 89 µg/dose for both Pentamer and Glycoprotein B peptide libraries. The Pentamer library produced the stronger response of the two antigen libraries with an individual maximal response in males of up to 6.99 and 8.96% in CD4+ and CD8+ T cells, respectively. The largest response to Glycoprotein B stimulation was at 89 µg/dose in males for CD4+ T cells at 3.17%, and in females at 4.76% for CD8+ T cells.

9.18. Gross Pathology

(Appendix 19)

9.18.1. Terminal Necropsy (Day 44)

mRNA-1647-related gross pathology findings are summarized in Text Table 17.

Text Table 17
Summary of Gross Pathology Findings – Terminal Necropsy (Day 44)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**8.9**	**27**	**89**	**0**	**8.9**	**27**	**89**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injection (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency, firm	0	1	5	9	0	3	5	7
Swelling	0	5	6	9	0	5	5	7
Focus, dark	0	0	0	0	0	1	1	3
Lymph Node, Inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	1	1	0	5	0	0	0	1
Lymph Node, Popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	7	7	0	8	6	7

At the intramuscular injection sites, dose-dependent mRNA-1647-related gross pathology observations of abnormal firm consistency, dark focus, and/or swelling were noted in animals given ≥ 8.9 µg/dose. These gross observations correlated microscopically with mixed cell inflammation of the subcutaneous and/or muscular tissue and/or subcutaneous edema at the injection site.

In the draining inguinal and/or popliteal lymph nodes, mRNA-1647-related gross enlargement was noted in animals given ≥ 8.9 µg/dose, and correlated microscopically to mixed cell inflammation. Gross enlargement and microscopic mixed cell inflammation most commonly involved the popliteal lymph nodes. Gross enlargement of the inguinal lymph node was noted in one male given the Reference Item, without any correlating microscopic finding.

Other gross pathology findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1647-related.

9.18.2. Recovery Necropsy (Day 57)

(Appendix 19)

There were no mRNA-1647-related gross pathology findings observed at the end of the 2-week recovery period.

All gross pathology findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1647-related.

9.19. Organ Weights

(Appendix 19)

9.19.1. Terminal Necropsy (Day 44)

(Appendix 19)

mRNA-1647-related organ weight changes are summarized in Text Table 18.

Text Table 18
Summary of Organ Weight Data – Terminal Necropsy (Day 44)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**8.9**	**27**	**89**	**8.9**	**27**	**89**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Spleen (No. Weighed)	10	10	10	10	10	10
Absolute weight	1.0794	1.0824	**1.2070** [b]	0.7125	**0.7566** [a]	**0.7934** [b]
% of body weight	**0.21190** [a]	**0.21678** [a]	**0.23429** [c]	0.22732	**0.24041** [b]	**0.25394** [c]
% of brain weight	48.79592	49.81185	**55.10209** [b]	34.70430	**36.98272** [a]	**38.80259** [b]

[a] Significantly different from Group 1value p≤0.05 (Dunnett).
[b] Significantly different from Group 1 value p≤0.01 (Dunnett).
[c] Significantly different from Group 1 value p≤0.001 (Dunnett).
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – P ≤ 0.05; refer to data tables for actual significance levels and tests used.

In the spleen, slight dose-dependent increases in absolute and/or relative organ weights were noted in males and females given ≥ 8.9 µg/dose. These changes were consistently statistically significant for increases in absolute and/or relative (to body and/or to brain) weights in males given 89 µg/dose and females given ≥ 27 µg/dose. These splenic weight changes were not correlated with any specific histopathology finding.

No other mRNA-1647-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or related to difference of sexual maturity and not mRNA-1647-related.

9.19.2. Recovery Necropsy (Day 57)

(Appendix 19)

mRNA-1647-related increased spleen weights noted at the terminal necropsy were also observed at the end of the 2-week recovery period and are summarized in Text Table 19.

Text Table 19
Summary of Organ Weight Data – Recovery Necropsy (Day 57)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**8.9**	**27**	**89**	**8.9**	**27**	**89**
No. Animals per Group	**0**	**0**	**5**	**0**	**0**	**5**
Spleen (No. Weighed)	0	0	5	0	0	5
Absolute value	-	-	1.1022	-	-	0.6522
% Difference	-	-	+18.90	-	-	+9.65
% of body weight	-	-	**0.18856** [a]	-	-	0.20057
% Difference	-	-	+21.50	-	-	+11.74
% of brain weight	-	-	48.35552	-	-	31.90101
% Difference	-	-	+19.86	-	-	+11.58

[a] Significantly different from Group 1 value p≤0.05 (T-Test).
Based upon statistical analysis of group means, values highlighted in bold are significantly different from Group 1– P ≤ 0.05; refer to data tables for actual significance levels and tests used.

In the spleen, a slight increase in absolute and/or relative organ weights were noted in males and females given 89 µg/dose. These changes were not statistically significant, with the exception of mean spleen weight relative to final body weight in the males; and thus, were considered to have limited toxicological importance. These splenic weight changes were not correlated with any specific histopathology finding.

No other mRNA-1647-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or related to difference of sexual maturity and not mRNA-1647-related.

9.20. Histopathology

(Appendix 19)

9.20.1. Terminal Necropsy (Day 44)

(Appendix 19)

mRNA-1647-related microscopic pathology findings were noted at the injection sites, the draining lymph nodes (popliteal and/or inguinal), sciatic nerve, bone marrow, and spleen and these findings are summarized in Text Table 20

Text Table 20
Summary of Microscopic Findings – Terminal Necropsy (Day 44)

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (µg/dose)	0	8.9	27	89	0	8.9	27	89
No. Animals Examined	10	10	10	10	10	10	10	10
Site, Injection (No. Examined)	10	10	10	10	10	10	10	10
Inflammation: mixed cell; subcutaneous	0	10	9	10	0	10	10	10
Minimal	-	1	0	0	0	1	1	1
Mild	-	6	3	4	0	7	8	2
Moderate	-	3	6	6	0	2	1	7
Edema; subcutaneous	0	5	8	9	0	6	8	10
Minimal	-	2	0	2	-	2	2	0
Mild	-	3	2	3	-	3	4	3
Moderate	-	0	6	4	-	1	2	7
Degeneration; myofiber	5	7	9	6	5	5	8	6
Minimal	5	7	8	5	4	4	6	6
Mild	0	0	1	1	1	1	2	0
Lymph Node, Popliteal (No. Examined)	10	10	10	10	10	10	10	10
Inflammation; mixed cell	0	2	10	9	0	10	10	10
Minimal	-	0	2	1	-	4	2	0
Mild	-	2	4	3	-	6	7	5
Moderate	-	0	4	4	-	0	1	5
Marked	-	0	0	1	-	0	0	0
Lymph Node, Inguinal (No. Examined)	10	10	10	10	10	10	10	10
Inflammation; mixed cell	0	0	1	3	0	0	0	0
Minimal	-	-	1	1	-	-	-	-
Mild	-	-	0	2	-	-	-	-
Sciatic Nerve (No. Examined)	10	10	10	10	10	10	10	10
Inflammation; mixed; perineurial	0	10	10	10	0	10	10	10
Minimal	-	0	2	1	-	4	3	1
Mild	-	2	4	1	-	2	4	1
Moderate	-	3	4	8	-	4	3	7
Marked	-	5	0	0	-	0	0	1
Bone Marrow (No. Examined)	10	10	10	10	10	10	10	10
Increased hematopoiesis; myeloid	0	0	4	9	0	0	2	9
Minimal	-	-	4	9	-	-	2	9
Spleen (No. Examined)	10	10	10	10	10	10	10	10
Decreased cellularity; periarteriolar lymphoid sheath	0	5	9	10	0	7	10	10
Minimal	-	1	5	3	-	5	6	1
Mild	-	4	4	7	-	2	4	9

Localized tissue reactions involved the intramuscular injection sites, the draining popliteal and/or inguinal lymph nodes, and the sciatic nerves. Systemic tissue reactions involved the bone marrow and spleen.

At the intramuscular injection sites, there was a dose-related inflammatory reaction characterized by minimal to moderate mixed cell inflammation involving the subcutaneous tissues, skeletal muscle, and to a lesser extent the dermis, as well as associated minimal to moderate subcutaneous edema and minimal to mild myofiber degeneration in animals given ≥ 8.9 µg/dose. The inflammatory reaction, which increased in severity with increasing dose, often extended along and expanded endomysial and perimysial tissue layers, encircling individual muscle fibers

and/or bundles. This reaction was characterized by varying numbers of intact and degenerating neutrophils, mononuclear cells, and macrophages (mixed cell inflammation); accumulations of protein-rich fluid (edema); and varying degrees of myofiber degeneration.

In the draining popliteal and/or inguinal lymph nodes, an increased incidence and/or severity of minimal to marked mixed cell inflammation were noted in animals given ≥ 8.9 µg/dose. The inflammation often involved the adventitia surrounding the lymph nodes, and most commonly involved the popliteal lymph nodes.

Minimal to marked mixed cell inflammation was frequently observed in the perineurial tissue surrounding the sciatic nerve of animals given ≥ 8.9 µg/dose. This finding was considered to be an extension of the inflammatory reaction at the intramuscular injection sites to this region.

In the bone marrow, minimal increased myeloid hematopoiesis was noted in animals given ≥ 27 µg/dose. This finding was characterized by increased numbers of myeloid precursors in the marrow, and was secondary or compensatory inflammatory reaction noted at the intramuscular injection sites.

In the spleen, a dose-dependent minimal to mild decreased cellularity of the periarteriolar lymphoid sheath was noted in animals given ≥ 8.9 µg/dose.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1647-related.

9.20.2. Recovery Necropsy (Day 57)

(Appendix 19)

Following the 2-week recovery period, microscopic pathology findings seen at the terminal necropsy were no longer present in the draining lymph nodes (popliteal and/or inguinal), consistent with a complete recovery of these findings.

Microscopic findings noted at the terminal necropsy were also observed at the recovery necropsy at the injection sites (however, a shift to mononuclear cell infiltration rather than mixed cell inflammation was observed), sciatic nerve, bone marrow, and spleen and these findings are summarized in Text Table 21.

Text Table 21
Summary of Microscopic Findings – Recovery Necropsy (Day 57)

	Males		Females	
Group	1	4	1	4
Dose (µg/dose)	0	89	0	89
No. Animals Examined	4	5	4	5
Site, Injection (No. Examined)	4	5	5	5
Infiltration, mononuclear cell; myofiber	0	2	0	5
Minimal	-	1	-	4
Mild	-	1	-	1
Nerve, Sciatic	4	5	5	5
Inflammation, mixed cell; perineurial	0	0	0	2
Minimal	-	-	-	2
Bone Marrow (No. Examined)	4	5	5	5
Increased hematopoiesis; myeloid	0	2	0	1
Minimal	-	2	-	1
Spleen (No. Examined)	4	5	5	5
Decreased cellularity; periarteriolar lymphoid sheath	0	2	0	0
Minimal	-	2	-	-

At the intramuscular injection sites, there was a residual inflammatory reaction characterized by minimal to mild mononuclear cell infiltration involving the subcutaneous tissues and skeletal muscle at 89 µg/dose. Minimal to mild myofiber degeneration did not differ in incidence or severity from the Reference Item-treated group.

Mixed cell inflammation involving the draining lymph nodes (popliteal and/or inguinal) and sciatic nerves, as noted as the terminal euthanasia, was not noted at the recovery necropsy, consistent with complete recovery.

Minimal mixed cell inflammation was observed in the perineurial tissue surrounding the sciatic nerve of females given 89 µg/dose. The incidence and severity of this finding was reduced compared to the terminal necropsy.

In the bone marrow, minimal increased myeloid hematopoiesis was noted in animals given 89 µg/dose. The incidence of this finding was reduced compared to the terminal necropsy.

In the spleen, a minimal decreased cellularity of the periarteriolar lymphoid sheath was noted in males given 89 µg/dose. The incidence and severity of this finding was reduced compared to the terminal necropsy.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1647-related.

10. CONCLUSION

In conclusion, administration of mRNA-1647 by intramuscular injection for 6 weeks (4 doses) was clinically well tolerated (no mortality, major decreases in body weight and no changes in food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 89 µg/dose. Starting at 8.9 µg/dose, generally dose-dependent changes in clinical signs at the injection site, clinical pathology parameters, cytokines and acute protein levels were consistent with an inflammatory response at the injection site. Dose-related target organ effects were limited to the injection site, the bone marrow, the inguinal and popliteal lymph nodes, the connective tissue surrounding the sciatic nerve and the spleen of animals given mRNA-1647. At the end of the 2-week recovery period, all changes were partially or fully recovered.

Figure 1

Summary of Body Weights - Males

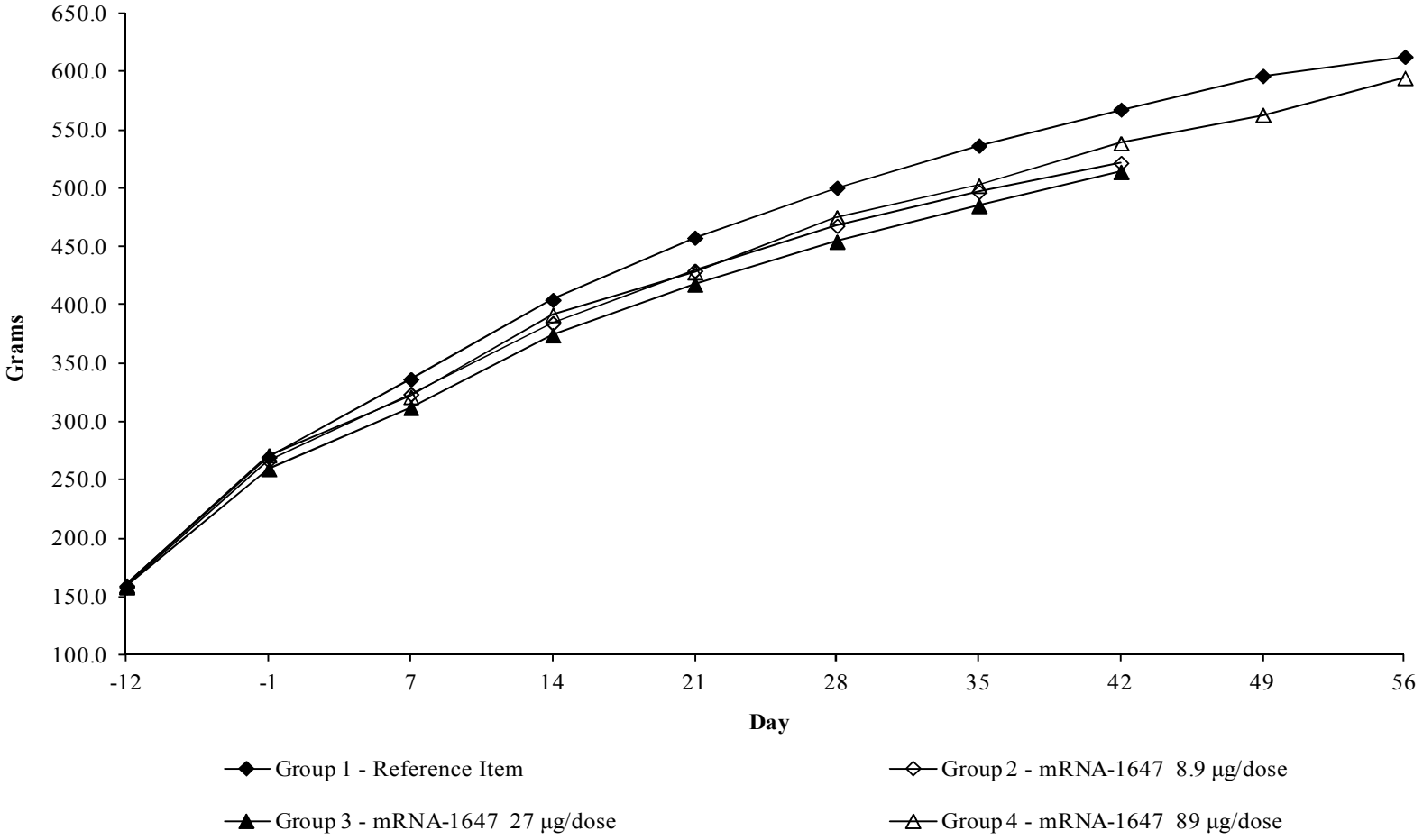

Figure 2

Summary of Body Weights - Females

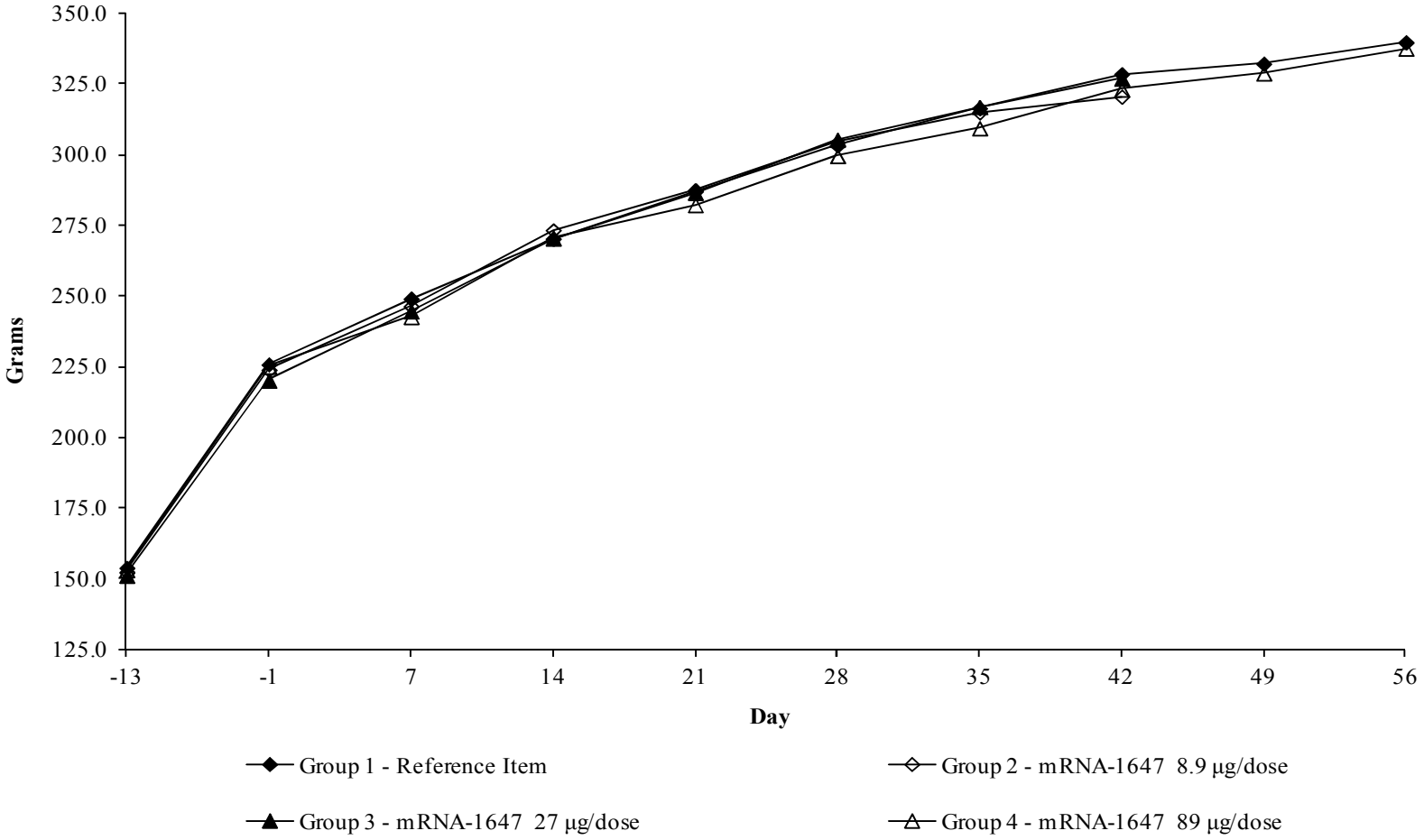

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Swollen Soft				
Number of Observations	.	10	13	13
Number of Animals	.	10	10	12
Days from - to	.	44 44	28 44	31 45
Swollen Firm				
Number of Observations	.	.	.	4
Number of Animals	.	.	.	3
Days from - to	.	.	.	31 44
Skin, Red				
Number of Observations	2	7	1	7
Number of Animals	2	2	1	6
Days from - to	7 44	14 44	14 14	31 45
Skin, Lesion w/ Discharge				
Number of Observations	.	1	.	.
Number of Animals	.	1	.	.
Days from - to	.	-1 -1	.	.
Skin, Scab				
Number of Observations	3	11	1	4
Number of Animals	3	4	1	2
Days from - to	7 44	-1 44	14 14	28 35
Fur, Erected				
Number of Observations	.	2	2	1
Number of Animals	.	2	2	1
Days from - to	.	44 44	44 44	44 44
Fur, Staining, Red				
Number of Observations	.	5	.	9
Number of Animals	.	2	.	3
Days from - to	.	28 44	.	14 57

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Fur, Thin Cover				
Number of Observations	3	1	.	1
Number of Animals	1	1	.	1
Days from - to	28 42	44 44	.	44 44
Malocclusion				
Number of Observations	.	.	7	.
Number of Animals	.	.	1	.
Days from - to	.	.	7 44	.
Testis, Enlarged				
Number of Observations	.	1	.	.
Number of Animals	.	1	.	.
Days from - to	.	28 28	.	.
Digit Bent				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	44 44	.

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Hyperreactive				
Number of Observations	.	3	.	.
Number of Animals	.	1	.	.
Days from - to	.	35 44	.	.
Hypersensitive				
Number of Observations	.	.	.	8
Number of Animals	.	.	.	1
Days from - to	.	.	.	7 44
Vocalization Increased				
Number of Observations	.	.	.	8
Number of Animals	.	.	.	1
Days from - to	.	.	.	7 44
Caught in Cage				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	28 28	.
Swollen Soft				
Number of Observations	.	10	11	14
Number of Animals	.	10	10	13
Days from - to	.	44 44	7 44	31 45
Swollen Firm				
Number of Observations	.	.	.	10
Number of Animals	.	.	.	10
Days from - to	.	.	.	31 31
Warm to Touch				
Number of Observations	.	.	.	2
Number of Animals	.	.	.	2
Days from - to	.	.	.	44 44

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Skin, Red				
Number of Observations	4	.	3	35
Number of Animals	2	.	2	15
Days from - to	21 38	.	7 35	17 56
Skin, Dry				
Number of Observations	7	.	.	9
Number of Animals	2	.	.	5
Days from - to	21 49	.	.	21 57
Skin, Lesion				
Number of Observations	1	.	1	.
Number of Animals	1	.	1	.
Days from - to	-1 -1	.	35 35	.
Skin, Lesion w/ Discharge				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	28 28	.
Skin, Scab				
Number of Observations	11	.	8	14
Number of Animals	4	.	5	7
Days from - to	-1 49	.	7 44	28 57
Fur, Staining, Red				
Number of Observations	11	6	5	9
Number of Animals	6	1	1	4
Days from - to	35 57	14 44	21 44	21 57
Fur, Thin Cover				
Number of Observations	16	.	9	1
Number of Animals	4	.	2	1
Days from - to	28 57	.	-14 44	57 57

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Teeth, Broken				
Number of Observations	.	.	.	8
Number of Animals	.	.	.	1
Days from - to	.	.	.	-1 44
Skin Staining				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	44 44	.

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day -12	-1	7	14	21	28	35
1M	Mean	159.5	269.5	336.4	404.4	457.7	500.5	536.7
	SD	5.0	13.5	19.3	27.8	31.4	36.3	40.5
	N	15	15	15	15	15	15	15
2M	Mean	158.3	266.7	323.6	384.4	429.3a	467.9	497.0a
	SD	5.2	12.1	17.6	23.3	30.0	42.9	48.7
	N	10	10	10	10	10	10	10
	%Diff G1	-0.7	-1.0	-3.8	-4.9	-6.2	-6.5	-7.4
3M	Mean	158.3	259.3	312.0b	374.1b	417.6b	454.3b	484.9b
	SD	6.1	7.6	10.7	15.1	20.2	25.3	28.9
	N	10	10	10	10	10	10	10
	%Diff G1	-0.7	-3.8	-7.3	-7.5	-8.8	-9.2	-9.7
4M	Mean	159.5	271.2	321.2a	391.5	428.1a	475.3	502.3a
	SD	4.8	14.9	16.2	20.1	22.6	26.0	27.2
	N	15	15	15	15	15	15	15
	%Diff G1	0.0	0.6	-4.5	-3.2	-6.5	-5.0	-6.4

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day 42	Day 49	Day 56
1M	Mean	567.5	596.3	612.8
	SD	46.3	44.3	45.5
	N	15	4	4
2M	Mean	521.8a	--	--
	SD	52.1	--	--
	N	10	--	--
	%Diff G1	-8.0	--	--
3M	Mean	514.1b	--	--
	SD	34.1	--	--
	N	10	--	--
	%Diff G1	-9.4	--	--
4M	Mean	538.7	563.0	594.6
	SD	29.2	27.1	25.9
	N	15	5	5
	%Diff G1	-5.1	-5.6	-3.0

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day -13	-1	7	14	21	28	35
1F	Mean	153.9	225.9	249.1	270.4	287.0	303.3	316.5
	SD	7.0	15.5	17.2	22.3	22.5	26.9	29.3
	N	15	15	15	15	15	15	15
2F	Mean	152.4	223.9	246.5	273.3	287.4	304.4	315.0
	SD	5.1	13.6	19.6	27.0	31.3	33.5	35.2
	N	10	10	10	10	10	10	10
	%Diff G1	-1.0	-0.9	-1.1	1.1	0.1	0.4	-0.5
3F	Mean	151.2	220.2	244.7	270.4	286.6	305.3	316.9
	SD	6.0	12.2	18.0	26.6	25.6	31.2	33.1
	N	10	10	10	10	10	10	10
	%Diff G1	-1.8	-2.5	-1.8	0.0	-0.1	0.7	0.1
4F	Mean	153.1	225.1	242.7	270.6	282.3	299.5	309.4
	SD	6.5	9.2	13.6	18.7	20.9	20.4	26.1
	N	15	15	15	15	15	15	15
	%Diff G1	-0.6	-0.4	-2.6	0.1	-1.6	-1.3	-2.2

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day 42	Day 49	Day 56
1F	Mean	328.5	332.2	339.8
	SD	31.4	31.9	31.3
	N	15	5	5
2F	Mean	320.6	--	--
	SD	36.5	--	--
	N	10	--	--
	%Diff G1	-2.4	--	--
3F	Mean	327.0	--	--
	SD	32.7	--	--
	N	10	--	--
	%Diff G1	-0.5	--	--
4F	Mean	323.1	328.8	337.6
	SD	26.1	36.6	33.5
	N	15	5	5
	%Diff G1	-1.7	-1.0	-0.6

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day Change -12 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1M	Mean	110.0	66.9	68.0	53.3	42.9	36.2	30.7
	SD	11.9	6.7	10.1	7.1	7.5	6.0	6.7
	N	15	15	15	15	15	15	15
2M	Mean	108.4	56.9b	60.8	44.9b	38.6	29.1a	24.8
	SD	9.4	8.4	9.5	7.9	13.6	7.0	8.0
	N	10	10	10	10	10	10	10
3M	Mean	101.0	52.7c	62.1	43.5b	36.7	30.6	29.2
	SD	7.4	8.2	5.6	6.7	7.6	4.8	7.4
	N	10	10	10	10	10	10	10
4M	Mean	111.7	50.0c	70.3	36.6c	47.2	26.9c	36.4
	SD	12.7	6.8	7.3	5.0	6.8	5.4	5.9
	N	15	15	15	15	15	15	15

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day Change -1 - 42	Change 42 - 49	Change 49 - 56	Change 42 - 56
1M	Mean	298.0	28.8	16.5	45.3
	SD	36.1	6.7	4.0	9.2
	N	15	4	4	4
2M	Mean	255.1a	--	--	--
	SD	47.3	--	--	--
	N	10	--	--	--
3M	Mean	254.8a	--	--	--
	SD	34.9	--	--	--
	N	10	--	--	--
4M	Mean	267.5	20.8	31.6e	52.4
	SD	23.9	3.6	7.6	7.0
	N	15	5	5	5

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)
d=p≤0.05,e=p≤0.01,f=p≤0.001 (T-test)

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day Change -13 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1F	Mean	72.0	23.2	21.3	16.6	16.3	13.2	12.1
	SD	14.6	6.8	8.9	7.6	7.6	6.5	6.1
	N	15	15	15	15	15	15	15
2F	Mean	71.5	22.6	26.8	14.1	17.0	10.6	5.6b
	SD	11.9	8.8	8.9	7.9	8.7	5.9	5.3
	N	10	10	10	10	10	10	10
3F	Mean	69.0	24.5	25.7	16.2	18.7	11.6	10.1
	SD	13.9	9.1	11.3	10.4	9.0	5.9	3.9
	N	10	10	10	10	10	10	10
4F	Mean	72.0	17.6	27.9	11.7	17.2	9.9	13.7
	SD	9.5	6.9	7.1	7.9	4.1	7.8	4.0
	N	15	15	15	15	15	15	15

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day Change -1 - 42	Change 42 - 49	Change 49 - 56	Change 42 - 56
1F	Mean	102.6	7.2	7.6	14.8
	SD	20.0	9.7	7.5	12.8
	N	15	5	5	5
2F	Mean	96.7	--	--	--
	SD	25.8	--	--	--
	N	10	--	--	--
3F	Mean	106.8	--	--	--
	SD	25.4	--	--	--
	N	10	--	--	--
4F	Mean	98.0	10.6	8.8	19.4
	SD	19.1	6.7	10.0	6.3
	N	15	5	5	5

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day (From/To)							
		-9/1	1/8	8/15	15/22	22/29	29/36	36/43	43/50
1M	Mean	29.79	32.44	33.35	34.38	35.31	35.08	35.83	34.50
	SD	2.04	2.32	2.78	2.09	1.99	1.90	1.89	0.60
	N	15	15	15	15	15	15	15	4
2M	Mean	30.26	31.32	33.02	33.52	34.60	33.55	33.85	--
	SD	0.71	0.57	1.67	1.61	1.11	1.67	1.63	--
	N	7	10	10	10	10	10	10	--
	%Diff G1	1.58	-3.45	-0.98	-2.50	-2.02	-4.36	-5.52	--
3M	Mean	27.69	28.56	31.18	31.72	32.89	31.89	33.51	--
	SD	0.76	1.51	1.13	0.94	1.04	1.40	1.62	--
	N	7	10	10	10	10	10	10	--
	%Diff G1	-7.05	-11.96	-6.50	-7.74	-6.86	-9.09	-6.47	--
4M	Mean	30.79	30.11	35.05	33.24	36.78	33.65	36.55	34.88
	SD	0.91	1.13	1.28	1.14	1.16	0.80	1.52	0.44
	N	15	15	15	15	15	15	15	5
	%Diff G1	3.36	-7.19	5.10	-3.32	4.15	-4.09	2.03	1.10

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day (From/To) 50/56
1M	Mean	34.23
	SD	1.35
	N	4
2M	Mean	--
	SD	--
	N	--
	%Diff G1	--
3M	Mean	--
	SD	--
	N	--
	%Diff G1	--
4M	Mean	37.18
	SD	0.66
	N	5
	%Diff G1	8.63

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day (From/To)							
		-9/1	1/8	8/15	15/22	22/29	29/36	36/43	43/50
1F	Mean	22.94	23.02	23.17	23.99	23.81	23.97	23.18	23.28
	SD	1.47	1.47	1.43	1.66	1.40	1.13	1.49	1.20
	N	12	15	15	15	15	15	15	5
2F	Mean	22.25	23.38	24.17	24.37	24.28	24.50	23.83	--
	SD	1.14	0.61	0.88	1.65	2.03	1.12	1.44	--
	N	10	10	10	10	10	10	10	--
	%Diff G1	-3.01	1.56	4.33	1.60	1.96	2.20	2.80	--
3F	Mean	22.13	23.37	24.13	24.19	24.72	24.45	24.64	--
	SD	0.23	0.60	0.91	1.12	1.31	1.57	1.04	--
	N	7	10	10	10	10	10	10	--
	%Diff G1	-3.54	1.52	4.16	0.85	3.81	1.99	6.30	--
4F	Mean	21.65	21.89	23.57	24.00	23.84	23.63	24.17	23.08
	SD	1.44	1.81	2.29	1.91	2.10	2.15	2.45	0.71
	N	15	15	15	15	15	15	15	5
	%Diff G1	-5.62	-4.92	1.76	0.06	0.11	-1.45	4.29	-0.86

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day (From/To) 50/56
1F	Mean	25.18
	SD	0.66
	N	5
2F	Mean	--
	SD	--
	N	--
	%Diff G1	--
3F	Mean	--
	SD	--
	N	--
	%Diff G1	--
4F	Mean	24.84
	SD	0.77
	N	5
	%Diff G1	-1.35

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1		Day 2	Day 43		Day 44
		pr	p		pr	p	
1M	Mean	36.24	35.26	37.45	36.23	36.79	36.91
	SD	0.44	0.88	0.50	0.41	0.56	0.65
	N	15	15	15	15	15	14
2M	Mean	36.82b	35.99	36.92d	36.89d	36.66	36.47
	SD	0.25	0.52	0.24	0.84	0.49	0.41
	N	10	10	10	10	10	10
	%Diff G1	1.60	2.07	-1.42	1.81	-0.36	-1.20
3M	Mean	36.64	36.66e	37.13	37.97f	37.60e	36.99
	SD	0.26	1.06	0.41	0.60	0.66	0.28
	N	10	10	10	10	10	10
	%Diff G1	1.10	3.97	-0.86	4.79	2.19	0.21
4M	Mean	36.61	38.05f	37.47	36.81d	37.53e	37.29
	SD	0.52	1.08	0.55	0.56	0.52	0.73
	N	15	15	15	15	15	15
	%Diff G1	1.01	7.90	0.05	1.60	2.01	1.01

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunn)
d=p≤0.05,e=p≤0.01,f=p≤0.001 (Dunnett)

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1		Day 2	Day 3	Day 43		Day 44
		pr	p			pr	p	
1F	Mean	37.32	36.25	37.62	--	38.01	37.04	37.39
	SD	0.41	0.50	0.33	--	0.61	0.58	0.71
	N	15	15	15	--	15	15	15
2F	Mean	37.59	36.79a	37.37	--	37.98	37.31	37.58
	SD	0.42	0.41	0.32	--	0.59	0.60	0.57
	N	10	10	10	--	10	10	10
	%Diff G1	0.72	1.48	-0.66	--	-0.07	0.73	0.52
3F	Mean	37.50	36.87b	37.67	--	38.43	37.78b	37.88
	SD	0.47	0.54	0.35	--	0.57	0.46	0.74
	N	10	10	10	--	10	10	10
	%Diff G1	0.48	1.70	0.13	--	1.11	2.00	1.32
4F	Mean	37.64	37.55c	38.56c	37.55	37.77	38.59c	38.12b
	SD	0.51	0.44	0.53	0.48	0.74	0.34	0.57
	N	15	15	15	15	15	15	15
	%Diff G1	0.86	3.59	2.50	--	-0.63	4.18	1.96

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1M	Mean	10.570	1.595	8.402	0.303	0.108	0.020	0.138
	SD	3.788	0.794	3.157	0.067	0.043	0.013	0.063
	N	10	10	10	10	10	10	10
2M	Mean	10.776	2.920	7.017	0.236	0.277b	0.020	0.304e
	SD	1.208	0.957	1.092	0.070	0.072	0.007	0.142
	N	10	10	10	10	10	10	10
	%Diff G1	1.949	83.072	-16.484	-22.112	156.481	0.000	120.290
3M	Mean	14.091	6.990f	6.259	0.216	0.301b	0.023	0.304e
	SD	2.499	1.908	1.840	0.114	0.068	0.009	0.104
	N	10	10	10	10	10	10	10
	%Diff G1	33.311	338.245	-25.506	-28.713	178.704	15.000	120.290
4M	Mean	18.827c	11.493f	6.487	0.188d	0.413c	0.023	0.251
	SD	3.862	2.497	1.959	0.098	0.147	0.013	0.092
	N	10	10	10	10	10	10	9
	%Diff G1	78.117	620.564	-22.792	-37.954	282.407	15.000	81.965

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunn)
d=p≤0.05,e=p≤0.01,f=p≤0.001 (Dunnett)

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.682	13.69	41.38	53.87	17.84	33.10	12.70
	SD	0.252	0.35	1.29	1.50	0.60	0.49	0.66
	N	10	10	10	10	10	10	10
2M	Mean	7.817	13.59	41.54	53.16	17.41	32.73	13.05
	SD	0.290	0.36	1.05	1.76	0.67	0.39	0.43
	N	10	10	10	10	10	10	10
	%Diff G1	1.757	-0.73	0.39	-1.32	-2.41	-1.12	2.76
3M	Mean	7.590	13.30	40.50	53.36	17.51	32.83	13.46b
	SD	0.228	0.41	1.32	0.98	0.31	0.27	0.52
	N	10	10	10	10	10	10	10
	%Diff G1	-1.198	-2.85	-2.13	-0.95	-1.85	-0.82	5.98
4M	Mean	7.900	13.93	42.58	53.88	17.66	32.74	13.82c
	SD	0.237	0.45	1.57	0.89	0.30	0.45	0.43
	N	10	10	10	10	10	10	10
	%Diff G1	2.838	1.75	2.90	0.02	-1.01	-1.09	8.82

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1078.6	220.08
	SD	95.1	27.59
	N	10	10
2M	Mean	1043.8	223.42
	SD	132.4	31.08
	N	10	10
	%Diff G1	-3.2	1.52
3M	Mean	1059.2	213.30
	SD	117.1	25.80
	N	10	10
	%Diff G1	-1.8	-3.08
4M	Mean	1063.1	218.49
	SD	73.4	26.57
	N	10	10
	%Diff G1	-1.4	-0.72

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	Mean	6.541	0.724	5.498	0.151	0.069	0.010	0.087
	SD	1.905	0.338	1.893	0.058	0.022	0.005	0.039
	N	10	10	10	10	10	10	10
2F	Mean	7.919	3.320	4.026	0.126	0.275b	0.008	0.166
	SD	1.209	0.645	0.880	0.061	0.057	0.006	0.100
	N	10	10	10	10	10	10	10
	%Diff G1	21.067	358.564	-26.773	-16.556	298.551	-20.000	90.805
3F	Mean	9.060a	4.490c	3.996	0.110	0.272b	0.009	0.181
	SD	1.455	0.983	0.772	0.039	0.122	0.003	0.085
	N	10	10	10	10	10	10	10
	%Diff G1	38.511	520.166	-27.319	-27.152	294.203	-10.000	108.046
4F	Mean	11.735c	6.434c	4.555	0.102	0.451c	0.012	0.176
	SD	3.029	1.624	1.495	0.036	0.265	0.009	0.105
	N	10	10	10	10	10	10	10
	%Diff G1	79.407	788.674	-17.152	-32.450	553.623	20.000	102.299

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunn)

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.102	12.75	38.01	53.50	17.98	33.56	11.51
	SD	0.224	0.44	1.31	0.89	0.34	0.21	0.44
	N	10	10	10	10	10	10	10
2F	Mean	6.916	12.51	37.43	54.11	18.12	33.47	11.89
	SD	0.302	0.63	1.86	0.91	0.38	0.60	0.55
	N	10	10	10	10	10	10	10
	%Diff G1	-2.619	-1.88	-1.53	1.14	0.78	-0.27	3.30
3F	Mean	6.960	12.69	37.90	54.53	18.26	33.47	12.19a
	SD	0.491	0.86	2.58	1.52	0.62	0.57	0.62
	N	10	10	10	10	10	10	10
	%Diff G1	-1.999	-0.47	-0.29	1.93	1.56	-0.27	5.91
4F	Mean	7.176	13.03	38.69	53.92	18.19	33.69	12.79c
	SD	0.274	0.37	1.25	0.99	0.31	0.50	0.49
	N	10	10	10	10	10	10	10
	%Diff G1	1.042	2.20	1.79	0.79	1.17	0.39	11.12

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1060.4	185.68
	SD	172.2	23.56
	N	10	10
2F	Mean	1019.1	196.20
	SD	100.9	32.57
	N	10	10
	%Diff G1	-3.9	5.67
3F	Mean	971.1	218.11
	SD	95.1	36.36
	N	10	10
	%Diff G1	-8.4	17.47
4F	Mean	868.1b	198.61
	SD	102.0	36.03
	N	10	10
	%Diff G1	-18.1	6.96

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1M	Mean	9.998	2.120	7.315	0.288	0.133	0.015	0.125
	SD	2.902	1.787	1.616	0.154	0.043	0.006	0.090
	N	4	4	4	4	4	4	4
4M	Mean	10.702	1.342	8.692	0.384	0.130	0.016	0.138
	SD	0.998	0.266	0.934	0.212	0.057	0.005	0.053
	N	5	5	5	5	5	5	5
	%Diff G1	7.047	-36.698	18.824	33.565	-1.887	6.667	10.400

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.843	13.63	40.90	52.18	17.38	33.33	12.73
	SD	0.207	0.17	0.89	0.67	0.41	0.63	0.57
	N	4	4	4	4	4	4	4
4M	Mean	7.656	13.36	41.00	53.54a	17.48	32.64	14.60b
	SD	0.250	0.33	1.16	0.68	0.40	0.40	0.61
	N	5	5	5	5	5	5	5
	%Diff G1	-2.378	-1.94	0.24	2.62	0.60	-2.06	14.73

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (T-test)

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	999.0	214.63
	SD	135.9	18.22
	N	4	4
4M	Mean	1105.6	265.30a
	SD	119.7	32.68
	N	5	5
	%Diff G1	10.7	23.61

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (T-test)

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	Mean	4.132	0.892	2.970	0.152	0.066	0.000	0.052
	SD	1.035	0.265	0.905	0.063	0.011	0.000	0.029
	N	5	5	5	5	5	5	5
4F	Mean	4.590	0.844	3.530	0.090	0.080	0.002	0.042
	SD	1.866	0.606	1.391	0.056	0.027	0.004	0.022
	N	5	5	5	5	5	5	5
	%Diff G1	11.084	-5.381	18.855	-40.789	21.212	--	-19.231

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	6.938	12.60	37.38	53.92	18.14	33.64	11.48
	SD	0.245	0.58	1.41	1.19	0.61	0.63	0.41
	N	5	5	5	5	5	5	5
4F	Mean	6.846	12.46	36.76	53.68	18.20	33.88	12.66b
	SD	0.206	0.47	1.30	1.36	0.33	0.54	0.47
	N	5	5	5	5	5	5	5
	%Diff G1	-1.326	-1.11	-1.66	-0.45	0.33	0.71	10.28

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (T-test)

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1044.0	163.78
	SD	139.5	16.45
	N	5	5
4F	Mean	1105.2	169.54
	SD	80.9	21.05
	N	5	5
	%Diff G1	5.9	3.52

Table 7

Summary of Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	17.61	15.50	302.6
	SD	0.86	0.75	26.0
	N	10	10	10
2M	Mean	17.55	16.21	514.2c
	SD	0.54	0.77	36.4
	N	10	10	10
	%Diff G1	-0.34	4.58	69.9
3M	Mean	17.51	17.62c	576.2c
	SD	0.74	0.69	53.6
	N	10	10	10
	%Diff G1	-0.57	13.68	90.4
4M	Mean	17.09	18.79c	645.7c
	SD	1.15	1.07	56.6
	N	10	10	10
	%Diff G1	-2.95	21.23	113.4

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 7

Summary of Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.13	14.97	252.0
	SD	0.76	1.58	33.1
	N	10	10	10
2F	Mean	17.44	17.99c	416.3c
	SD	0.78	1.24	50.2
	N	10	10	10
	%Diff G1	1.81	20.17	65.2
3F	Mean	16.70	17.80b	473.7c
	SD	0.95	2.09	59.3
	N	10	10	10
	%Diff G1	-2.51	18.90	88.0
4F	Mean	16.72	18.35c	526.3c
	SD	0.63	1.41	73.5
	N	10	10	10
	%Diff G1	-2.39	22.58	108.8

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 7

Summary of Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	18.10	16.08	288.5
	SD	0.77	0.22	22.5
	N	4	4	4
4M	Mean	18.38	15.96	274.4
	SD	0.81	0.69	11.5
	N	5	5	5
	%Diff G1	1.55	-0.72	-4.9

Table 7

Summary of Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.74	15.64	195.4
	SD	0.64	0.96	19.9
	N	5	5	5
4F	Mean	17.98	15.00	218.8
	SD	1.00	1.08	38.5
	N	5	5	5
	%Diff G1	1.35	-4.09	12.0

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1M	Mean	99.8	40.0	113.1	2.0	560.1	0.069	13.2
	SD	21.7	5.3	21.4	0.0	424.7	0.021	2.6
	N	10	10	10	10	10	10	10
2M	Mean	98.7	40.8	114.7	2.0	500.5	0.073	15.0
	SD	15.0	6.2	14.2	0.0	181.9	0.023	2.5
	N	10	10	10	10	10	10	10
	%Diff G1	-1.1	2.0	1.4	0.0	-10.6	5.797	13.6
3M	Mean	97.2	44.3	119.9	2.0	447.2	0.082	16.2a
	SD	34.3	12.6	30.2	0.0	256.7	0.023	1.9
	N	10	10	10	10	10	10	10
	%Diff G1	-2.6	10.8	6.0	0.0	-20.2	18.841	22.7
4M	Mean	102.7	38.7	121.2	2.0	495.6	0.082	13.8
	SD	18.5	3.7	16.6	0.0	265.4	0.021	1.7
	N	10	10	10	10	10	10	10
	%Diff G1	2.9	-3.3	7.2	0.0	-11.5	18.841	4.5

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	Mean	0.34	188.2	68.1	88.8	5.77	3.64	2.13
	SD	0.05	29.0	16.2	38.8	0.21	0.13	0.19
	N	10	10	10	10	10	10	10
2M	Mean	0.37	194.6	74.9	70.6	5.88	3.38c	2.50c
	SD	0.05	44.0	17.1	38.1	0.21	0.18	0.12
	N	10	10	10	10	10	10	10
	%Diff G1	8.82	3.4	10.0	-20.5	1.91	-7.14	17.37
3M	Mean	0.39	197.6	75.5	63.1	5.85	3.29c	2.56c
	SD	0.06	30.7	8.8	15.8	0.26	0.09	0.22
	N	10	10	10	10	10	10	10
	%Diff G1	14.71	5.0	10.9	-28.9	1.39	-9.62	20.19
4M	Mean	0.39	178.8	71.8	68.7	5.94	3.27c	2.67c
	SD	0.03	31.4	15.1	24.2	0.26	0.15	0.20
	N	10	10	10	10	10	10	10
	%Diff G1	14.71	-5.0	5.4	-22.6	2.95	-10.16	25.35

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.72	10.23	8.02	140.2	5.19	100.7
	SD	0.18	0.30	0.81	1.3	0.46	1.2
	N	10	10	10	10	10	10
2M	Mean	1.37c	10.20	7.80	139.8	5.49	100.1
	SD	0.11	0.29	0.45	1.2	0.36	1.7
	N	10	10	10	10	10	10
	%Diff G1	-20.35	-0.29	-2.74	-0.3	5.78	-0.6
3M	Mean	1.29c	10.42	7.96	139.4	5.67a	100.1
	SD	0.11	0.24	0.68	1.2	0.39	1.6
	N	10	10	10	10	10	10
	%Diff G1	-25.00	1.86	-0.75	-0.6	9.25	-0.6
4M	Mean	1.22c	10.42	8.36	140.3	5.76b	100.4
	SD	0.11	0.40	0.71	1.3	0.21	1.4
	N	10	10	10	10	10	10
	%Diff G1	-29.07	1.86	4.24	0.1	10.98	-0.3

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1F	Mean	89.7	36.7	62.8	2.0	365.5	0.064	14.2
	SD	23.0	7.6	16.7	0.0	208.8	0.019	2.0
	N	10	10	10	10	10	10	10
2F	Mean	100.1	38.6	68.1	2.0	427.6	0.077	15.5
	SD	25.8	8.6	11.6	0.0	243.6	0.018	3.0
	N	10	10	10	10	10	10	10
	%Diff G1	11.6	5.2	8.4	0.0	17.0	20.313	9.2
3F	Mean	105.0	40.1	64.6	2.0	477.4	0.085	15.7
	SD	40.5	16.0	18.8	0.0	317.6	0.025	1.8
	N	10	10	10	10	10	10	10
	%Diff G1	17.1	9.3	2.9	0.0	30.6	32.813	10.6
4F	Mean	106.6	38.3	74.4	2.0	500.5	0.087	17.5a
	SD	25.0	10.8	12.1	0.0	282.0	0.025	2.7
	N	10	10	10	10	10	10	10
	%Diff G1	18.8	4.4	18.5	0.0	36.9	35.938	23.2

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	Mean	0.42	209.9	82.2	79.8	6.51	4.54	1.97
	SD	0.04	37.4	13.1	62.9	0.41	0.27	0.18
	N	10	10	10	10	10	10	10
2F	Mean	0.40	192.0	88.1	47.3	6.32	4.02c	2.30c
	SD	0.05	24.9	17.3	7.7	0.39	0.35	0.15
	N	10	10	10	10	10	10	10
	%Diff G1	-4.76	-8.5	7.2	-40.7	-2.92	-11.45	16.75
3F	Mean	0.42	181.3	85.5	57.7	6.40	4.07b	2.33c
	SD	0.06	23.2	13.9	14.9	0.16	0.21	0.12
	N	10	10	10	10	10	10	10
	%Diff G1	0.00	-13.6	4.0	-27.7	-1.69	-10.35	18.27
4F	Mean	0.45	182.3	76.5	56.4	6.35	3.93c	2.42c
	SD	0.05	20.2	15.2	17.2	0.22	0.24	0.15
	N	10	10	10	10	10	10	10
	%Diff G1	7.14	-13.1	-6.9	-29.3	-2.46	-13.44	22.84

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.32	10.82	6.59	139.6	4.76	101.2
	SD	0.17	0.24	0.82	1.4	0.21	1.6
	N	10	10	10	10	10	10
2F	Mean	1.75c	10.65	6.90	140.2	4.99	101.8
	SD	0.18	0.39	0.71	1.1	0.34	1.5
	N	10	10	10	10	10	10
	%Diff G1	-24.57	-1.57	4.70	0.4	4.83	0.6
3F	Mean	1.76c	10.78	7.05	140.5	4.96	101.5
	SD	0.16	0.30	0.64	1.3	0.32	2.7
	N	10	10	10	10	10	10
	%Diff G1	-24.14	-0.37	6.98	0.6	4.20	0.3
4F	Mean	1.64c	10.62	7.12	139.8	5.09	101.1
	SD	0.16	0.28	0.71	0.8	0.18	2.0
	N	10	10	10	10	10	10
	%Diff G1	-29.31	-1.85	8.04	0.1	6.93	-0.1

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1M	Mean	97.8	40.5	120.0	2.0	661.5	0.073	17.0
	SD	11.5	11.5	11.0	0.0	195.7	0.021	3.2
	N	4	4	4	4	4	4	4
4M	Mean	77.2	40.8	104.6	2.0	323.4a	0.064	15.0
	SD	14.7	4.3	18.0	0.0	119.2	0.009	2.9
	N	5	5	5	5	5	5	5
	%Diff G1	-21.0	0.7	-12.8	0.0	-51.1	-11.724	-11.8

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (T-test)

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	Mean	0.33	188.8	81.0	107.8	5.93	3.65	2.28
	SD	0.05	23.2	16.1	34.2	0.15	0.10	0.10
	N	4	4	4	4	4	4	4
4M	Mean	0.34	260.2	65.8	98.2	5.62a	3.60	2.02b
	SD	0.05	62.8	7.9	33.1	0.13	0.10	0.08
	N	5	5	5	5	5	5	5
	%Diff G1	4.62	37.9	-18.8	-8.9	-5.15	-1.37	-11.21

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (T-test)

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.60	10.45	7.05	140.3	5.20	99.8
	SD	0.08	0.26	0.41	1.3	0.16	2.2
	N	4	4	4	4	4	4
4M	Mean	1.80a	10.50	7.60	137.4a	5.24	98.8
	SD	0.10	0.56	0.42	1.5	0.29	2.3
	N	5	5	5	5	5	5
	%Diff G1	12.50	0.48	7.80	-2.0	0.77	-1.0

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (T-test)

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1F	Mean	104.0	44.0	58.8	2.0	644.2	0.068	19.6
	SD	14.5	7.5	10.9	0.0	186.1	0.016	3.4
	N	5	5	5	5	5	5	5
4F	Mean	78.4b	36.4	74.2	2.0	213.0b	0.052	19.0
	SD	5.0	4.4	21.1	0.0	64.2	0.013	2.7
	N	5	5	5	5	5	5	5
	%Diff G1	-24.6	-17.3	26.2	0.0	-66.9	-23.529	-3.1

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (T-test)

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	Mean	0.44	195.2	82.4	135.2	6.52	4.68	1.84
	SD	0.05	27.5	21.8	45.7	0.15	0.11	0.13
	N	5	5	5	5	5	5	5
4F	Mean	0.42	182.2	65.6	59.4a	6.12	4.30a	1.82
	SD	0.04	38.5	8.7	3.0	0.41	0.30	0.15
	N	5	5	5	5	5	5	5
	%Diff G1	-4.55	-6.7	-20.4	-56.1	-6.13	-8.12	-1.09

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Wilcoxon)

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.54	10.90	5.82	138.8	4.64	100.4
	SD	0.21	0.29	0.83	1.3	0.23	1.5
	N	5	5	5	5	5	5
4F	Mean	2.36	10.56	6.56	138.0	4.58	100.2
	SD	0.15	0.42	1.10	1.0	0.31	1.6
	N	5	5	5	5	5	5
	%Diff G1	-7.09	-3.12	12.71	-0.6	-1.29	-0.2

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	94.060	23.506
	SD	29.429	12.169
	N	10	10
2	Mean	257.432 C	115.194
	SD	43.395	68.816
	N	10	10
	% Diff (G1)	174	390
3	Mean	390.988 C	293.504 F
	SD	56.379	237.643
	N	10	10
	% Diff (G1)	316	1149
4	Mean	551.569 C	382.531 F
	SD	151.980	211.063
	N	10	10
	% Diff (G1)	486	1527

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	72.220	42.357
	SD	24.521	20.773
	N	10	10
2	Mean	235.634 C	55.994
	SD	52.630	15.029
	N	10	10
	% Diff (G1)	226	32
3	Mean	339.454 C	123.631 E
	SD	50.928	113.492
	N	10	10
	% Diff (G1)	370	192
4	Mean	505.421 C	186.357 E
	SD	137.000	249.663
	N	10	10
	% Diff (G1)	600	340

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 57
Males

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	88.440	20.773
	SD	8.092	4.717
	N	4	4
4	Mean	87.166	37.996 a
	SD	12.415	12.667
	N	5	5
	% Diff (G1)	-1	83

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 57
Females

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	68.932	35.152
	SD	4.834	13.723
	N	5	5
4	Mean	75.622	54.802
	SD	10.977	38.529
	N	5	5
	% Diff (G1)	10	56

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IL-1β (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	81.768	21.700	59.374	124.482	51.913
	SD	151.835	24.183	88.301	265.269	92.125
	N	4	5	5	5	4
4	Mean	58.354	44.110	58.726	39.250	15.068
	SD	52.019	36.995	80.621	48.320	20.612
	N	5	5	5	5	5
	% Diff (G1)	-29	103	-1	-68	-71

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IL-6 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	176.000	176.000	176.000	176.000	176.000
	SD	0.000	0.000	0.000	0.000	0.000
	N	4	5	5	5	4
4	Mean	176.000	176.000	176.000	176.000	176.000
	SD	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	0	0

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

TNF-α (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	1.470	2.534	1.470	2.450	3.098
	SD	0.000	2.379	0.000	2.191	3.255
	N	4	5	5	5	4
4	Mean	1.470	3.648	1.470	3.746	1.470
	SD	0.000	3.010	0.000	3.170	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	44	0	53	-53

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IP-10 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	Day 15 - 6 h Post Dose	Day 29 - 6 h Post Dose	Day 43 - 6 h Post Dose	Day 57
1	Mean	119.183	81.600	108.196	114.608	111.973
	SD	55.636	18.170	42.739	70.494	79.736
	N	4	5	5	5	4
4	Mean	1215.712 b	882.356 d	993.816 b	667.464 c	70.600
	SD	481.589	311.841	523.188	176.698	19.924
	N	5	5	5	5	5
	% Diff (G1)	920	981	819	482	-37

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

MIP-1-α (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	5.850	5.850	5.850	5.850	5.850
	SD	0.000	0.000	0.000	0.000	0.000
	N	4	5	5	5	4
4	Mean	5.850	9.986	5.850	5.850	5.850
	SD	0.000	9.248	0.000	0.000	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	71	0	0	0

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

MCP-1 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	385.368	407.454	387.200	352.102	209.503
	SD	84.450	64.383	87.399	29.006	161.154
	N	4	5	5	5	4
4	Mean	531.784	649.598	563.292	484.526	166.148
	SD	127.495	337.498	151.572	283.312	130.973
	N	5	5	5	5	5
	% Diff (G1)	38	59	45	38	-21

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IL-1β (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	81.260	81.770	24.666	51.744	14.792
	SD	67.051	93.939	29.166	52.373	12.313
	N	4	5	5	5	5
4	Mean	25.924	25.974	15.594	23.160	9.680
	SD	44.887	44.999	21.788	38.706	8.564
	N	5	5	5	5	5
	% Diff (G1)	-68	-68	-37	-55	-35

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IL-6 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	176.000	176.000	176.000	176.000	176.000
	SD	0.000	0.000	0.000	0.000	0.000
	N	4	5	5	5	5
4	Mean	176.000	176.000	176.000	176.000	176.000
	SD	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	0	0

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

TNF-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	1.470	2.790	1.470	1.470	3.682
	SD	0.000	2.952	0.000	0.000	3.031
	N	4	5	5	5	5
4	Mean	1.470	4.792	3.996	2.544	1.470
	SD	0.000	4.765	3.459	2.402	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	72	172	73	-60

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IP-10 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	101.380	78.686	75.830	105.752	52.852
	SD	45.097	30.456	30.099	35.779	18.137
	N	4	5	5	5	5
4	Mean	1484.720 d	1254.524 c	1374.798 d	947.402 d	47.134
	SD	308.884	241.636	414.653	333.750	13.418
	N	5	5	5	5	5
	% Diff (G1)	1365	1494	1713	796	-11

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

MIP-1-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	5.850	5.850	5.850	5.850	5.850
	SD	0.000	0.000	0.000	0.000	0.000
	N	4	5	5	5	5
4	Mean	20.474	25.098	24.632	10.984	5.850
	SD	13.535	18.462	17.515	11.480	0.000
	N	5	5	5	5	5
	% Diff (G1)	250	329	321	88	0

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

MCP-1 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	Day 15 - 6 h Post Dose	Day 29 - 6 h Post Dose	Day 43 - 6 h Post Dose	Day 57
1	Mean	128.680	158.156	174.606	169.772	113.614
	SD	116.360	120.028	143.082	136.358	96.406
	N	4	5	5	5	5
4	Mean	525.168 a	1032.490 a	1032.040 b	397.324	132.256
	SD	272.356	668.447	408.110	461.595	138.091
	N	5	5	5	5	5
	% Diff (G1)	308	553	491	134	16

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

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FINAL STUDY PLAN

Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
200 Technology Square, Third Floor
Cambridge, MA 02139, USA

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
1580 Ida-Metivier
Sherbrooke, QC J1E 0B5
Canada

08 March 2017

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA 1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	mRNA

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date:	08 Mar 2017
Experimental Completion Date:	To be included by amendment (Last date data are collected from the study)
Animal Arrival:	08 Mar 2017
Initiation of Dosing:	20 Mar 2017 (Male) 21 Mar 2017 (Female)
Completion of In-life:	03 May 2017 (Main) 16 May 2017 (Recovery) (Last date of necropsy)
Unaudited Draft Report:	To be included by amendment
Audited Draft Report:	To be included by amendment
Final Report:	To be included by amendment (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

The design of this study was based on the study objective(s), the overall product development strategy for the Test Item, and the following study design guidelines:

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 November 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

4. REGULATORY COMPLIANCE

The study will be performed in accordance with the OECD Principles of Good Laboratory Practice and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in the USA will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration. United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines, α2-macroglobulin, α1-acid glycoprotein, anti-therapeutic antibody and PBMCs will be conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- Pathology peer review

5. QUALITY ASSURANCE

5.1. Test Facility

The Test Facility Quality Assurance Program (QAP) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAP will review the study plan, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to

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assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

The Test Facility QAP contact for this study is indicated below:

(b) (6),
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

The following study phases performed by Test Facility-designated subcontractors will be audited by the Test Facility QAP:

- Ophthalmology

6. SPONSOR

Sponsor Representative

(b) (6)
Address as cited for Sponsor
Tel: (b) (6)
E-mail: (b) (6)

7. RESPONSIBLE PERSONNEL

Study Director

(b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
Address as cited for Test Facility
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)

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Individual Scientists (IS) at the Test Facility

Ophthalmology

(b) (6)

22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Analytical Chemistry
(Concentration and
Particle size Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Immunology
(Purity Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

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Immunology (Cytokine, Alpha-2 Macroglobulin and Alpha-1 Glycoprotein Analysis)	(b) (6) Charles River Laboratories Montreal ULC Sherbrooke Site (CR SHB) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Pathology	To be included by amendment

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

PIs at Sponsor or Sponsor-designated Test Site(s)

Anti-Therapeutic Antibody Analysis	(b) (6) Integrated BioTherapeutics, Inc. 4 Research Court Suite 300 Rockville, MD 20850, USA Tel: (b) (6) Fax: (b) (6) E-mail: (b) (6)
PBMC Analysis	(b) (6) Southern Research - Cell Biology and Immunology Birmingham Alabama 35205 Tel: (b) (6) E-mail: (b) (6)

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Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1647
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP16015
Concentration:	2 mg/mL
Retest Date:	An end-of-use analysis of the bulk Test Item will be performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanopacticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C

8.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Supplier:	Will be included in the Final Report
Batch (Lot) Number:	Will be included in the Final Report
Expiration Date:	Will be included in the Final Report
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

8.3. Test Item Characterization

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity and composition for the Test Item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor will also provide information concerning the regulatory standard that was followed for these evaluations.

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The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the Test Item, and this information is available to the appropriate regulatory agencies should it be requested.

8.4. Analysis of Test Item

A sample (2 vials) of the Test Item will be taken on the completion of the dosing period. Analysis of bulk Test Item for concentration, particle size and purity will be performed.

The first vial will be transferred (on ice pack) to the analytical laboratory at the Test Facility for concentration and particle size analysis.

The second vial will be transferred (on ice pack) to the molecular biology laboratory at the Test Facility for purity analysis.

Purity and Particle size analysis will be performed by IEX- HPLC, Differential Light Scattering (DLS) and capillary electrophoresis (CE) using validated analytical procedures.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 mL or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned on dry ice to the Sponsor (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
800 Technology Sq, 8th Floor
Cambridge MA 02476
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

The safety precautions for the Test Item and dose formulations will be documented in a Test Material Safety Data Sheet (TMSDS) based on the information provided by the Sponsor either by an MSDS or similar document.

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

The Reference Item, Phosphate-buffered Saline (PBS) pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15, 29 and 43) for administration to Group 1 control animals and will be used as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots will be stored in a refrigerator set to maintain 4°C until use. They will be removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

Any residual volumes will be discarded unless otherwise requested by the Study Director.

10.2. Preparation of Test Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

Test Item formulations will be diluted with PBS pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15, 29 and 43) and will be stored in a refrigerator set to maintain 4°C. The dose formulations will be allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots can be transferred directly to room temperature. When possible, stock vials will be used only once.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and discarded prior to report finalization.

10.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 43	N/A	All groups	Dosing container

N/A = Not applicable.

[a] The homogeneity results obtained from the top, middle and bottom preparations will be averaged and utilized as the concentration results.

[b] Samples will be collected on the first preparation of the study and on the last preparation of the study.

Samples to be analyzed will be submitted as soon as possible following collection.

All samples to be analyzed will be transferred (on ice pack) to the analytical laboratory.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

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10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. To be included by amendment).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis:	Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Backup Samples:	Triplicate top, middle, and bottom samples (Triplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Sampling Containers:	Appropriate sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study however, end of use stability analysis of the stock solution will be performed at the end of the dosing period.

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks

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Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

The actual age, weight, and number of animals received will be listed in the Final Report.

11.1. Justification of Test System and Number of Animals

The Sprague Dawley rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the Test Item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

11.2. Animal Identification

Each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 14 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

11.4. Selection, Assignment, Replacement, and Disposition of Animals

Animals will be assigned to groups by a stratified randomization scheme designed to achieve similar group mean body weights. Males and females will be randomized separately. Animals in poor health or at extremes of body weight range will not be assigned to groups.

Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-Test Item-related health issues, or similar circumstances.

The alternate animals may be used as replacements on the study within 3 days.

The disposition of all animals will be documented in the study records.

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12. HUSBANDRY

12.1. Housing

Animals will be group housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions will be maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room(s) in which the animals will be kept will be documented in the study records.

Animals will be separated during designated procedures/activities. Each cage will be clearly labeled with a color-coded cage card indicating study, group, animal number(s), and sex. Cages will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the Test Item treated animals.

12.2. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	19°C to 25°C
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

12.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 will be provided ad libitum throughout the study, except during designated procedures. The same diet in meal form may be provided to individual animals as warranted by clinical signs (e.g., broken/damaged incisors or other health changes).

The feed is analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis are provided by the supplier and are on file at the Test Facility.

It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

12.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation will be freely available to each animal via an automatic watering system (except during designated procedures). Water bottles can be provided, if required.

Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility.

It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

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12.5. Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and will be provided with items such as a hiding tube and a chewing object, except during study procedures/activities.

12.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments, if any, will be documented in the study records.

In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director or Scientific designate. All such actions will be properly documented in the study records and, when appropriate, by study plan amendment. Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or clinical veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10	200	0.05	10	10	-	-
3	mRNA-1647	30	200	0.15	10	10	-	-
4	mRNA-1647	100	200	0.5	10	10	5	5

- : Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, 29 and 43, the injection site will be alternated on each dosing occasion (site 1= left; site 2= right). The volume for each dose will be administered using a syringe/needle within the demarcated area. The first day of dosing will be designated as Day 1 (exception: alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

The injection area will be marked as frequently as required to allow appropriate visualization of administration sites. Hair may be clipped or shaved if required to improve visualization of the injection sites. The injection site will be documented in the raw data for each dose administered.

13.2. Justification of Route and Dose Levels

The intramuscular route of exposure was selected because this is the intended route of human exposure.

The dose levels for this toxicology study were chosen to approximate a substantial multiple of the anticipated clinical starting dose and top clinical dose. The highest dose to be tested is expected to represent the intended maximum human clinical dose and volume and will be administered by the clinical route (intramuscular). At this dose level, minimal systemic toxicity is expected, but it is possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below including Laboratory Investigations listed in section below will be performed for all main study and recovery animals, unless otherwise indicated in the respective section. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

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14.1. Mortality/Moribundity Checks

Frequency: Twice daily, once in the morning and once in the afternoon, throughout the study.

Procedure: Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 43 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 44.

Procedure: All animals will have the dose injection site examined for signs of erythema/edema. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

Erythema (Redness)	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Mild erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness to slight eschar formation, injury in depth)	4
Notable dermal lesion (maximized)	M
Edema (Swelling)	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema	2
Moderate edema	3
Severe edema	4

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Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.
Procedure:	Animals will be individually weighed. A fasted weight will be recorded on the day of necropsy. Terminal body weights will not be collected from animals found dead or euthanized moribund.

14.5. Food Consumption

Frequency:	Weekly, starting Day -7, throughout the dosing and recovery periods.
Procedure:	Food consumption will be quantitatively measured except for on the day of scheduled euthanasia.

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 6 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 43 at predose, and 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0°C to 38.0°C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes measurements may be taken at the discretion of the Study Director.
Procedure:	Rectal body temperature will be recorded on un-sedated animals.

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15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

Blood will be collected from the abdominal aorta following isoflurane anesthesia. After collection, samples will be transferred to the appropriate laboratory for processing.

Animals will be fasted overnight before blood sampling (for clinical chemistry). Samples will be collected according to the following table.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	α1-acid glycoprotein/ α2-macroglubulin
1 to 4[a]	Day 44	X	X	X	X
1 and 4	Day 57	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X	X

X = Sample to be collected

[a] Samples will only be collected from those animals scheduled for euthanasia on Day 44.

Any residual/retained clinical pathology samples will be discarded before issue of the Final Report.

15.1.2. Hematology

Target Volume: 0.5 mL

Anticoagulant: EDTA

Hematology Parameters

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red Blood Cell Distribution Width Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute) Platelet count	White blood cell count Neutrophil count (absolute) Lymphocyte count (absolute) Monocyte count (absolute) Eosinophil count (absolute) Basophil count (absolute) Large unstained cells (absolute)

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. Blood smears may be read to investigate results. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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15.1.3. Coagulation

Target Volume: 1.2 mL (in a 1.3 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tube

Processing: To serum

Clinical Chemistry Parameters

Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine Kinase Total bilirubin[a] Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample Quality

[a] When total bilirubin is > 0.5 mg/dL, indirect and direct bilirubin will also be measured.

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.1.6. α1-acid Glycoprotein and α2-macroglobulin Analysis

Blood will be collected via the abdominal aorta following isoflurane anesthesia before scheduled and unscheduled euthanasia for all animals.

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: Blood samples to clot at ambient room temperature. Centrifugation for (b) (4) set at (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) Samples will be processed to

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serum by the Immunology Department. Serum will be aliquoted into 1 x 75 µL aliquot for α2-macroglobulin and 2 x 75 µL aliquot and a leftover (if available) for α1-acid glycoprotein.

Storage conditions: Stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin will be conducted using a qualified ELISA method by the Immunology Department. The procedure to be followed along with the assay acceptance criteria will be detailed in the appropriate analytical procedure.

Samples will be analyzed in duplicate. Any residual/retained samples will be discarded prior to report finalization.

15.2. Laboratory Investigations (Cytokine Analysis)

Blood will be collected from the jugular vein of all recovery animals and preterminally euthanized animals (recovery animals only). After collection, blood samples for serum will be transferred at ambient room temperature and blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hrs**	**No. of Males/ Females**	IFN-α	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	5/5	X	X
15	6	5/5	X	X
29	6	5/5	X	X
43	6	5/5	X	X
57	NA	5/5	X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR-SHB	CR-SHB

X = Sample to be collected; N/A = not applicable

The number of aliquots and volumes are targets that may be adjusted based on sample volume availability.

The samples will be analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 will be conducted using a multiplex Luminex method. An ELISA

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method will be used for the analysis of IFN-α. The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.

Following Study Director approval, any residual/retained samples will be discarded prior to report finalization.

An Immunology Report for cytokine analysis will be included as an appendix to the Final Report.

15.3. Anti Therapeutic Antibody (ATA) Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	Before initiation of dosing, Day 43 (main animals only) and Day 57 (recovery animals).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and kept under ambient conditions until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
21 Firstfield Road
Suite 100
Gaithersburg, MD 20878, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at -80°C.

The samples will be analyzed for rat anti-CMV antibodies using a qualified ELISA method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

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An Anti-therapeutic Antibody Report will be included as an appendix to the Final Report.

15.4. PBMC Analysis

Blood will be collected by abdominal aorta following isoflurane anesthesia from the appropriate animals.

Time Points:	On Day 44 (main animals only).
Target Volume:	0.5 mL
Anticoagulant:	Sodium Heparin
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

Samples will be shipped at controlled temperature set to maintain 21°C via overnight courier to the Immunology laboratory, for whole blood stimulation and cytokine analysis, to:

Shipping Contact
(b) (6)
Cell Biology and Immunology
Southern Research
2000 Ninth Ave S
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at room temperature.

The PBMC samples will be analyzed using a qualified method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Immunology Report for PBMC analysis will be included as an appendix to the Final Report.

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	44	X	X	X	Full Tissue[a]	Full Tissue[a]
2	10	10					Full Tissue[a]	Gross Lesions Target Tissues
3	10	10					Full Tissue[a]	Gross Lesions Target Tissues
4	10	10					Full Tissue[a]	Full Tissue[a]
1	5	5	57	X	X	X	Full Tissue[a]	Full Tissue[a]
4	5	5					Full Tissue[a]	Full Tissue[a]
Unscheduled Deaths				X	X	-	Full Tissue[a]	Full Tissue[a]
Replaced animals (prestudy)[b]				X	Standard Diagnostic List	-	-	-
Replaced animals (after dosing start)				X	X	-	-	-

X = Procedure to be conducted; - = Not applicable.
[a] See Tissue Collection and Preservation table for listing of tissues.
[b] Animals found dead or euthanized before the initiation of dosing.

16.1. Unscheduled Deaths

If a main study or recovery animal dies on study, a complete necropsy examination will be conducted and specified tissues will be saved. If necessary, the animal will be refrigerated to minimize autolysis.

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of laboratory evaluation will be obtained if possible as specified in Section 15. These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

Animals found dead or euthanized before the initiation of dosing will be subject to complete necropsy examination and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to complete necropsy examination and tissues will be retained (as per Tissue Collection and Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

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16.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia will have a terminal body weight recorded, samples for laboratory evaluation will be collected (as appropriate), and will be euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. When possible, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day. Animals will be fasted overnight before their scheduled necropsy.

16.3. Necropsy

Main and recovery animals will be subjected to a complete necropsy examination, which will include evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Necropsy procedures will be performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, will be available.

At the discretion of the necropsy supervising pathologist, images may be generated for illustration of or consultation on gross observations. Generation of such images will be documented and communicated to the Study Director. Images and associated documentation will be retained and archived.

16.4. Organ Weights

The organs identified for weighing in the Tissues Collection and Preservation table will be weighed at necropsy for all scheduled euthanasia animals. Organ weights will not be recorded for animals found dead or euthanized in poor condition or in extremis. Paired organs will be weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight will be calculated.

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

Tissues in the Tissue Collection and Preservation table from animals identified in the Terminal Procedures table will be embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. Target tissues identified by the study pathologist during microscopic evaluation will be communicated to the study Director; tissues will be evaluated and reported. Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by study plan amendment following discussion with the Study Director and in consultation the Sponsor.

At the discretion of the study pathologist and after acknowledgement by the Study Director, images may be captured for consultation purposes.

17.3. Pathology Peer Review

A on-site pathology peer review will be conducted by:

(b) (6)
Moderna Therapeutics
200 Technology Square, 3rd Floor
Cambridge, MA 02116
Tel: (b) (6)
E-mail: (b) (6)

The peer review statement or equivalent documentation will be included as an appendix to the Final Report.

18. CONSTRUCTED VARIABLES

Body Weight Gains	Calculated between at least each interval as well as between the beginning and end of each phase
Organ Weight relative to Body Weight	Calculated against the Terminal body weight for scheduled intervals
Organ Weight relative to Brain Weight	Calculated against the brain weight for scheduled intervals

19. STATISTICAL ANALYSIS

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two sided tests and will be reported at the 0.1%, 1%, and 5% levels.

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Numerical data collected on scheduled occasions for the listed variables will be analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) will be reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics will be performed according to the matrix below when possible, but will exclude semi-quantitative data, and any group with less than 3 observations.

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
α2-macroglobulin	X
α1-acid glycoprotein	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

Levene's test will be used to assess the homogeneity of group variances.

Datasets with at least 3 groups will be compared using an overall one-way ANOVA *F*-test if Levene's test is not significant or the Kruskal-Wallis test if it is. If the overall *F*-test or Kruskal-Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunnett's or Dunn's test, respectively.

Datasets with 2 groups (the designated control group and 1 other group) will be compared using a *t*-test if Levene's test is not significant or Wilcoxon Rank-Sum test if it is.

20. COMPUTERIZED SYSTEMS

The following critical computerized systems may be used in the study. The actual critical computerized systems used will be specified in the Final Report.

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Data for parameters not required by study plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by study plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
BioPlex Manager	Cytokine data collection
Softmax Pro GxP	Elisa data collection
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS

21. AMENDMENTS AND DEVIATIONS

Changes to the approved study plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary study plan changes in advance with the Sponsor.

All study plan and SOP deviations will be documented in the study records. Deviations from the study plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred

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to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Study Plan, study plan amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Test and Reference Item receipt, identification, preparation, and analysis
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final) along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation. An original copy of the report with the Test Facility's handwritten signatures will be retained.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Test Facility unless other arrangements are made by the Sponsor.

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

The study plan and any amendment(s) or procedures involving the care and use of animals in this study will be reviewed and approved by CR SHB Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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TEST FACILITY APPROVAL

The signature below acknowledges Test Facility Management's responsibility to the study as defined by the relevant GLP regulations.

(b) (6)
(b) (6)

Date: 08 Mar 2017

The signature below indicates that the Study Director approves the study plan.

(b) (6)
(b) (6) (b) (6)

Date: 08 Mar 2017

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SPONSOR APPROVAL

The Study Plan was approved by the Sponsor by email on 08 March 2017. The signature below confirms the approval of the Study Plan by the Sponsor Representative

(b) (6) _____ Date: 09Mar17

(b) (6)

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ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	-	Level 4 processed to slide for evaluation of olfactory bulb. Nasal structures will not be examined.
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for last injection
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

X = Procedure to be conducted; - = Not applicable.

[a] At the discretion of the Study Pathologist, findings for extraneous tissues (nonspecified tissues in the Study Plan that may be present on a slide as a result of collection of Study Plan tissues) will be recorded when observed.

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STUDY PLAN AMENDMENT 01

Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
200 Technology Square, Third Floor
Cambridge, MA 02139, USA

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
1580 Ida-Metivier
Sherbrooke, QC J1E 0B5
Canada

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 8 Mar 2017

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
Amendment 1	**Date: 15-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To update the schedule due to delay in the test item documentation.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
10.3.1. Analytical Method	To include validation number.
10.3.1.2. Stability Analysis	To clarify that stability analysis will be performed on the bulk Test Item.
15.2. Laboratory Investigations (Cytokine Analysis)	To correct a typographical error and to include clarification for sample processing.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To clarify the processing of samples and update the shipping contact information.
15.4. PBMC Analysis	To change the blood collection procedure.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA 1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	mRNA

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date:	08 Mar 2017
Experimental Completion Date:	**29 Aug 2017** ~~**To be included by amendment**~~ (Last date data are collected from the study)
Animal Arrival:	08 Mar 2017
Initiation of Dosing:	~~**20**~~ **22** Mar 2017 (Male) ~~**21**~~ **23** Mar 2017 (Female)
Completion of In-life:	~~**03**~~ **05** May 2017 (Main) ~~**16**~~ **18** May 2017 (Recovery) (Last date of necropsy)
Unaudited Draft Report:	**17 Jul 2017** ~~**To be included by amendment**~~
Audited Draft Report:	**22 Aug 2017** ~~**To be included by amendment**~~
Final Report:	**29 Aug 2017** ~~**To be included by amendment**~~ (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

The design of this study was based on the study objective(s), the overall product development strategy for the Test Item, and the following study design guidelines:

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 November 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

4. REGULATORY COMPLIANCE

The study will be performed in accordance with the OECD Principles of Good Laboratory Practice and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in the USA will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration. United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines, α2-macroglobulin, α1-acid glycoprotein, anti-therapeutic antibody and PBMCs will be conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- Pathology peer review

5. QUALITY ASSURANCE

5.1. Test Facility

The Test Facility Quality Assurance Program (QAP) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAP will review the study plan, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to

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assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

The Test Facility QAP contact for this study is indicated below:

(b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

The following study phases performed by Test Facility-designated subcontractors will be audited by the Test Facility QAP:

- Ophthalmology

6. SPONSOR

Sponsor Representative

(b) (6)
Address as cited for Sponsor
Tel: (b) (6)
E-mail: (b) (6)

7. RESPONSIBLE PERSONNEL

Study Director

(b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
Address as cited for Test Facility
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)

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Individual Scientists (IS) at the Test Facility

Ophthalmology

(b) (6)

22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Analytical Chemistry
(Concentration and
Particle size Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Immunology
(Purity Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

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Immunology (Cytokine, Alpha-2 Macroglobulin and Alpha-1 Glycoprotein Analysis)	(b) (6) Charles River Laboratories Montreal ULC Sherbrooke Site (CR SHB) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Pathology	To be included by amendment

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

PIs at Sponsor or Sponsor-designated Test Site(s)

Anti-Therapeutic Antibody Analysis	(b) (6) Integrated BioTherapeutics, Inc. 4 Research Court Suite 300 Rockville, MD 20850, USA Tel: (b) (6) Fax: (b) (6) E-mail: (b) (6)
PBMC Analysis	(b) (6) Southern Research - Cell Biology and Immunology Birmingham Alabama 35205 Tel: (b) (6) E-mail: (b) (6)

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Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1647
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP16015
Concentration:	2 mg/mL
Retest Date:	An end-of-use analysis of the bulk Test Item will be performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanopacticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C

8.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Supplier:	Will be included in the Final Report
Batch (Lot) Number:	Will be included in the Final Report
Expiration Date:	Will be included in the Final Report
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

8.3. Test Item Characterization

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity and composition for the Test Item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor will also provide information concerning the regulatory standard that was followed for these evaluations.

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The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the Test Item, and this information is available to the appropriate regulatory agencies should it be requested.

8.4. Analysis of Test Item

A sample (2 vials) of the Test Item will be taken on the completion of the dosing period. Analysis of bulk Test Item for concentration, particle size and purity will be performed.

The first vial will be transferred (on ice pack) to the analytical laboratory at the Test Facility for concentration and particle size analysis.

The second vial will be transferred (on ice pack) to the molecular biology laboratory at the Test Facility for purity analysis.

Purity and Particle size analysis will be performed by IEX- HPLC, Differential Light Scattering (DLS) and capillary electrophoresis (CE) using validated analytical procedures.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 mL or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned on dry ice to the Sponsor (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
800 Technology Sq, 8th Floor
Cambridge MA 02476
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

The safety precautions for the Test Item and dose formulations will be documented in a Test Material Safety Data Sheet (TMSDS) based on the information provided by the Sponsor either by an MSDS or similar document.

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

The Reference Item, Phosphate-buffered Saline (PBS) pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15, 29 and 43) for administration to Group 1 control animals and will be used as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots will be stored in a refrigerator set to maintain 4°C until use. They will be removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

Any residual volumes will be discarded unless otherwise requested by the Study Director.

10.2. Preparation of Test Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

Test Item formulations will be diluted with PBS pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15, 29 and 43) and will be stored in a refrigerator set to maintain 4°C. The dose formulations will be allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots can be transferred directly to room temperature. When possible, stock vials will be used only once.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and discarded prior to report finalization.

10.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 43	N/A	All groups	Dosing container

N/A = Not applicable.

[a] The homogeneity results obtained from the top, middle and bottom preparations will be averaged and utilized as the concentration results.

[b] Samples will be collected on the first preparation of the study and on the last preparation of the study.

Samples to be analyzed will be submitted as soon as possible following collection.

All samples to be analyzed will be transferred (on ice pack) to the analytical laboratory.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

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10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No.**1802050** ~~**To be included by amendment**~~).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis:	Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Backup Samples:	Triplicate top, middle, and bottom samples (Triplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Sampling Containers:	Appropriate sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study however, end of use stability analysis of the ~~**stock solution**~~ **bulk test item** will be performed at the end of the dosing period.

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks

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Target Weight at Arrival: 126 to 150 g (males)
101 to 125 g (females)

The actual age, weight, and number of animals received will be listed in the Final Report.

11.1. Justification of Test System and Number of Animals

The Sprague Dawley rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the Test Item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

11.2. Animal Identification

Each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 14 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

11.4. Selection, Assignment, Replacement, and Disposition of Animals

Animals will be assigned to groups by a stratified randomization scheme designed to achieve similar group mean body weights. Males and females will be randomized separately. Animals in poor health or at extremes of body weight range will not be assigned to groups.

Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-Test Item-related health issues, or similar circumstances.

The alternate animals may be used as replacements on the study within 3 days.

The disposition of all animals will be documented in the study records.

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12. HUSBANDRY

12.1. Housing

Animals will be group housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions will be maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room(s) in which the animals will be kept will be documented in the study records.

Animals will be separated during designated procedures/activities. Each cage will be clearly labeled with a color-coded cage card indicating study, group, animal number(s), and sex. Cages will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the Test Item treated animals.

12.2. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	19°C to 25°C
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

12.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 will be provided ad libitum throughout the study, except during designated procedures. The same diet in meal form may be provided to individual animals as warranted by clinical signs (e.g., broken/damaged incisors or other health changes).

The feed is analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis are provided by the supplier and are on file at the Test Facility.

It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

12.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation will be freely available to each animal via an automatic watering system (except during designated procedures). Water bottles can be provided, if required.

Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility.

It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

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12.5. Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and will be provided with items such as a hiding tube and a chewing object, except during study procedures/activities.

12.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments, if any, will be documented in the study records.

In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director or Scientific designate. All such actions will be properly documented in the study records and, when appropriate, by study plan amendment. Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or clinical veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10	200	0.05	10	10	-	-
3	mRNA-1647	30	200	0.15	10	10	-	-
4	mRNA-1647	100	200	0.5	10	10	5	5

- : Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, 29 and 43, the injection site will be alternated on each dosing occasion (site 1= left; site 2= right). The volume for each dose will be administered using a syringe/needle within the demarcated area. The first day of dosing will be designated as Day 1 (exception: alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

The injection area will be marked as frequently as required to allow appropriate visualization of administration sites. Hair may be clipped or shaved if required to improve visualization of the injection sites. The injection site will be documented in the raw data for each dose administered.

13.2. Justification of Route and Dose Levels

The intramuscular route of exposure was selected because this is the intended route of human exposure.

The dose levels for this toxicology study were chosen to approximate a substantial multiple of the anticipated clinical starting dose and top clinical dose. The highest dose to be tested is expected to represent the intended maximum human clinical dose and volume and will be administered by the clinical route (intramuscular). At this dose level, minimal systemic toxicity is expected, but it is possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below including Laboratory Investigations listed in section below will be performed for all main study and recovery animals, unless otherwise indicated in the respective section. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

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14.1. Mortality/Moribundity Checks

Frequency: Twice daily, once in the morning and once in the afternoon, throughout the study.

Procedure: Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 43 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 44.

Procedure: All animals will have the dose injection site examined for signs of erythema/edema. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

Erythema (Redness)	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Mild erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness to slight eschar formation, injury in depth)	4
Notable dermal lesion (maximized)	M
Edema (Swelling)	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema	2
Moderate edema	3
Severe edema	4

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Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.
Procedure:	Animals will be individually weighed. A fasted weight will be recorded on the day of necropsy. Terminal body weights will not be collected from animals found dead or euthanized moribund.

14.5. Food Consumption

Frequency:	Weekly, starting Day -7, throughout the dosing and recovery periods.
Procedure:	Food consumption will be quantitatively measured except for on the day of scheduled euthanasia.

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 6 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 43 at predose, and 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0°C to 38.0°C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes measurements may be taken at the discretion of the Study Director.
Procedure:	Rectal body temperature will be recorded on un-sedated animals.

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15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

Blood will be collected from the abdominal aorta following isoflurane anesthesia. After collection, samples will be transferred to the appropriate laboratory for processing.

Animals will be fasted overnight before blood sampling (for clinical chemistry). Samples will be collected according to the following table.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	α1-acid glycoprotein/ α2-macroglubulin
1 to 4[a]	Day 44	X	X	X	X
1 and 4	Day 57	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X	X

X = Sample to be collected

[a] Samples will only be collected from those animals scheduled for euthanasia on Day 44.

Any residual/retained clinical pathology samples will be discarded before issue of the Final Report.

15.1.2. Hematology

Target Volume: 0.5 mL

Anticoagulant: EDTA

Hematology Parameters

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red Blood Cell Distribution Width Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute) Platelet count	White blood cell count Neutrophil count (absolute) Lymphocyte count (absolute) Monocyte count (absolute) Eosinophil count (absolute) Basophil count (absolute) Large unstained cells (absolute)

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. Blood smears may be read to investigate results. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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15.1.3. Coagulation

Target Volume: 1.2 mL (in a 1.3 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tube

Processing: To serum

Clinical Chemistry Parameters

Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine Kinase Total bilirubin[a] Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample Quality

[a] When total bilirubin is > 0.5 mg/dL, indirect and direct bilirubin will also be measured.

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.1.6. α1-acid Glycoprotein and α2-macroglobulin Analysis

Blood will be collected via the abdominal aorta following isoflurane anesthesia before scheduled and unscheduled euthanasia for all animals.

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: Blood samples to clot at ambient room temperature. Centrifugation for (b) (4) set at (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) Samples will be processed to

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serum by the Immunology Department. Serum will be aliquoted into 1 x 75 µL aliquot for α2-macroglobulin and 2 x 75 µL aliquot and a leftover (if available) for α1-acid glycoprotein.

Storage conditions: Stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin will be conducted using a qualified ELISA method by the Immunology Department. The procedure to be followed along with the assay acceptance criteria will be detailed in the appropriate analytical procedure.

Samples will be analyzed in duplicate. Any residual/retained samples will be discarded prior to report finalization.

15.2. Laboratory Investigations (Cytokine Analysis)

Blood will be collected from the jugular vein of all recovery animals and preterminally euthanized animals (recovery animals only). After collection, blood samples for serum will be **allowed to clot** ~~**transferred**~~ at ambient room temperature and blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hrs**	**No. of Males/ Females**	IFN-α	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	5/5	X	X
15	6	5/5	X	X
29	6	5/5	X	X
43	6	5/5	X	X
57	N/A	5/5	X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR-SHB	CR-SHB

X = Sample to be collected; N/A = not applicable

The number of aliquots and volumes are targets that may be adjusted based on sample volume availability.

The samples will be analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 will be conducted using a multiplex Luminex method. An ELISA

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method will be used for the analysis of IFN-α. The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.

Following Study Director approval, any residual/retained samples will be discarded prior to report finalization.

An Immunology Report for cytokine analysis will be included as an appendix to the Final Report.

15.3. Anti Therapeutic Antibody (ATA) Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	Before initiation of dosing, Day 43 (main animals only) and Day 57 (recovery animals).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and **allow to clot at ambient room temperature** ~~**kept under ambient conditions**~~ until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
21 Firstfield Road
Suite 100
Gaithersburg, MD 20878, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at -80°C.

The samples will be analyzed for rat anti-CMV antibodies using a qualified ELISA method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the

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Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Anti-therapeutic Antibody Report will be included as an appendix to the Final Report.

15.4. PBMC Analysis

Blood will be collected by **jugular venipuncture** ~~**abdominal aorta following isoflurane anesthesia**~~ from the appropriate animals.

Time Points:	On Day 44 (main animals only).
Target Volume:	0.5 mL
Anticoagulant:	Sodium Heparin
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

Samples will be shipped at controlled temperature set to maintain 21°C via overnight courier to the Immunology laboratory, for whole blood stimulation and cytokine analysis, to:

Shipping Contact
(b) (6)
Cell Biology and Immunology
Southern Research
2000 Ninth Ave S
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at room temperature.

The PBMC samples will be analyzed using a qualified method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Immunology Report for PBMC analysis will be included as an appendix to the Final Report.

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	44	X	X	X	Full Tissue[a]	Full Tissue[a]
2	10	10					Full Tissue[a]	Gross Lesions Target Tissues
3	10	10					Full Tissue[a]	Gross Lesions Target Tissues
4	10	10					Full Tissue[a]	Full Tissue[a]
1	5	5	57	X	X	X	Full Tissue[a]	Full Tissue[a]
4	5	5					Full Tissue[a]	Full Tissue[a]
Unscheduled Deaths				X	X	-	Full Tissue[a]	Full Tissue[a]
Replaced animals (prestudy)[b]				X	Standard Diagnostic List	-	-	-
Replaced animals (after dosing start)				X	X	-	-	-

X = Procedure to be conducted; - = Not applicable.
[a] See Tissue Collection and Preservation table for listing of tissues.
[b] Animals found dead or euthanized before the initiation of dosing.

16.1. Unscheduled Deaths

If a main study or recovery animal dies on study, a complete necropsy examination will be conducted and specified tissues will be saved. If necessary, the animal will be refrigerated to minimize autolysis.

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of laboratory evaluation will be obtained if possible as specified in Section 15. These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

Animals found dead or euthanized before the initiation of dosing will be subject to complete necropsy examination and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to complete necropsy examination and tissues will be retained (as per Tissue Collection and Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

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16.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia will have a terminal body weight recorded, samples for laboratory evaluation will be collected (as appropriate), and will be euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. When possible, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day. Animals will be fasted overnight before their scheduled necropsy.

16.3. Necropsy

Main and recovery animals will be subjected to a complete necropsy examination, which will include evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Necropsy procedures will be performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, will be available.

At the discretion of the necropsy supervising pathologist, images may be generated for illustration of or consultation on gross observations. Generation of such images will be documented and communicated to the Study Director. Images and associated documentation will be retained and archived.

16.4. Organ Weights

The organs identified for weighing in the Tissues Collection and Preservation table will be weighed at necropsy for all scheduled euthanasia animals. Organ weights will not be recorded for animals found dead or euthanized in poor condition or in extremis. Paired organs will be weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight will be calculated.

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

Tissues in the Tissue Collection and Preservation table from animals identified in the Terminal Procedures table will be embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. Target tissues identified by the study pathologist during microscopic evaluation will be communicated to the study Director; tissues will be evaluated and reported. Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by study plan amendment following discussion with the Study Director and in consultation the Sponsor.

At the discretion of the study pathologist and after acknowledgement by the Study Director, images may be captured for consultation purposes.

17.3. Pathology Peer Review

A on-site pathology peer review will be conducted by:

(b) (6)
Moderna Therapeutics
200 Technology Square, 3rd Floor
Cambridge, MA 02116
Tel: (b) (6)
E-mail: (b) (6)

The peer review statement or equivalent documentation will be included as an appendix to the Final Report.

18. CONSTRUCTED VARIABLES

Body Weight Gains	Calculated between at least each interval as well as between the beginning and end of each phase
Organ Weight relative to Body Weight	Calculated against the Terminal body weight for scheduled intervals
Organ Weight relative to Brain Weight	Calculated against the brain weight for scheduled intervals

19. STATISTICAL ANALYSIS

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two sided tests and will be reported at the 0.1%, 1%, and 5% levels.

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Numerical data collected on scheduled occasions for the listed variables will be analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) will be reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics will be performed according to the matrix below when possible, but will exclude semi-quantitative data, and any group with less than 3 observations.

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
α2-macroglobulin	X
α1-acid glycoprotein	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

Levene's test will be used to assess the homogeneity of group variances.

Datasets with at least 3 groups will be compared using an overall one-way ANOVA *F*-test if Levene's test is not significant or the Kruskal-Wallis test if it is. If the overall *F*-test or Kruskal-Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunnett's or Dunn's test, respectively.

Datasets with 2 groups (the designated control group and 1 other group) will be compared using a *t*-test if Levene's test is not significant or Wilcoxon Rank-Sum test if it is.

20. COMPUTERIZED SYSTEMS

The following critical computerized systems may be used in the study. The actual critical computerized systems used will be specified in the Final Report.

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Data for parameters not required by study plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by study plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
BioPlex Manager	Cytokine data collection
Softmax Pro GxP	Elisa data collection
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS

21. AMENDMENTS AND DEVIATIONS

Changes to the approved study plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary study plan changes in advance with the Sponsor.

All study plan and SOP deviations will be documented in the study records. Deviations from the study plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred

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to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Study Plan, study plan amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Test and Reference Item receipt, identification, preparation, and analysis
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final) along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation. An original copy of the report with the Test Facility's handwritten signatures will be retained.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Test Facility unless other arrangements are made by the Sponsor.

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

The study plan and any amendment(s) or procedures involving the care and use of animals in this study will be reviewed and approved by CR SHB Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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AMENDMENT APPROVAL

(b) (6) _____ Date: 15 Mar 2017

(b) (6) (b) (6)

As authorized by the Sponsor on 15 Mar 2017

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ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	-	Level 4 processed to slide for evaluation of olfactory bulb. Nasal structures will not be examined.
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for last injection
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

X = Procedure to be conducted; - = Not applicable.

[a] At the discretion of the Study Pathologist, findings for extraneous tissues (nonspecified tissues in the Study Plan that may be present on a slide as a result of collection of Study Plan tissues) will be recorded when observed.

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STUDY PLAN AMENDMENT 02

Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
200 Technology Square, Third Floor
Cambridge, MA 02139, USA

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
1580 Ida-Metivier
Sherbrooke, QC J1E 0B5
Canada

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 8 Mar 2017

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
Amendment 1	**Date: 15-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To update the schedule due to delay in the test item documentation.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
10.3.1. Analytical Method	To include validation number.
10.3.1.2. Stability Analysis	To clarify that stability analysis will be performed on the bulk Test Item.
15.2. Laboratory Investigations (Cytokine Analysis)	To correct a typographical error and to include clarification for sample processing.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To clarify the processing of samples and update the shipping contact information.
15.4. PBMC Analysis	To change the blood collection procedure.
Amendment 2	**Date: 22-Mar-2017**
8.1. Test Item	To update information based on Summary of Analysis and to correct a typographical error.
10.2. Preparation of Test Item	To include missing information from study plan about the residual test item following formulation.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To update the shipping contact information.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA 1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	mRNA

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date:	08 Mar 2017
Experimental Completion Date:	29 Aug 2017 (Last date data are collected from the study)
Animal Arrival:	08 Mar 2017
Initiation of Dosing:	22 Mar 2017 (Male) 23 Mar 2017 (Female)
Completion of In-life:	05 May 2017 (Main) 18 May 2017 (Recovery) (Last date of necropsy)
Unaudited Draft Report:	17 Jul 2017
Audited Draft Report:	22 Aug 2017
Final Report:	29 Aug 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

The design of this study was based on the study objective(s), the overall product development strategy for the Test Item, and the following study design guidelines:

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 November 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

4. REGULATORY COMPLIANCE

The study will be performed in accordance with the OECD Principles of Good Laboratory Practice and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in the USA will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration. United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines, α2-macroglobulin, α1-acid glycoprotein, anti-therapeutic antibody and PBMCs will be conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- Pathology peer review

5. QUALITY ASSURANCE

5.1. Test Facility

The Test Facility Quality Assurance Program (QAP) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAP will review the study plan, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to

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assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

The Test Facility QAP contact for this study is indicated below:

(b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

The following study phases performed by Test Facility-designated subcontractors will be audited by the Test Facility QAP:

- Ophthalmology

6. SPONSOR

Sponsor Representative

(b) (6)
Address as cited for Sponsor
Tel: (b) (6)
E-mail: (b) (6)

7. RESPONSIBLE PERSONNEL

Study Director

(b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
Address as cited for Test Facility
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)

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Individual Scientists (IS) at the Test Facility

Ophthalmology

(b) (6)

22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Analytical Chemistry
(Concentration and
Particle size Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Immunology
(Purity Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

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Immunology (Cytokine, Alpha-2 Macroglobulin and Alpha-1 Glycoprotein Analysis)	(b) (6) Charles River Laboratories Montreal ULC Sherbrooke Site (CR SHB) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Pathology	To be included by amendment

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

PIs at Sponsor or Sponsor-designated Test Site(s)

Anti-Therapeutic Antibody Analysis	(b) (6) Integrated BioTherapeutics, Inc. 4 Research Court Suite 300 Rockville, MD 20850, USA Tel: (b) (6) Fax: (b) (6) E-mail: (b) (6)
PBMC Analysis	(b) (6) Southern Research - Cell Biology and Immunology Birmingham Alabama 35205 Tel: (b) (6) E-mail: (b) (6)

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Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1647
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	~~**MTDP16015**~~ **MTDP17015**
Concentration:	2**.7** mg/mL
Retest Date:	An end-of-use analysis of the bulk Test Item will be performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanopa~~e~~**r**ticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C

8.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Supplier:	Will be included in the Final Report
Batch (Lot) Number:	Will be included in the Final Report
Expiration Date:	Will be included in the Final Report
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

8.3. Test Item Characterization

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity and composition for the Test Item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor will also provide information concerning the regulatory standard that was followed for these evaluations.

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The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the Test Item, and this information is available to the appropriate regulatory agencies should it be requested.

8.4. Analysis of Test Item

A sample (2 vials) of the Test Item will be taken on the completion of the dosing period. Analysis of bulk Test Item for concentration, particle size and purity will be performed.

The first vial will be transferred (on ice pack) to the analytical laboratory at the Test Facility for concentration and particle size analysis.

The second vial will be transferred (on ice pack) to the molecular biology laboratory at the Test Facility for purity analysis.

Purity and Particle size analysis will be performed by IEX- HPLC, Differential Light Scattering (DLS) and capillary electrophoresis (CE) using validated analytical procedures.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 mL or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned on dry ice to the Sponsor (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
800 Technology Sq, 8th Floor
Cambridge MA 02476
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

The safety precautions for the Test Item and dose formulations will be documented in a Test Material Safety Data Sheet (TMSDS) based on the information provided by the Sponsor either by an MSDS or similar document.

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

The Reference Item, Phosphate-buffered Saline (PBS) pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15, 29 and 43) for administration to Group 1 control animals and will be used as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots will be stored in a refrigerator set to maintain 4°C until use. They will be removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

Any residual volumes will be discarded unless otherwise requested by the Study Director.

10.2. Preparation of Test Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

Test Item formulations will be diluted with PBS pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15, 29 and 43) and will be stored in a refrigerator set to maintain 4°C. The dose formulations will be allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots can be transferred directly to room temperature. When possible, stock vials will be used only once.

Any residual volumes of formulated Test Item **and stock test item** will be stored in a refrigerator set at 4°C and discarded prior to report finalization.

10.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 43	N/A	All groups	Dosing container

N/A = Not applicable.

[a] The homogeneity results obtained from the top, middle and bottom preparations will be averaged and utilized as the concentration results.

[b] Samples will be collected on the first preparation of the study and on the last preparation of the study.

Samples to be analyzed will be submitted as soon as possible following collection.

All samples to be analyzed will be transferred (on ice pack) to the analytical laboratory.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

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10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No.1802050).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis:	Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Backup Samples:	Triplicate top, middle, and bottom samples (Triplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Sampling Containers:	Appropriate sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study however, end of use stability analysis of the bulk test item will be performed at the end of the dosing period.

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks

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Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

The actual age, weight, and number of animals received will be listed in the Final Report.

11.1. Justification of Test System and Number of Animals

The Sprague Dawley rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the Test Item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

11.2. Animal Identification

Each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 14 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

11.4. Selection, Assignment, Replacement, and Disposition of Animals

Animals will be assigned to groups by a stratified randomization scheme designed to achieve similar group mean body weights. Males and females will be randomized separately. Animals in poor health or at extremes of body weight range will not be assigned to groups.

Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-Test Item-related health issues, or similar circumstances.

The alternate animals may be used as replacements on the study within 3 days.

The disposition of all animals will be documented in the study records.

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12. HUSBANDRY

12.1. Housing

Animals will be group housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions will be maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room(s) in which the animals will be kept will be documented in the study records.

Animals will be separated during designated procedures/activities. Each cage will be clearly labeled with a color-coded cage card indicating study, group, animal number(s), and sex. Cages will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the Test Item treated animals.

12.2. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	19°C to 25°C
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

12.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 will be provided ad libitum throughout the study, except during designated procedures. The same diet in meal form may be provided to individual animals as warranted by clinical signs (e.g., broken/damaged incisors or other health changes).

The feed is analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis are provided by the supplier and are on file at the Test Facility.

It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

12.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation will be freely available to each animal via an automatic watering system (except during designated procedures). Water bottles can be provided, if required.

Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility.

It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

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12.5. Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and will be provided with items such as a hiding tube and a chewing object, except during study procedures/activities.

12.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments, if any, will be documented in the study records.

In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director or Scientific designate. All such actions will be properly documented in the study records and, when appropriate, by study plan amendment. Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or clinical veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10	200	0.05	10	10	-	-
3	mRNA-1647	30	200	0.15	10	10	-	-
4	mRNA-1647	100	200	0.5	10	10	5	5

- : Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, 29 and 43, the injection site will be alternated on each dosing occasion (site 1= left; site 2= right). The volume for each dose will be administered using a syringe/needle within the demarcated area. The first day of dosing will be designated as Day 1 (exception: alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

The injection area will be marked as frequently as required to allow appropriate visualization of administration sites. Hair may be clipped or shaved if required to improve visualization of the injection sites. The injection site will be documented in the raw data for each dose administered.

13.2. Justification of Route and Dose Levels

The intramuscular route of exposure was selected because this is the intended route of human exposure.

The dose levels for this toxicology study were chosen to approximate a substantial multiple of the anticipated clinical starting dose and top clinical dose. The highest dose to be tested is expected to represent the intended maximum human clinical dose and volume and will be administered by the clinical route (intramuscular). At this dose level, minimal systemic toxicity is expected, but it is possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below including Laboratory Investigations listed in section below will be performed for all main study and recovery animals, unless otherwise indicated in the respective section. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

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14.1. Mortality/Moribundity Checks

Frequency: Twice daily, once in the morning and once in the afternoon, throughout the study.

Procedure: Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 43 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 44.

Procedure: All animals will have the dose injection site examined for signs of erythema/edema. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

Erythema (Redness)	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Mild erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness to slight eschar formation, injury in depth)	4
Notable dermal lesion (maximized)	M
Edema (Swelling)	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema	2
Moderate edema	3
Severe edema	4

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Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.
Procedure:	Animals will be individually weighed. A fasted weight will be recorded on the day of necropsy. Terminal body weights will not be collected from animals found dead or euthanized moribund.

14.5. Food Consumption

Frequency:	Weekly, starting Day -7, throughout the dosing and recovery periods.
Procedure:	Food consumption will be quantitatively measured except for on the day of scheduled euthanasia.

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 6 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 43 at predose, and 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0°C to 38.0°C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes measurements may be taken at the discretion of the Study Director.
Procedure:	Rectal body temperature will be recorded on un-sedated animals.

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15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

Blood will be collected from the abdominal aorta following isoflurane anesthesia. After collection, samples will be transferred to the appropriate laboratory for processing.

Animals will be fasted overnight before blood sampling (for clinical chemistry). Samples will be collected according to the following table.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	α1-acid glycoprotein/ α2-macroglubulin
1 to 4[a]	Day 44	X	X	X	X
1 and 4	Day 57	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X	X

X = Sample to be collected

[a] Samples will only be collected from those animals scheduled for euthanasia on Day 44.

Any residual/retained clinical pathology samples will be discarded before issue of the Final Report.

15.1.2. Hematology

Target Volume: 0.5 mL

Anticoagulant: EDTA

Hematology Parameters

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red Blood Cell Distribution Width Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute) Platelet count	White blood cell count Neutrophil count (absolute) Lymphocyte count (absolute) Monocyte count (absolute) Eosinophil count (absolute) Basophil count (absolute) Large unstained cells (absolute)

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. Blood smears may be read to investigate results. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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15.1.3. Coagulation

Target Volume: 1.2 mL (in a 1.3 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tube

Processing: To serum

Clinical Chemistry Parameters

Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine Kinase Total bilirubin[a] Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample Quality

[a] When total bilirubin is > 0.5 mg/dL, indirect and direct bilirubin will also be measured.

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.1.6. α1-acid Glycoprotein and α2-macroglobulin Analysis

Blood will be collected via the abdominal aorta following isoflurane anesthesia before scheduled and unscheduled euthanasia for all animals.

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: Blood samples to clot at ambient room temperature. Centrifugation for (b) (4) set at (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)). Samples will be processed to

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serum by the Immunology Department. Serum will be aliquoted into 1 x 75 µL aliquot for α2-macroglobulin and 2 x 75 µL aliquot and a leftover (if available) for α1-acid glycoprotein.

Storage conditions: Stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin will be conducted using a qualified ELISA method by the Immunology Department. The procedure to be followed along with the assay acceptance criteria will be detailed in the appropriate analytical procedure.

Samples will be analyzed in duplicate. Any residual/retained samples will be discarded prior to report finalization.

15.2. Laboratory Investigations (Cytokine Analysis)

Blood will be collected from the jugular vein of all recovery animals and preterminally euthanized animals (recovery animals only). After collection, blood samples for serum will be allowed to clot at ambient room temperature and blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hrs**	**No. of Males/ Females**	IFN-α	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	5/5	X	X
15	6	5/5	X	X
29	6	5/5	X	X
43	6	5/5	X	X
57	N/A	5/5	X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR-SHB	CR-SHB

X = Sample to be collected; N/A = not applicable

The number of aliquots and volumes are targets that may be adjusted based on sample volume availability.

The samples will be analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 will be conducted using a multiplex Luminex method. An ELISA

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method will be used for the analysis of IFN-α. The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.

Following Study Director approval, any residual/retained samples will be discarded prior to report finalization.

An Immunology Report for cytokine analysis will be included as an appendix to the Final Report.

15.3. Anti Therapeutic Antibody (ATA) Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	Before initiation of dosing, Day 43 (main animals only) and Day 57 (recovery animals).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and allow to clot at ambient room temperature until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
~~**21 Firstfield Road**~~
~~**Suite 100**~~
~~**Gaithersburg, MD 20878, USA**~~
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at -80°C.

The samples will be analyzed for rat anti-CMV antibodies using a qualified ELISA method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively,

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residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Anti-therapeutic Antibody Report will be included as an appendix to the Final Report.

15.4. PBMC Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	On Day 44 (main animals only).
Target Volume:	0.5 mL
Anticoagulant:	Sodium Heparin
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

Samples will be shipped at controlled temperature set to maintain 21°C via overnight courier to the Immunology laboratory, for whole blood stimulation and cytokine analysis, to:

Shipping Contact
(b) (6)
Cell Biology and Immunology
Southern Research
2000 Ninth Ave S
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at room temperature.

The PBMC samples will be analyzed using a qualified method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Immunology Report for PBMC analysis will be included as an appendix to the Final Report.

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	44	X	X	X	Full Tissue[a]	Full Tissue[a]
2	10	10					Full Tissue[a]	Gross Lesions Target Tissues
3	10	10					Full Tissue[a]	Gross Lesions Target Tissues
4	10	10					Full Tissue[a]	Full Tissue[a]
1	5	5	57	X	X	X	Full Tissue[a]	Full Tissue[a]
4	5	5					Full Tissue[a]	Full Tissue[a]
Unscheduled Deaths				X	X	-	Full Tissue[a]	Full Tissue[a]
Replaced animals (prestudy)[b]				X	Standard Diagnostic List	-	-	-
Replaced animals (after dosing start)				X	X	-	-	-

X = Procedure to be conducted; - = Not applicable.
[a] See Tissue Collection and Preservation table for listing of tissues.
[b] Animals found dead or euthanized before the initiation of dosing.

16.1. Unscheduled Deaths

If a main study or recovery animal dies on study, a complete necropsy examination will be conducted and specified tissues will be saved. If necessary, the animal will be refrigerated to minimize autolysis.

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of laboratory evaluation will be obtained if possible as specified in Section 15. These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

Animals found dead or euthanized before the initiation of dosing will be subject to complete necropsy examination and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to complete necropsy examination and tissues will be retained (as per Tissue Collection and Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

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16.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia will have a terminal body weight recorded, samples for laboratory evaluation will be collected (as appropriate), and will be euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. When possible, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day. Animals will be fasted overnight before their scheduled necropsy.

16.3. Necropsy

Main and recovery animals will be subjected to a complete necropsy examination, which will include evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Necropsy procedures will be performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, will be available.

At the discretion of the necropsy supervising pathologist, images may be generated for illustration of or consultation on gross observations. Generation of such images will be documented and communicated to the Study Director. Images and associated documentation will be retained and archived.

16.4. Organ Weights

The organs identified for weighing in the Tissues Collection and Preservation table will be weighed at necropsy for all scheduled euthanasia animals. Organ weights will not be recorded for animals found dead or euthanized in poor condition or in extremis. Paired organs will be weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight will be calculated.

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

Tissues in the Tissue Collection and Preservation table from animals identified in the Terminal Procedures table will be embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. Target tissues identified by the study pathologist during microscopic evaluation will be communicated to the study Director; tissues will be evaluated and reported. Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by study plan amendment following discussion with the Study Director and in consultation the Sponsor.

At the discretion of the study pathologist and after acknowledgement by the Study Director, images may be captured for consultation purposes.

17.3. Pathology Peer Review

A on-site pathology peer review will be conducted by:

(b) (6)
Moderna Therapeutics
200 Technology Square, 3rd Floor
Cambridge, MA 02116
Tel: (b) (6)
E-mail: (b) (6)

The peer review statement or equivalent documentation will be included as an appendix to the Final Report.

18. CONSTRUCTED VARIABLES

Body Weight Gains	Calculated between at least each interval as well as between the beginning and end of each phase
Organ Weight relative to Body Weight	Calculated against the Terminal body weight for scheduled intervals
Organ Weight relative to Brain Weight	Calculated against the brain weight for scheduled intervals

19. STATISTICAL ANALYSIS

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two sided tests and will be reported at the 0.1%, 1%, and 5% levels.

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Numerical data collected on scheduled occasions for the listed variables will be analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) will be reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics will be performed according to the matrix below when possible, but will exclude semi-quantitative data, and any group with less than 3 observations.

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
α2-macroglobulin	X
α1-acid glycoprotein	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

Levene's test will be used to assess the homogeneity of group variances.

Datasets with at least 3 groups will be compared using an overall one-way ANOVA *F*-test if Levene's test is not significant or the Kruskal-Wallis test if it is. If the overall *F*-test or Kruskal-Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunnett's or Dunn's test, respectively.

Datasets with 2 groups (the designated control group and 1 other group) will be compared using a *t*-test if Levene's test is not significant or Wilcoxon Rank-Sum test if it is.

20. COMPUTERIZED SYSTEMS

The following critical computerized systems may be used in the study. The actual critical computerized systems used will be specified in the Final Report.

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Data for parameters not required by study plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by study plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
BioPlex Manager	Cytokine data collection
Softmax Pro GxP	Elisa data collection
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS

21. AMENDMENTS AND DEVIATIONS

Changes to the approved study plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary study plan changes in advance with the Sponsor.

All study plan and SOP deviations will be documented in the study records. Deviations from the study plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred

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to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Study Plan, study plan amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Test and Reference Item receipt, identification, preparation, and analysis
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final) along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation. An original copy of the report with the Test Facility's handwritten signatures will be retained.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Test Facility unless other arrangements are made by the Sponsor.

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

The study plan and any amendment(s) or procedures involving the care and use of animals in this study will be reviewed and approved by CR SHB Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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AMENDMENT APPROVAL

(b) (6)
(b) (6) (b) (6)

Date: 22 Mar 2017

As authorized by the Sponsor on 22 Mar 2017

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ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	-	Level 4 processed to slide for evaluation of olfactory bulb. Nasal structures will not be examined.
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for last injection
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

X = Procedure to be conducted; - = Not applicable.

[a] At the discretion of the Study Pathologist, findings for extraneous tissues (nonspecified tissues in the Study Plan that may be present on a slide as a result of collection of Study Plan tissues) will be recorded when observed.

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STUDY PLAN AMENDMENT 03

Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
200 Technology Square, Third Floor
Cambridge, MA 02139, USA

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
1580 Ida-Metivier
Sherbrooke, QC J1E 0B5
Canada

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 8 Mar 2017

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
Amendment 1	**Date: 15-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To update the schedule due to delay in the test item documentation.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
10.3.1. Analytical Method	To include validation number.
10.3.1.2. Stability Analysis	To clarify that stability analysis will be performed on the bulk Test Item.
15.2. Laboratory Investigations (Cytokine Analysis)	To correct a typographical error and to include clarification for sample processing.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To clarify the processing of samples and update the shipping contact information.
15.4. PBMC Analysis	To change the blood collection procedure.
Amendment 2	**Date: 22-Mar-2017**
8.1. Test Item	To update information based on Summary of Analysis and to correct a typographical error.
10.2. Preparation of Test Item	To include missing information from study plan about the residual test item following formulation.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To update the shipping contact information.
Amendment 3	**Date: 13-Apr-2017**
7. RESPONSIBLE PERSONNEL	To add the email address of the management contact.
8.4. Analysis of Test Item	To correct the storage conditions for samples transfer.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To add a blood collection occasion on Day 29.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA 1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	mRNA

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date:	08 Mar 2017
Experimental Completion Date:	29 Aug 2017 (Last date data are collected from the study)
Animal Arrival:	08 Mar 2017
Initiation of Dosing:	22 Mar 2017 (Male) 23 Mar 2017 (Female)
Completion of In-life:	05 May 2017 (Main) 18 May 2017 (Recovery) (Last date of necropsy)
Unaudited Draft Report:	17 Jul 2017
Audited Draft Report:	22 Aug 2017
Final Report:	29 Aug 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

The design of this study was based on the study objective(s), the overall product development strategy for the Test Item, and the following study design guidelines:

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 November 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

4. REGULATORY COMPLIANCE

The study will be performed in accordance with the OECD Principles of Good Laboratory Practice and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in the USA will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration. United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines, α2-macroglobulin, α1-acid glycoprotein, anti-therapeutic antibody and PBMCs will be conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- Pathology peer review

5. QUALITY ASSURANCE

5.1. Test Facility

The Test Facility Quality Assurance Program (QAP) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAP will review the study plan, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to

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assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

The Test Facility QAP contact for this study is indicated below:

(b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

The following study phases performed by Test Facility-designated subcontractors will be audited by the Test Facility QAP:

- Ophthalmology

6. SPONSOR

Sponsor Representative

(b) (6)
Address as cited for Sponsor
Tel: (b) (6)
E-mail: (b) (6)

7. RESPONSIBLE PERSONNEL

Study Director

(b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
Address as cited for Test Facility
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)
E-mail: (b) (6)

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Individual Scientists (IS) at the Test Facility

Ophthalmology

(b) (6)

22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Analytical Chemistry
(Concentration and
Particle size Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Immunology
(Purity Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

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Immunology (Cytokine, Alpha-2 Macroglobulin and Alpha-1 Glycoprotein Analysis)	(b) (6) Charles River Laboratories Montreal ULC Sherbrooke Site (CR SHB) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Pathology	To be included by amendment

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

PIs at Sponsor or Sponsor-designated Test Site(s)

Anti-Therapeutic Antibody Analysis	(b) (6) Integrated BioTherapeutics, Inc. 4 Research Court Suite 300 Rockville, MD 20850, USA Tel: (b) (6) Fax: (b) (6) E-mail: (b) (6)
PBMC Analysis	(b) (6) Southern Research - Cell Biology and Immunology Birmingham Alabama 35205 Tel: (b) (6) E-mail: (b) (6)

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Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1647
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17015
Concentration:	2.7 mg/mL
Retest Date:	An end-of-use analysis of the bulk Test Item will be performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanopa~~e~~r**r**ticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C

8.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Supplier:	Will be included in the Final Report
Batch (Lot) Number:	Will be included in the Final Report
Expiration Date:	Will be included in the Final Report
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

8.3. Test Item Characterization

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity and composition for the Test Item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor will also provide information concerning the regulatory standard that was followed for these evaluations.

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The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the Test Item, and this information is available to the appropriate regulatory agencies should it be requested.

8.4. Analysis of Test Item

A sample (2 vials) of the Test Item will be taken on the completion of the dosing period. Analysis of bulk Test Item for concentration, particle size and purity will be performed.

The first vial will be transferred (on **dry** ice ~~**pack**~~) to the analytical laboratory at the Test Facility for concentration and particle size analysis.

The second vial will be transferred (on **dry** ice ~~**pack**~~) to the molecular biology laboratory at the Test Facility for purity analysis.

Purity and Particle size analysis will be performed by IEX- HPLC, Differential Light Scattering (DLS) and capillary electrophoresis (CE) using validated analytical procedures.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 mL or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned on dry ice to the Sponsor (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
800 Technology Sq, 8th Floor
Cambridge MA 02476
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

The safety precautions for the Test Item and dose formulations will be documented in a Test Material Safety Data Sheet (TMSDS) based on the information provided by the Sponsor either by an MSDS or similar document.

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

The Reference Item, Phosphate-buffered Saline (PBS) pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15, 29 and 43) for administration to Group 1 control animals and will be used as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots will be stored in a refrigerator set to maintain 4°C until use. They will be removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

Any residual volumes will be discarded unless otherwise requested by the Study Director.

10.2. Preparation of Test Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

Test Item formulations will be diluted with PBS pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15, 29 and 43) and will be stored in a refrigerator set to maintain 4°C. The dose formulations will be allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots can be transferred directly to room temperature. When possible, stock vials will be used only once.

Any residual volumes of formulated Test Item and stock test item will be stored in a refrigerator set at 4°C and discarded prior to report finalization.

10.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 43	N/A	All groups	Dosing container

N/A = Not applicable.

[a] The homogeneity results obtained from the top, middle and bottom preparations will be averaged and utilized as the concentration results.

[b] Samples will be collected on the first preparation of the study and on the last preparation of the study.

Samples to be analyzed will be submitted as soon as possible following collection.

All samples to be analyzed will be transferred (on ice pack) to the analytical laboratory.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

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10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No.1802050).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis:	Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Backup Samples:	Triplicate top, middle, and bottom samples (Triplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Sampling Containers:	Appropriate sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study however, end of use stability analysis of the bulk test item will be performed at the end of the dosing period.

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks

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Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

The actual age, weight, and number of animals received will be listed in the Final Report.

11.1. Justification of Test System and Number of Animals

The Sprague Dawley rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the Test Item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

11.2. Animal Identification

Each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 14 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

11.4. Selection, Assignment, Replacement, and Disposition of Animals

Animals will be assigned to groups by a stratified randomization scheme designed to achieve similar group mean body weights. Males and females will be randomized separately. Animals in poor health or at extremes of body weight range will not be assigned to groups.

Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-Test Item-related health issues, or similar circumstances.

The alternate animals may be used as replacements on the study within 3 days.

The disposition of all animals will be documented in the study records.

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12. HUSBANDRY

12.1. Housing

Animals will be group housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions will be maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room(s) in which the animals will be kept will be documented in the study records.

Animals will be separated during designated procedures/activities. Each cage will be clearly labeled with a color-coded cage card indicating study, group, animal number(s), and sex. Cages will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the Test Item treated animals.

12.2. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	19°C to 25°C
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

12.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 will be provided ad libitum throughout the study, except during designated procedures. The same diet in meal form may be provided to individual animals as warranted by clinical signs (e.g., broken/damaged incisors or other health changes).

The feed is analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis are provided by the supplier and are on file at the Test Facility.

It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

12.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation will be freely available to each animal via an automatic watering system (except during designated procedures). Water bottles can be provided, if required.

Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility.

It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

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12.5. Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and will be provided with items such as a hiding tube and a chewing object, except during study procedures/activities.

12.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments, if any, will be documented in the study records.

In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director or Scientific designate. All such actions will be properly documented in the study records and, when appropriate, by study plan amendment. Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or clinical veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10	200	0.05	10	10	-	-
3	mRNA-1647	30	200	0.15	10	10	-	-
4	mRNA-1647	100	200	0.5	10	10	5	5

- : Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, 29 and 43, the injection site will be alternated on each dosing occasion (site 1= left; site 2= right). The volume for each dose will be administered using a syringe/needle within the demarcated area. The first day of dosing will be designated as Day 1 (exception: alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

The injection area will be marked as frequently as required to allow appropriate visualization of administration sites. Hair may be clipped or shaved if required to improve visualization of the injection sites. The injection site will be documented in the raw data for each dose administered.

13.2. Justification of Route and Dose Levels

The intramuscular route of exposure was selected because this is the intended route of human exposure.

The dose levels for this toxicology study were chosen to approximate a substantial multiple of the anticipated clinical starting dose and top clinical dose. The highest dose to be tested is expected to represent the intended maximum human clinical dose and volume and will be administered by the clinical route (intramuscular). At this dose level, minimal systemic toxicity is expected, but it is possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below including Laboratory Investigations listed in section below will be performed for all main study and recovery animals, unless otherwise indicated in the respective section. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

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14.1. Mortality/Moribundity Checks

Frequency: Twice daily, once in the morning and once in the afternoon, throughout the study.

Procedure: Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 43 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 44.

Procedure: All animals will have the dose injection site examined for signs of erythema/edema. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

Erythema (Redness)	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Mild erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness to slight eschar formation, injury in depth)	4
Notable dermal lesion (maximized)	M
Edema (Swelling)	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema	2
Moderate edema	3
Severe edema	4

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Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.
Procedure:	Animals will be individually weighed. A fasted weight will be recorded on the day of necropsy. Terminal body weights will not be collected from animals found dead or euthanized moribund.

14.5. Food Consumption

Frequency:	Weekly, starting Day -7, throughout the dosing and recovery periods.
Procedure:	Food consumption will be quantitatively measured except for on the day of scheduled euthanasia.

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 6 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 43 at predose, and 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0°C to 38.0°C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes measurements may be taken at the discretion of the Study Director.
Procedure:	Rectal body temperature will be recorded on un-sedated animals.

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15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

Blood will be collected from the abdominal aorta following isoflurane anesthesia. After collection, samples will be transferred to the appropriate laboratory for processing.

Animals will be fasted overnight before blood sampling (for clinical chemistry). Samples will be collected according to the following table.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	α1-acid glycoprotein/ α2-macroglubulin
1 to 4[a]	Day 44	X	X	X	X
1 and 4	Day 57	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X	X

X = Sample to be collected

[a] Samples will only be collected from those animals scheduled for euthanasia on Day 44.

Any residual/retained clinical pathology samples will be discarded before issue of the Final Report.

15.1.2. Hematology

Target Volume: 0.5 mL

Anticoagulant: EDTA

Hematology Parameters

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red Blood Cell Distribution Width Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute) Platelet count	White blood cell count Neutrophil count (absolute) Lymphocyte count (absolute) Monocyte count (absolute) Eosinophil count (absolute) Basophil count (absolute) Large unstained cells (absolute)

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. Blood smears may be read to investigate results. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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15.1.3. Coagulation

Target Volume: 1.2 mL (in a 1.3 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tube

Processing: To serum

Clinical Chemistry Parameters

Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine Kinase Total bilirubin[a] Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample Quality

[a] When total bilirubin is > 0.5 mg/dL, indirect and direct bilirubin will also be measured.

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.1.6. α1-acid Glycoprotein and α2-macroglobulin Analysis

Blood will be collected via the abdominal aorta following isoflurane anesthesia before scheduled and unscheduled euthanasia for all animals.

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: Blood samples to clot at ambient room temperature. Centrifugation for (b) (4) set at (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)). Samples will be processed to

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serum by the Immunology Department. Serum will be aliquoted into 1 x 75 µL aliquot for α2-macroglobulin and 2 x 75 µL aliquot and a leftover (if available) for α1-acid glycoprotein.

Storage conditions: Stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin will be conducted using a qualified ELISA method by the Immunology Department. The procedure to be followed along with the assay acceptance criteria will be detailed in the appropriate analytical procedure.

Samples will be analyzed in duplicate. Any residual/retained samples will be discarded prior to report finalization.

15.2. Laboratory Investigations (Cytokine Analysis)

Blood will be collected from the jugular vein of all recovery animals and preterminally euthanized animals (recovery animals only). After collection, blood samples for serum will be allowed to clot at ambient room temperature and blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hrs**	**No. of Males/ Females**	IFN-α	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	5/5	X	X
15	6	5/5	X	X
29	6	5/5	X	X
43	6	5/5	X	X
57	N / A	5/5	X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR-SHB	CR-SHB

X = Sample to be collected; N/A = not applicable

The number of aliquots and volumes are targets that may be adjusted based on sample volume availability.

The samples will be analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 will be conducted using a multiplex Luminex method. An ELISA

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method will be used for the analysis of IFN-α. The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.

Following Study Director approval, any residual/retained samples will be discarded prior to report finalization.

An Immunology Report for cytokine analysis will be included as an appendix to the Final Report.

15.3. Anti Therapeutic Antibody (ATA) Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	Before initiation of dosing, **Day 29 (before dosing),** Day 43 (main animals only) and Day 57 (recovery animals).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and allow to clot at ambient room temperature until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)) at (b) (4). The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at -80°C.

The samples will be analyzed for rat anti-CMV antibodies using a qualified ELISA method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

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An Anti-therapeutic Antibody Report will be included as an appendix to the Final Report.

15.4. PBMC Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	On Day 44 (main animals only).
Target Volume:	0.5 mL
Anticoagulant:	Sodium Heparin
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

Samples will be shipped at controlled temperature set to maintain 21°C via overnight courier to the Immunology laboratory, for whole blood stimulation and cytokine analysis, to:

Shipping Contact
(b) (6)
Cell Biology and Immunology
Southern Research
2000 Ninth Ave S
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at room temperature.

The PBMC samples will be analyzed using a qualified method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Immunology Report for PBMC analysis will be included as an appendix to the Final Report.

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	44	X	X	X	Full Tissue[a]	Full Tissue[a]
2	10	10					Full Tissue[a]	Gross Lesions Target Tissues
3	10	10					Full Tissue[a]	Gross Lesions Target Tissues
4	10	10					Full Tissue[a]	Full Tissue[a]
1	5	5	57	X	X	X	Full Tissue[a]	Full Tissue[a]
4	5	5					Full Tissue[a]	Full Tissue[a]
Unscheduled Deaths				X	X	-	Full Tissue[a]	Full Tissue[a]
Replaced animals (prestudy)[b]				X	Standard Diagnostic List	-	-	-
Replaced animals (after dosing start)				X	X	-	-	-

X = Procedure to be conducted; - = Not applicable.
[a] See Tissue Collection and Preservation table for listing of tissues.
[b] Animals found dead or euthanized before the initiation of dosing.

16.1. Unscheduled Deaths

If a main study or recovery animal dies on study, a complete necropsy examination will be conducted and specified tissues will be saved. If necessary, the animal will be refrigerated to minimize autolysis.

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of laboratory evaluation will be obtained if possible as specified in Section 15. These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

Animals found dead or euthanized before the initiation of dosing will be subject to complete necropsy examination and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to complete necropsy examination and tissues will be retained (as per Tissue Collection and Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

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16.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia will have a terminal body weight recorded, samples for laboratory evaluation will be collected (as appropriate), and will be euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. When possible, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day. Animals will be fasted overnight before their scheduled necropsy.

16.3. Necropsy

Main and recovery animals will be subjected to a complete necropsy examination, which will include evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Necropsy procedures will be performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, will be available.

At the discretion of the necropsy supervising pathologist, images may be generated for illustration of or consultation on gross observations. Generation of such images will be documented and communicated to the Study Director. Images and associated documentation will be retained and archived.

16.4. Organ Weights

The organs identified for weighing in the Tissues Collection and Preservation table will be weighed at necropsy for all scheduled euthanasia animals. Organ weights will not be recorded for animals found dead or euthanized in poor condition or in extremis. Paired organs will be weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight will be calculated.

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

Tissues in the Tissue Collection and Preservation table from animals identified in the Terminal Procedures table will be embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. Target tissues identified by the study pathologist during microscopic evaluation will be communicated to the study Director; tissues will be evaluated and reported. Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by study plan amendment following discussion with the Study Director and in consultation the Sponsor.

At the discretion of the study pathologist and after acknowledgement by the Study Director, images may be captured for consultation purposes.

17.3. Pathology Peer Review

A on-site pathology peer review will be conducted by:

(b) (6)
Moderna Therapeutics
200 Technology Square, 3rd Floor
Cambridge, MA 02116
Tel: (b) (6)
E-mail: (b) (6)

The peer review statement or equivalent documentation will be included as an appendix to the Final Report.

18. CONSTRUCTED VARIABLES

Body Weight Gains	Calculated between at least each interval as well as between the beginning and end of each phase
Organ Weight relative to Body Weight	Calculated against the Terminal body weight for scheduled intervals
Organ Weight relative to Brain Weight	Calculated against the brain weight for scheduled intervals

19. STATISTICAL ANALYSIS

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two sided tests and will be reported at the 0.1%, 1%, and 5% levels.

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Numerical data collected on scheduled occasions for the listed variables will be analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) will be reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics will be performed according to the matrix below when possible, but will exclude semi-quantitative data, and any group with less than 3 observations.

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
α2-macroglobulin	X
α1-acid glycoprotein	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

Levene's test will be used to assess the homogeneity of group variances.

Datasets with at least 3 groups will be compared using an overall one-way ANOVA *F*-test if Levene's test is not significant or the Kruskal-Wallis test if it is. If the overall *F*-test or Kruskal-Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunnett's or Dunn's test, respectively.

Datasets with 2 groups (the designated control group and 1 other group) will be compared using a *t*-test if Levene's test is not significant or Wilcoxon Rank-Sum test if it is.

20. COMPUTERIZED SYSTEMS

The following critical computerized systems may be used in the study. The actual critical computerized systems used will be specified in the Final Report.

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Data for parameters not required by study plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by study plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
BioPlex Manager	Cytokine data collection
Softmax Pro GxP	Elisa data collection
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS

21. AMENDMENTS AND DEVIATIONS

Changes to the approved study plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary study plan changes in advance with the Sponsor.

All study plan and SOP deviations will be documented in the study records. Deviations from the study plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred

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to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Study Plan, study plan amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Test and Reference Item receipt, identification, preparation, and analysis
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final) along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation. An original copy of the report with the Test Facility's handwritten signatures will be retained.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Test Facility unless other arrangements are made by the Sponsor.

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

The study plan and any amendment(s) or procedures involving the care and use of animals in this study will be reviewed and approved by CR SHB Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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AMENDMENT APPROVAL

(b) (6)
(b) (6) (b) (6)

Date: 13 Apr 2017

As authorized by the Sponsor on 13 Apr 2017

Appendix 1

ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	-	Level 4 processed to slide for evaluation of olfactory bulb. Nasal structures will not be examined.
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for last injection
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

X = Procedure to be conducted; - = Not applicable.

[a] At the discretion of the Study Pathologist, findings for extraneous tissues (nonspecified tissues in the Study Plan that may be present on a slide as a result of collection of Study Plan tissues) will be recorded when observed.

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STUDY PLAN AMENDMENT 04

Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
200 Technology Square, Third Floor
Cambridge, MA 02139, USA

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
1580 Ida-Metivier
Sherbrooke, QC J1E 0B5
Canada

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 8 Mar 2017

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
Amendment 1	**Date: 15-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To update the schedule due to delay in the test item documentation.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
10.3.1. Analytical Method	To include validation number.
10.3.1.2. Stability Analysis	To clarify that stability analysis will be performed on the bulk Test Item.
15.2. Laboratory Investigations (Cytokine Analysis)	To correct a typographical error and to include clarification for sample processing.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To clarify the processing of samples and update the shipping contact information.
15.4. PBMC Analysis	To change the blood collection procedure.
Amendment 2	**Date: 22-Mar-2017**
8.1. Test Item	To update information based on Summary of Analysis and to correct a typographical error.
10.2. Preparation of Test Item	To include missing information from study plan about the residual test item following formulation.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To update the shipping contact information.
Amendment 3	**Date: 13-Apr-2017**
7. RESPONSIBLE PERSONNEL	To add the email address of the management contact.
8.4. Analysis of Test Item	To correct the storage conditions for samples transfer.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To add a blood collection occasion on Day 29.
Amendment 4	**Date: 02-May-2017**
5.2. Test Facility-designated Subcontractor(s)	To include histopathology phase.
7. RESPONSIBLE PERSONNEL	To include the pathologist assigned to the study and to clarify the test item purity analysis.
8.4. Analysis of Test Item	To correct the wording for purity analysis as it will be performed by the analytical laboratory.
17.2. Histopathology	To include that slides will be shipped to the pathologist Test Site.
17.3. Pathology Peer Review	To update as the pathology peer review will not be performed at the Test Facility.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA 1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	mRNA

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date:	08 Mar 2017
Experimental Completion Date:	29 Aug 2017 (Last date data are collected from the study)
Animal Arrival:	08 Mar 2017
Initiation of Dosing:	22 Mar 2017 (Male) 23 Mar 2017 (Female)
Completion of In-life:	05 May 2017 (Main) 18 May 2017 (Recovery) (Last date of necropsy)
Unaudited Draft Report:	17 Jul 2017
Audited Draft Report:	22 Aug 2017
Final Report:	29 Aug 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

The design of this study was based on the study objective(s), the overall product development strategy for the Test Item, and the following study design guidelines:

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 November 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

4. REGULATORY COMPLIANCE

The study will be performed in accordance with the OECD Principles of Good Laboratory Practice and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in the USA will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration. United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines, α2-macroglobulin, α1-acid glycoprotein, anti-therapeutic antibody and PBMCs will be conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- Pathology peer review

5. QUALITY ASSURANCE

5.1. Test Facility

The Test Facility Quality Assurance Program (QAP) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAP will review the study plan, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to

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assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

The Test Facility QAP contact for this study is indicated below:

(b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

The following study phases performed by Test Facility-designated subcontractors will be audited by the Test Facility QAP:

- Ophthalmology

The following study phases performed by Test Facility-designated subcontractors will be audited by the respective subcontractor QAP(s):

- **Histopathology**

For all study phase(s) inspected by subcontractor QAP(s), copies of each periodic inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility QAP.

6. SPONSOR

Sponsor Representative

(b) (6)
Address as cited for Sponsor
Tel: (b) (6)
E-mail: (b) (6)

7. RESPONSIBLE PERSONNEL

Study Director

(b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
Address as cited for Test Facility
Tel: (b) (6)

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Fax: (b) (6)
E-mail: (b) (6)

Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)
E-mail: (b) (6)

Individual Scientists (IS) at the Test Facility

Ophthalmology

(b) (6)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Analytical Chemistry
(Concentration, **and**
Particle size **and**
Purity Analysis)

(b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

~~**Immunology**~~
~~**(Purity Analysis)**~~

(b) (6)
~~**Charles River Laboratories Montreal ULC**~~
~~**Senneville Site (CR-MTL)**~~
~~**22022 Transcanadienne**~~
~~**Senneville, QC H9X 3R3**~~
~~**Canada**~~
~~**Tel:**~~ (b) (6)
~~**E-mail:**~~ (b) (6)

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Immunology (Cytokine, Alpha-2 Macroglobulin and Alpha-1 Glycoprotein Analysis)	(b) (6) Charles River Laboratories Montreal ULC Sherbrooke Site (CR SHB) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
~~**Pathology**~~	~~**To be included by amendment**~~

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

Principal Investigators (PI) at a Test Facility-designated Test Site

Pathology	(b) (6) **Charles River Laboratories, Inc.** **4025 Stirrup Creek Drive, Suite 150** **Durham, NC 27703, USA** **Tel.:** (b) (6) **E-mail:** (b) (6)

Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- **A Statement of Compliance**
- **A QA Statement**
- **The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)**
- **A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase**

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PIs at Sponsor or Sponsor-designated Test Site(s)

Anti-Therapeutic Antibody Analysis

(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

PBMC Analysis

(b) (6)
Southern Research - Cell Biology and Immunology
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1647
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17015
Concentration:	2.7 mg/mL
Retest Date:	An end-of-use analysis of the bulk Test Item will be performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanoparticle dispersion

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Storage Conditions: Kept in a freezer set to maintain -20°C

8.2. Reference Item

Identification: Phosphate-buffered Saline (PBS) pH 7.2

Supplier: Will be included in the Final Report

Batch (Lot) Number: Will be included in the Final Report

Expiration Date: Will be included in the Final Report

Physical Description: Liquid

Storage Conditions: Kept in a controlled temperature area set to maintain 21°C

8.3. Test Item Characterization

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity and composition for the Test Item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor will also provide information concerning the regulatory standard that was followed for these evaluations.

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the Test Item, and this information is available to the appropriate regulatory agencies should it be requested.

8.4. Analysis of Test Item

A sample (2 vials) of the Test Item will be taken on the completion of the dosing period. Analysis of bulk Test Item for concentration, particle size and purity will be performed.

The first vial will be transferred (on dry ice) to the analytical laboratory at the Test Facility for concentration and particle size analysis.

The second vial will be transferred (on dry ice) to the **analytical laboratory** ~~**molecular biology**~~ laboratory at the Test Facility for purity analysis.

Concentration, Purity and Particle size analysis will be performed by IEX- HPLC, Differential Light Scattering (DLS) and **rHPLC** ~~**capillary electrophoresis (CE)**~~ using validated **or qualified** analytical procedures.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 mL or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

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8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned on dry ice to the Sponsor (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
800 Technology Sq, 8th Floor
Cambridge MA 02476
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

The safety precautions for the Test Item and dose formulations will be documented in a Test Material Safety Data Sheet (TMSDS) based on the information provided by the Sponsor either by an MSDS or similar document.

10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

The Reference Item, Phosphate-buffered Saline (PBS) pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15, 29 and 43) for administration to Group 1 control animals and will be used as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots will be stored in a refrigerator set to maintain 4°C until use. They will be removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

Any residual volumes will be discarded unless otherwise requested by the Study Director.

10.2. Preparation of Test Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

Test Item formulations will be diluted with PBS pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15, 29 and 43) and will be stored in a refrigerator set to maintain 4°C. The dose formulations will be allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots can be transferred directly to room temperature. When possible, stock vials will be used only once.

Any residual volumes of formulated Test Item and stock test item will be stored in a refrigerator set at 4°C and discarded prior to report finalization.

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10.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 43	N/A	All groups	Dosing container

N/A = Not applicable.

[a] The homogeneity results obtained from the top, middle and bottom preparations will be averaged and utilized as the concentration results.

[b] Samples will be collected on the first preparation of the study and on the last preparation of the study.

Samples to be analyzed will be submitted as soon as possible following collection.

All samples to be analyzed will be transferred (on ice pack) to the analytical laboratory.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No.1802050).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis:	Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Backup Samples:	Triplicate top, middle, and bottom samples (Triplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Sampling Containers:	Appropriate sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for

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acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study however, end of use stability analysis of the bulk test item will be performed at the end of the dosing period.

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

The actual age, weight, and number of animals received will be listed in the Final Report.

11.1. Justification of Test System and Number of Animals

The Sprague Dawley rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the Test Item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

11.2. Animal Identification

Each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 14 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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11.4. Selection, Assignment, Replacement, and Disposition of Animals

Animals will be assigned to groups by a stratified randomization scheme designed to achieve similar group mean body weights. Males and females will be randomized separately. Animals in poor health or at extremes of body weight range will not be assigned to groups.

Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-Test Item-related health issues, or similar circumstances.

The alternate animals may be used as replacements on the study within 3 days.

The disposition of all animals will be documented in the study records.

12. HUSBANDRY

12.1. Housing

Animals will be group housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions will be maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room(s) in which the animals will be kept will be documented in the study records.

Animals will be separated during designated procedures/activities. Each cage will be clearly labeled with a color-coded cage card indicating study, group, animal number(s), and sex. Cages will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the Test Item treated animals.

12.2. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	19°C to 25°C
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

12.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 will be provided ad libitum throughout the study, except during designated procedures. The same diet in meal form may be provided to individual animals as warranted by clinical signs (e.g., broken/damaged incisors or other health changes).

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The feed is analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis are provided by the supplier and are on file at the Test Facility.

It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

12.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation will be freely available to each animal via an automatic watering system (except during designated procedures). Water bottles can be provided, if required.

Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility.

It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

12.5. Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and will be provided with items such as a hiding tube and a chewing object, except during study procedures/activities.

12.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments, if any, will be documented in the study records.

In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director or Scientific designate. All such actions will be properly documented in the study records and, when appropriate, by study plan amendment. Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or clinical veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10	200	0.05	10	10	-	-
3	mRNA-1647	30	200	0.15	10	10	-	-
4	mRNA-1647	100	200	0.5	10	10	5	5

- : Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, 29 and 43, the injection site will be alternated on each dosing occasion (site 1= left; site 2= right). The volume for each dose will be administered using a syringe/needle within the demarcated area. The first day of dosing will be designated as Day 1 (exception: alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

The injection area will be marked as frequently as required to allow appropriate visualization of administration sites. Hair may be clipped or shaved if required to improve visualization of the injection sites. The injection site will be documented in the raw data for each dose administered.

13.2. Justification of Route and Dose Levels

The intramuscular route of exposure was selected because this is the intended route of human exposure.

The dose levels for this toxicology study were chosen to approximate a substantial multiple of the anticipated clinical starting dose and top clinical dose. The highest dose to be tested is expected to represent the intended maximum human clinical dose and volume and will be administered by the clinical route (intramuscular). At this dose level, minimal systemic toxicity is expected, but it is possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below including Laboratory Investigations listed in section below will be performed for all main study and recovery animals, unless otherwise indicated in the respective section. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

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14.1. Mortality/Moribundity Checks

Frequency: Twice daily, once in the morning and once in the afternoon, throughout the study.

Procedure: Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 43 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 44.

Procedure: All animals will have the dose injection site examined for signs of erythema/edema. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

Erythema (Redness)	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Mild erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness to slight eschar formation, injury in depth)	4
Notable dermal lesion (maximized)	M
Edema (Swelling)	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema	2
Moderate edema	3
Severe edema	4

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Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.
Procedure:	Animals will be individually weighed. A fasted weight will be recorded on the day of necropsy. Terminal body weights will not be collected from animals found dead or euthanized moribund.

14.5. Food Consumption

Frequency:	Weekly, starting Day -7, throughout the dosing and recovery periods.
Procedure:	Food consumption will be quantitatively measured except for on the day of scheduled euthanasia.

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 6 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 43 at predose, and 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0°C to 38.0°C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes measurements may be taken at the discretion of the Study Director.
Procedure:	Rectal body temperature will be recorded on un-sedated animals.

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15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

Blood will be collected from the abdominal aorta following isoflurane anesthesia. After collection, samples will be transferred to the appropriate laboratory for processing.

Animals will be fasted overnight before blood sampling (for clinical chemistry). Samples will be collected according to the following table.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	α1-acid glycoprotein/ α2-macroglubulin
1 to 4[a]	Day 44	X	X	X	X
1 and 4	Day 57	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X	X

X = Sample to be collected

[a] Samples will only be collected from those animals scheduled for euthanasia on Day 44.

Any residual/retained clinical pathology samples will be discarded before issue of the Final Report.

15.1.2. Hematology

Target Volume: 0.5 mL

Anticoagulant: EDTA

Hematology Parameters

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red Blood Cell Distribution Width Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute) Platelet count	White blood cell count Neutrophil count (absolute) Lymphocyte count (absolute) Monocyte count (absolute) Eosinophil count (absolute) Basophil count (absolute) Large unstained cells (absolute)

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. Blood smears may be read to investigate results. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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15.1.3. Coagulation

Target Volume: 1.2 mL (in a 1.3 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tube

Processing: To serum

Clinical Chemistry Parameters

Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine Kinase Total bilirubin[a] Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample Quality

[a] When total bilirubin is > 0.5 mg/dL, indirect and direct bilirubin will also be measured.

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.1.6. α1-acid Glycoprotein and α2-macroglobulin Analysis

Blood will be collected via the abdominal aorta following isoflurane anesthesia before scheduled and unscheduled euthanasia for all animals.

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: Blood samples to clot at ambient room temperature. Centrifugation for (b) (4) set at (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) Samples will be processed to

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serum by the Immunology Department. Serum will be aliquoted into 1 x 75 µL aliquot for α2-macroglobulin and 2 x 75 µL aliquot and a leftover (if available) for α1-acid glycoprotein.

Storage conditions: Stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin will be conducted using a qualified ELISA method by the Immunology Department. The procedure to be followed along with the assay acceptance criteria will be detailed in the appropriate analytical procedure.

Samples will be analyzed in duplicate. Any residual/retained samples will be discarded prior to report finalization.

15.2. Laboratory Investigations (Cytokine Analysis)

Blood will be collected from the jugular vein of all recovery animals and preterminally euthanized animals (recovery animals only). After collection, blood samples for serum will be allowed to clot at ambient room temperature and blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hrs**	**No. of Males/ Females**	IFN-α	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	5/5	X	X
15	6	5/5	X	X
29	6	5/5	X	X
43	6	5/5	X	X
57	N / A	5/5	X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR-SHB	CR-SHB

X = Sample to be collected; N/A = not applicable

The number of aliquots and volumes are targets that may be adjusted based on sample volume availability.

The samples will be analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 will be conducted using a multiplex Luminex method. An ELISA

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method will be used for the analysis of IFN-α. The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.

Following Study Director approval, any residual/retained samples will be discarded prior to report finalization.

An Immunology Report for cytokine analysis will be included as an appendix to the Final Report.

15.3. Anti Therapeutic Antibody (ATA) Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	Before initiation of dosing, Day 29 (before dosing), Day 43 (main animals only) and Day 57 (recovery animals).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and allow to clot at ambient room temperature until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at -80°C.

The samples will be analyzed for rat anti-CMV antibodies using a qualified ELISA method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

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An Anti-therapeutic Antibody Report will be included as an appendix to the Final Report.

15.4. PBMC Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	On Day 44 (main animals only).
Target Volume:	0.5 mL
Anticoagulant:	Sodium Heparin
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

Samples will be shipped at controlled temperature set to maintain 21°C via overnight courier to the Immunology laboratory, for whole blood stimulation and cytokine analysis, to:

Shipping Contact
(b) (6)
Cell Biology and Immunology
Southern Research
2000 Ninth Ave S
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at room temperature.

The PBMC samples will be analyzed using a qualified method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Immunology Report for PBMC analysis will be included as an appendix to the Final Report.

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	44	X	X	X	Full Tissue[a]	Full Tissue[a]
2	10	10					Full Tissue[a]	Gross Lesions Target Tissues
3	10	10					Full Tissue[a]	Gross Lesions Target Tissues
4	10	10					Full Tissue[a]	Full Tissue[a]
1	5	5	57	X	X	X	Full Tissue[a]	Full Tissue[a]
4	5	5					Full Tissue[a]	Full Tissue[a]
Unscheduled Deaths				X	X	-	Full Tissue[a]	Full Tissue[a]
Replaced animals (prestudy)[b]				X	Standard Diagnostic List	-	-	-
Replaced animals (after dosing start)				X	X	-	-	-

X = Procedure to be conducted; - = Not applicable.
[a] See Tissue Collection and Preservation table for listing of tissues.
[b] Animals found dead or euthanized before the initiation of dosing.

16.1. Unscheduled Deaths

If a main study or recovery animal dies on study, a complete necropsy examination will be conducted and specified tissues will be saved. If necessary, the animal will be refrigerated to minimize autolysis.

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of laboratory evaluation will be obtained if possible as specified in Section 15. These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

Animals found dead or euthanized before the initiation of dosing will be subject to complete necropsy examination and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to complete necropsy examination and tissues will be retained (as per Tissue Collection and Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

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16.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia will have a terminal body weight recorded, samples for laboratory evaluation will be collected (as appropriate), and will be euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. When possible, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day. Animals will be fasted overnight before their scheduled necropsy.

16.3. Necropsy

Main and recovery animals will be subjected to a complete necropsy examination, which will include evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Necropsy procedures will be performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, will be available.

At the discretion of the necropsy supervising pathologist, images may be generated for illustration of or consultation on gross observations. Generation of such images will be documented and communicated to the Study Director. Images and associated documentation will be retained and archived.

16.4. Organ Weights

The organs identified for weighing in the Tissues Collection and Preservation table will be weighed at necropsy for all scheduled euthanasia animals. Organ weights will not be recorded for animals found dead or euthanized in poor condition or in extremis. Paired organs will be weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight will be calculated.

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

Tissues in the Tissue Collection and Preservation table from animals identified in the Terminal Procedures table will be embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. Target tissues identified by the study pathologist during microscopic evaluation will be communicated to the study Director; tissues will be evaluated and reported. Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by study plan amendment following discussion with the Study Director and in consultation the Sponsor.

At the discretion of the study pathologist and after acknowledgement by the Study Director, images may be captured for consultation purposes.

The appropriate Charles River Laboratories, Pathology Associates Test Site will be contacted for the slide shipping address.

17.3. Pathology Peer Review

A ~~**on-site**~~ pathology peer review will be conducted by:

(b) (6)
Moderna Therapeutics
200 Technology Square, 3rd Floor
Cambridge, MA 02116
Tel: (b) (6)
E-mail: (b) (6)

The peer review statement or equivalent documentation will be included as an appendix to the Final Report.

18. CONSTRUCTED VARIABLES

Body Weight Gains	Calculated between at least each interval as well as between the beginning and end of each phase
Organ Weight relative to Body Weight	Calculated against the Terminal body weight for scheduled intervals
Organ Weight relative to Brain Weight	Calculated against the brain weight for scheduled intervals

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19. STATISTICAL ANALYSIS

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two sided tests and will be reported at the 0.1%, 1%, and 5% levels.

Numerical data collected on scheduled occasions for the listed variables will be analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) will be reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics will be performed according to the matrix below when possible, but will exclude semi-quantitative data, and any group with less than 3 observations.

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
α2-macroglobulin	X
α1-acid glycoprotein	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

Levene's test will be used to assess the homogeneity of group variances.

Datasets with at least 3 groups will be compared using an overall one-way ANOVA *F*-test if Levene's test is not significant or the Kruskal-Wallis test if it is. If the overall *F*-test or Kruskal-Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunnett's or Dunn's test, respectively.

Datasets with 2 groups (the designated control group and 1 other group) will be compared using a *t*-test if Levene's test is not significant or Wilcoxon Rank-Sum test if it is.

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20. COMPUTERIZED SYSTEMS

The following critical computerized systems may be used in the study. The actual critical computerized systems used will be specified in the Final Report.

Data for parameters not required by study plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by study plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
BioPlex Manager	Cytokine data collection
Softmax Pro GxP	Elisa data collection
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS

21. AMENDMENTS AND DEVIATIONS

Changes to the approved study plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary study plan changes in advance with the Sponsor.

All study plan and SOP deviations will be documented in the study records. Deviations from the study plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

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22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Study Plan, study plan amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Test and Reference Item receipt, identification, preparation, and analysis
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final) along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation. An original copy of the report with the Test Facility's handwritten signatures will be retained.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Test Facility unless other arrangements are made by the Sponsor.

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

The study plan and any amendment(s) or procedures involving the care and use of animals in this study will be reviewed and approved by CR SHB Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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AMENDMENT APPROVAL

(b) (6) Date: 02 May 2017

(b) (6) (b) (6)

As authorized by the Sponsor on 02 May 2017

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ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	-	Level 4 processed to slide for evaluation of olfactory bulb. Nasal structures will not be examined.
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for last injection
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

X = Procedure to be conducted; - = Not applicable.

[a] At the discretion of the Study Pathologist, findings for extraneous tissues (nonspecified tissues in the Study Plan that may be present on a slide as a result of collection of Study Plan tissues) will be recorded when observed.

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STUDY PLAN AMENDMENT 05

Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
200 Technology Square, Third Floor
Cambridge, MA 02139, USA

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
1580 Ida-Metivier
Sherbrooke, QC J1E 0B5
Canada

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 8 Mar 2017

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
Amendment 1	**Date: 15-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To update the schedule due to delay in the test item documentation.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
10.3.1. Analytical Method	To include validation number.
10.3.1.2. Stability Analysis	To clarify that stability analysis will be performed on the bulk Test Item.
15.2. Laboratory Investigations (Cytokine Analysis)	To correct a typographical error and to include clarification for sample processing.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To clarify the processing of samples and update the shipping contact information.
15.4. PBMC Analysis	To change the blood collection procedure.
Amendment 2	**Date: 22-Mar-2017**
8.1. Test Item	To update information based on Summary of Analysis and to correct a typographical error.
10.2. Preparation of Test Item	To include missing information from study plan about the residual test item following formulation.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To update the shipping contact information.
Amendment 3	**Date: 13-Apr-2017**
7. RESPONSIBLE PERSONNEL	To add the email address of the management contact.
8.4. Analysis of Test Item	To correct the storage conditions for samples transfer.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To add a blood collection occasion on Day 29.
Amendment 4	**Date: 02-May-2017**
5.2. Test Facility-designated Subcontractor(s)	To include histopathology phase.
7. RESPONSIBLE PERSONNEL	To include the pathologist assigned to the study and to clarify the test item purity analysis.
8.4. Analysis of Test Item	To correct the wording for purity analysis as it will be performed by the analytical laboratory.
17.2. Histopathology	To include that slides will be shipped to the pathologist Test Site.
17.3. Pathology Peer Review	To update as the pathology peer review will not be performed at the Test Facility.
Amendment 5	
8.1. Test Item	To include clarification for TI concentration based on new summary of analysis (SoA) issued.
13. EXPERIMENTAL DESIGN	To include clarification to dose levels and dose concentrations based on new SoA issued.
17.3. Pathology Peer Review	To update as the pathology peer review will be done by EPL.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA 1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	mRNA

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date:	08 Mar 2017
Experimental Completion Date:	29 Aug 2017 (Last date data are collected from the study)
Animal Arrival:	08 Mar 2017
Initiation of Dosing:	22 Mar 2017 (Male) 23 Mar 2017 (Female)
Completion of In-life:	05 May 2017 (Main) 18 May 2017 (Recovery) (Last date of necropsy)
Unaudited Draft Report:	17 Jul 2017
Audited Draft Report:	22 Aug 2017
Final Report:	29 Aug 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

The design of this study was based on the study objective(s), the overall product development strategy for the Test Item, and the following study design guidelines:

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 November 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

4. REGULATORY COMPLIANCE

The study will be performed in accordance with the OECD Principles of Good Laboratory Practice and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in the USA will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration. United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines, α2-macroglobulin, α1-acid glycoprotein, anti-therapeutic antibody and PBMCs will be conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- Pathology peer review

5. QUALITY ASSURANCE

5.1. Test Facility

The Test Facility Quality Assurance Program (QAP) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAP will review the study plan, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to

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assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

The Test Facility QAP contact for this study is indicated below:

(b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

The following study phases performed by Test Facility-designated subcontractors will be audited by the Test Facility QAP:

- Ophthalmology

The following study phases performed by Test Facility-designated subcontractors will be audited by the respective subcontractor QAP(s):

- Histopathology

For all study phase(s) inspected by subcontractor QAP(s), copies of each periodic inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility QAP.

6. SPONSOR

Sponsor Representative

(b) (6)
Address as cited for Sponsor
Tel: (b) (6)
E-mail: (b) (6)

7. RESPONSIBLE PERSONNEL

Study Director

(b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
Address as cited for Test Facility
Tel: (b) (6)

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Fax: (b) (6)
E-mail: (b) (6)

Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)
E-mail: (b) (6)

Individual Scientists (IS) at the Test Facility

Ophthalmology

(b) (6)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Analytical Chemistry (Concentration, and Particle size and Purity Analysis)

(b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

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Immunology
(Cytokine, Alpha-2
Macroglobulin and
Alpha-1 Glycoprotein
Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
Address as cited for Test Facility
Tel: (b) (6)
E-mail: (b) (6)

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

Principal Investigators (PI) at a Test Facility-designated Test Site

Pathology

(b) (6)

Charles River Laboratories, Inc.
4025 Stirrup Creek Drive, Suite 150
Durham, NC 27703, USA
Tel.: (b) (6)
E-mail: (b) (6)

Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A Statement of Compliance
- A QA Statement
- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

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PIs at Sponsor or Sponsor-designated Test Site(s)

Anti-Therapeutic Antibody Analysis

(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

PBMC Analysis

(b) (6)
Southern Research - Cell Biology and Immunology
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1647
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17015
Concentration:	2.7 / 2.4*mg/mL
Retest Date:	An end-of-use analysis of the bulk Test Item will be performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanoparticle dispersion

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Storage Conditions: Kept in a freezer set to maintain -20°C

* Concentration based on SoA released on 16 March 2017 /Concentration based on SoA released on 31 May 2017

8.2. Reference Item

Identification: Phosphate-buffered Saline (PBS) pH 7.2

Supplier: Will be included in the Final Report

Batch (Lot) Number: Will be included in the Final Report

Expiration Date: Will be included in the Final Report

Physical Description: Liquid

Storage Conditions: Kept in a controlled temperature area set to maintain 21°C

8.3. Test Item Characterization

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity and composition for the Test Item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor will also provide information concerning the regulatory standard that was followed for these evaluations.

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the Test Item, and this information is available to the appropriate regulatory agencies should it be requested.

8.4. Analysis of Test Item

A sample (2 vials) of the Test Item will be taken on the completion of the dosing period. Analysis of bulk Test Item for concentration, particle size and purity will be performed.

The first vial will be transferred (on dry ice) to the analytical laboratory at the Test Facility for concentration and particle size analysis.

The second vial will be transferred (on dry ice) to the analytical laboratory laboratory at the Test Facility for purity analysis.

Concentration, Purity and Particle size analysis will be performed by IEX- HPLC, Differential Light Scattering (DLS) and rHPLC using validated or qualified analytical procedures.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 mL or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

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8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned on dry ice to the Sponsor (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
800 Technology Sq, 8th Floor
Cambridge MA 02476
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

The safety precautions for the Test Item and dose formulations will be documented in a Test Material Safety Data Sheet (TMSDS) based on the information provided by the Sponsor either by an MSDS or similar document.

10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

The Reference Item, Phosphate-buffered Saline (PBS) pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15, 29 and 43) for administration to Group 1 control animals and will be used as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots will be stored in a refrigerator set to maintain 4°C until use. They will be removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

Any residual volumes will be discarded unless otherwise requested by the Study Director.

10.2. Preparation of Test Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

Test Item formulations will be diluted with PBS pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15, 29 and 43) and will be stored in a refrigerator set to maintain 4°C. The dose formulations will be allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots can be transferred directly to room temperature. When possible, stock vials will be used only once.

Any residual volumes of formulated Test Item and stock test item will be stored in a refrigerator set at 4°C and discarded prior to report finalization.

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10.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 43	N/A	All groups	Dosing container

N/A = Not applicable.

[a] The homogeneity results obtained from the top, middle and bottom preparations will be averaged and utilized as the concentration results.

[b] Samples will be collected on the first preparation of the study and on the last preparation of the study.

Samples to be analyzed will be submitted as soon as possible following collection.

All samples to be analyzed will be transferred (on ice pack) to the analytical laboratory.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No.1802050).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis:	Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Backup Samples:	Triplicate top, middle, and bottom samples (Triplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Sampling Containers:	Appropriate sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for

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acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study however, end of use stability analysis of the bulk test item will be performed at the end of the dosing period.

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

The actual age, weight, and number of animals received will be listed in the Final Report.

11.1. Justification of Test System and Number of Animals

The Sprague Dawley rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the Test Item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

11.2. Animal Identification

Each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 14 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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11.4. Selection, Assignment, Replacement, and Disposition of Animals

Animals will be assigned to groups by a stratified randomization scheme designed to achieve similar group mean body weights. Males and females will be randomized separately. Animals in poor health or at extremes of body weight range will not be assigned to groups.

Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-Test Item-related health issues, or similar circumstances.

The alternate animals may be used as replacements on the study within 3 days.

The disposition of all animals will be documented in the study records.

12. HUSBANDRY

12.1. Housing

Animals will be group housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions will be maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room(s) in which the animals will be kept will be documented in the study records.

Animals will be separated during designated procedures/activities. Each cage will be clearly labeled with a color-coded cage card indicating study, group, animal number(s), and sex. Cages will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the Test Item treated animals.

12.2. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	19°C to 25°C
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

12.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 will be provided ad libitum throughout the study, except during designated procedures. The same diet in meal form may be provided to individual animals as warranted by clinical signs (e.g., broken/damaged incisors or other health changes).

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The feed is analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis are provided by the supplier and are on file at the Test Facility.

It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

12.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation will be freely available to each animal via an automatic watering system (except during designated procedures). Water bottles can be provided, if required.

Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility.

It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

12.5. Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and will be provided with items such as a hiding tube and a chewing object, except during study procedures/activities.

12.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments, if any, will be documented in the study records.

In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director or Scientific designate. All such actions will be properly documented in the study records and, when appropriate, by study plan amendment. Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or clinical veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10/**8.9**	200	0.05/**0.045**	10	10	-	-
3	mRNA-1647	30/**27**	200	0.15/**0.14**	10	10	-	-
4	mRNA-1647	100/**89**	200	0.5/**0.45**	10	10	5	5

- : Not applicable

[a] **Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.**

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, 29 and 43, the injection site will be alternated on each dosing occasion (site 1= left; site 2= right). The volume for each dose will be administered using a syringe/needle within the demarcated area. The first day of dosing will be designated as Day 1 (exception: alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

The injection area will be marked as frequently as required to allow appropriate visualization of administration sites. Hair may be clipped or shaved if required to improve visualization of the injection sites. The injection site will be documented in the raw data for each dose administered.

13.2. Justification of Route and Dose Levels

The intramuscular route of exposure was selected because this is the intended route of human exposure.

The dose levels for this toxicology study were chosen to approximate a substantial multiple of the anticipated clinical starting dose and top clinical dose. The highest dose to be tested is expected to represent the intended maximum human clinical dose and volume and will be administered by the clinical route (intramuscular). At this dose level, minimal systemic toxicity is expected, but it is possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below including Laboratory Investigations listed in section below will be performed for all main study and recovery animals, unless otherwise indicated in the respective section. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or

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Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

Frequency: Twice daily, once in the morning and once in the afternoon, throughout the study.

Procedure: Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 43 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 44.

Procedure: All animals will have the dose injection site examined for signs of erythema/edema. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

Erythema (Redness)	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Mild erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness to slight eschar formation, injury in depth)	4
Notable dermal lesion (maximized)	M
Edema (Swelling)	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema	2
Moderate edema	3

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Severe edema	4

Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

Frequency: Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.

Procedure: Animals will be individually weighed. A fasted weight will be recorded on the day of necropsy. Terminal body weights will not be collected from animals found dead or euthanized moribund.

14.5. Food Consumption

Frequency: Weekly, starting Day -7, throughout the dosing and recovery periods.

Procedure: Food consumption will be quantitatively measured except for on the day of scheduled euthanasia.

14.6. Ophthalmic Examinations

Frequency: Once prestudy and again toward the end of Week 6 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.

Procedure: All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.

Evaluation: A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency: On Day 1 and Day 43 at predose, and 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0°C to 38.0°C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes measurements may be taken at the discretion of the Study Director.

Procedure: Rectal body temperature will be recorded on un-sedated animals.

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15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

Blood will be collected from the abdominal aorta following isoflurane anesthesia. After collection, samples will be transferred to the appropriate laboratory for processing.

Animals will be fasted overnight before blood sampling (for clinical chemistry). Samples will be collected according to the following table.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	α1-acid glycoprotein/ α2-macroglubulin
1 to 4[a]	Day 44	X	X	X	X
1 and 4	Day 57	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X	X

X = Sample to be collected

[a] Samples will only be collected from those animals scheduled for euthanasia on Day 44.

Any residual/retained clinical pathology samples will be discarded before issue of the Final Report.

15.1.2. Hematology

Target Volume: 0.5 mL

Anticoagulant: EDTA

Hematology Parameters

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red Blood Cell Distribution Width Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute) Platelet count	White blood cell count Neutrophil count (absolute) Lymphocyte count (absolute) Monocyte count (absolute) Eosinophil count (absolute) Basophil count (absolute) Large unstained cells (absolute)

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. Blood smears may be read to investigate results. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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15.1.3. Coagulation

Target Volume: 1.2 mL (in a 1.3 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tube

Processing: To serum

Clinical Chemistry Parameters

Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine Kinase Total bilirubin[a] Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample Quality

[a] When total bilirubin is > 0.5 mg/dL, indirect and direct bilirubin will also be measured.

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.1.6. α1-acid Glycoprotein and α2-macroglobulin Analysis

Blood will be collected via the abdominal aorta following isoflurane anesthesia before scheduled and unscheduled euthanasia for all animals.

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: Blood samples to clot at ambient room temperature. Centrifugation for (b) (4) set at (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)). Samples will be processed to

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serum by the Immunology Department. Serum will be aliquoted into 1 x 75 µL aliquot for α2-macroglobulin and 2 x 75 µL aliquot and a leftover (if available) for α1-acid glycoprotein.

Storage conditions: Stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin will be conducted using a qualified ELISA method by the Immunology Department. The procedure to be followed along with the assay acceptance criteria will be detailed in the appropriate analytical procedure.

Samples will be analyzed in duplicate. Any residual/retained samples will be discarded prior to report finalization.

15.2. Laboratory Investigations (Cytokine Analysis)

Blood will be collected from the jugular vein of all recovery animals and preterminally euthanized animals (recovery animals only). After collection, blood samples for serum will be allowed to clot at ambient room temperature and blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hrs**	**No. of Males/ Females**	IFN-α	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	5/5	X	X
15	6	5/5	X	X
29	6	5/5	X	X
43	6	5/5	X	X
57	N / A	5/5	X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR-SHB	CR-SHB

X = Sample to be collected; N/A = not applicable

The number of aliquots and volumes are targets that may be adjusted based on sample volume availability.

The samples will be analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 will be conducted using a multiplex Luminex method. An ELISA

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method will be used for the analysis of IFN-α. The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.

Following Study Director approval, any residual/retained samples will be discarded prior to report finalization.

An Immunology Report for cytokine analysis will be included as an appendix to the Final Report.

15.3. Anti Therapeutic Antibody (ATA) Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	Before initiation of dosing, Day 29 (before dosing), Day 43 (main animals only) and Day 57 (recovery animals).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and allow to clot at ambient room temperature until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at -80°C.

The samples will be analyzed for rat anti-CMV antibodies using a qualified ELISA method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

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An Anti-therapeutic Antibody Report will be included as an appendix to the Final Report.

15.4. PBMC Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	On Day 44 (main animals only).
Target Volume:	0.5 mL
Anticoagulant:	Sodium Heparin
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

Samples will be shipped at controlled temperature set to maintain 21°C via overnight courier to the Immunology laboratory, for whole blood stimulation and cytokine analysis, to:

Shipping Contact
(b) (6)
Cell Biology and Immunology
Southern Research
2000 Ninth Ave S
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at room temperature.

The PBMC samples will be analyzed using a qualified method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Immunology Report for PBMC analysis will be included as an appendix to the Final Report.

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	44	X	X	X	Full Tissue[a]	Full Tissue[a]
2	10	10					Full Tissue[a]	Gross Lesions Target Tissues
3	10	10					Full Tissue[a]	Gross Lesions Target Tissues
4	10	10					Full Tissue[a]	Full Tissue[a]
1	5	5	57	X	X	X	Full Tissue[a]	Full Tissue[a]
4	5	5					Full Tissue[a]	Full Tissue[a]
Unscheduled Deaths				X	X	-	Full Tissue[a]	Full Tissue[a]
Replaced animals (prestudy)[b]				X	Standard Diagnostic List	-	-	-
Replaced animals (after dosing start)				X	X	-	-	-

X = Procedure to be conducted; - = Not applicable.
[a] See Tissue Collection and Preservation table for listing of tissues.
[b] Animals found dead or euthanized before the initiation of dosing.

16.1. Unscheduled Deaths

If a main study or recovery animal dies on study, a complete necropsy examination will be conducted and specified tissues will be saved. If necessary, the animal will be refrigerated to minimize autolysis.

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of laboratory evaluation will be obtained if possible as specified in Section 15. These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

Animals found dead or euthanized before the initiation of dosing will be subject to complete necropsy examination and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to complete necropsy examination and tissues will be retained (as per Tissue Collection and Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

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16.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia will have a terminal body weight recorded, samples for laboratory evaluation will be collected (as appropriate), and will be euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. When possible, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day. Animals will be fasted overnight before their scheduled necropsy.

16.3. Necropsy

Main and recovery animals will be subjected to a complete necropsy examination, which will include evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Necropsy procedures will be performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, will be available.

At the discretion of the necropsy supervising pathologist, images may be generated for illustration of or consultation on gross observations. Generation of such images will be documented and communicated to the Study Director. Images and associated documentation will be retained and archived.

16.4. Organ Weights

The organs identified for weighing in the Tissues Collection and Preservation table will be weighed at necropsy for all scheduled euthanasia animals. Organ weights will not be recorded for animals found dead or euthanized in poor condition or in extremis. Paired organs will be weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight will be calculated.

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

Tissues in the Tissue Collection and Preservation table from animals identified in the Terminal Procedures table will be embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. Target tissues identified by the study pathologist during microscopic evaluation will be communicated to the study Director; tissues will be evaluated and reported. Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by study plan amendment following discussion with the Study Director and in consultation the Sponsor.

At the discretion of the study pathologist and after acknowledgement by the Study Director, images may be captured for consultation purposes.

The appropriate Charles River Laboratories, Pathology Associates Test Site will be contacted for the slide shipping address.

17.3. Pathology Peer Review

A pathology peer review will be conducted by **a Sponsor-designated pathologist**:

(b) (6)
~~**Moderna Therapeutics**~~
~~**200 Technology Square, 3rd Floor**~~
~~**Cambridge, MA 02116**~~
~~**Tel:**~~ (b) (6)
~~**E-mail:**~~ (b) (6)

(b) (6)
Experimental Pathology Laboratories, Inc.
PO Box 12766
Research Triangle Park, NC 27709
Tel.: (b) (6)
Fax: (b) (6)
Email: (b) (6)

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The peer review statement or equivalent documentation will be included as an appendix to the Final Report.

18. CONSTRUCTED VARIABLES

Body Weight Gains	Calculated between at least each interval as well as between the beginning and end of each phase
Organ Weight relative to Body Weight	Calculated against the Terminal body weight for scheduled intervals
Organ Weight relative to Brain Weight	Calculated against the brain weight for scheduled intervals

19. STATISTICAL ANALYSIS

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two sided tests and will be reported at the 0.1%, 1%, and 5% levels.

Numerical data collected on scheduled occasions for the listed variables will be analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) will be reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics will be performed according to the matrix below when possible, but will exclude semi-quantitative data, and any group with less than 3 observations.

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
α2-macroglobulin	X
α1-acid glycoprotein	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

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19.1. Parametric/Non-Parametric

Levene's test will be used to assess the homogeneity of group variances.

Datasets with at least 3 groups will be compared using an overall one-way ANOVA *F*-test if Levene's test is not significant or the Kruskal-Wallis test if it is. If the overall *F*-test or Kruskal-Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunnett's or Dunn's test, respectively.

Datasets with 2 groups (the designated control group and 1 other group) will be compared using a *t*-test if Levene's test is not significant or Wilcoxon Rank-Sum test if it is.

20. COMPUTERIZED SYSTEMS

The following critical computerized systems may be used in the study. The actual critical computerized systems used will be specified in the Final Report.

Data for parameters not required by study plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by study plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
BioPlex Manager	Cytokine data collection
Softmax Pro GxP	Elisa data collection
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS

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21. AMENDMENTS AND DEVIATIONS

Changes to the approved study plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary study plan changes in advance with the Sponsor.

All study plan and SOP deviations will be documented in the study records. Deviations from the study plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Study Plan, study plan amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Test and Reference Item receipt, identification, preparation, and analysis
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

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The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final) along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation. An original copy of the report with the Test Facility's handwritten signatures will be retained.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Test Facility unless other arrangements are made by the Sponsor.

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

The study plan and any amendment(s) or procedures involving the care and use of animals in this study will be reviewed and approved by CR SHB Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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AMENDMENT APPROVAL

(b) (6) _____ Date: 27 Jun 2017

As authorized by the Sponsor on 26 Jun 2017

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ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	-	Level 4 processed to slide for evaluation of olfactory bulb. Nasal structures will not be examined.
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for last injection
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

X = Procedure to be conducted; - = Not applicable.

[a] At the discretion of the Study Pathologist, findings for extraneous tissues (nonspecified tissues in the Study Plan that may be present on a slide as a result of collection of Study Plan tissues) will be recorded when observed.

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STUDY PLAN AMENDMENT 06

Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
200 Technology Square, Third Floor
Cambridge, MA 02139, USA

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
1580 Ida-Metivier
Sherbrooke, QC J1E 0B5
Canada

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 8 Mar 2017

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
Amendment 1	**Date: 15-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To update the schedule due to delay in the test item documentation.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
10.3.1. Analytical Method	To include validation number.
10.3.1.2. Stability Analysis	To clarify that stability analysis will be performed on the bulk Test Item.
15.2. Laboratory Investigations (Cytokine Analysis)	To correct a typographical error and to include clarification for sample processing.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To clarify the processing of samples and update the shipping contact information.
15.4. PBMC Analysis	To change the blood collection procedure.
Amendment 2	**Date: 22-Mar-2017**
8.1. Test Item	To update information based on Summary of Analysis and to correct a typographical error.
10.2. Preparation of Test Item	To include missing information from study plan about the residual test item following formulation.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To update the shipping contact information.
Amendment 3	**Date: 13-Apr-2017**
7. RESPONSIBLE PERSONNEL	To add the email address of the management contact.
8.4. Analysis of Test Item	To correct the storage conditions for samples transfer.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To add a blood collection occasion on Day 29.
Amendment 4	**Date: 02-May-2017**
5.2. Test Facility-designated Subcontractor(s)	To include histopathology phase.
7. RESPONSIBLE PERSONNEL	To include the pathologist assigned to the study and to clarify the test item purity analysis.
8.4. Analysis of Test Item	To correct the wording for purity analysis as it will be performed by the analytical laboratory.
17.2. Histopathology	To include that slides will be shipped to the pathologist Test Site.
17.3. Pathology Peer Review	To update as the pathology peer review will not be performed at the Test Facility.
Amendment 5	**Date: 27-Jun-2017**
8.1. Test Item	To include clarification for TI concentration based on new summary of analysis (SoA) issued.
13. EXPERIMENTAL DESIGN	To include clarification to dose levels and dose concentrations based on new SoA issued.
17.3. Pathology Peer Review	To update as the pathology peer review will be done by EPL.
Amendment 6	

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Item or Section(s)	Justification
15.2 Laboratory Investigations (Cytokine Analysis)	To remove IFN-α from the list of cytokine to be analyzed as we were not able to appropriately validate an assay for the analysis.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA 1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	mRNA

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date:	08 Mar 2017
Experimental Completion Date:	29 Aug 2017 (Last date data are collected from the study)
Animal Arrival:	08 Mar 2017
Initiation of Dosing:	22 Mar 2017 (Male) 23 Mar 2017 (Female)
Completion of In-life:	05 May 2017 (Main) 18 May 2017 (Recovery) (Last date of necropsy)
Unaudited Draft Report:	17 Jul 2017
Audited Draft Report:	22 Aug 2017
Final Report:	29 Aug 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

The design of this study was based on the study objective(s), the overall product development strategy for the Test Item, and the following study design guidelines:

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 November 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

4. REGULATORY COMPLIANCE

The study will be performed in accordance with the OECD Principles of Good Laboratory Practice and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Any portion of this study conducted in the USA will be performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration. United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines, α2-macroglobulin, α1-acid glycoprotein, anti-therapeutic antibody and PBMCs will be conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- Pathology peer review

5. QUALITY ASSURANCE

5.1. Test Facility

The Test Facility Quality Assurance Program (QAP) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAP will review the study plan, conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to

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assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

The Test Facility QAP contact for this study is indicated below:

(b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

The following study phases performed by Test Facility-designated subcontractors will be audited by the Test Facility QAP:

- Ophthalmology

The following study phases performed by Test Facility-designated subcontractors will be audited by the respective subcontractor QAP(s):

- Histopathology

For all study phase(s) inspected by subcontractor QAP(s), copies of each periodic inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility QAP.

6. SPONSOR

Sponsor Representative

(b) (6)
Address as cited for Sponsor
Tel: (b) (6)
E-mail: (b) (6)

7. RESPONSIBLE PERSONNEL

Study Director

(b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
Address as cited for Test Facility
Tel: (b) (6)

Appendix 1

Fax: (b) (6)
E-mail: (b) (6)

Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)
E-mail: (b) (6)

Individual Scientists (IS) at the Test Facility

Ophthalmology

(b) (6)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Analytical Chemistry (Concentration, and Particle size and Purity Analysis)

(b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

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Immunology
(Cytokine, Alpha-2
Macroglobulin and
Alpha-1 Glycoprotein
Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
Address as cited for Test Facility
Tel: (b) (6)
E-mail: (b) (6)

Each IS is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each IS will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

Principal Investigators (PI) at a Test Facility-designated Test Site

Pathology

(b) (6)

Charles River Laboratories, Inc.
4025 Stirrup Creek Drive, Suite 150
Durham, NC 27703, USA
Tel.: (b) (6)
E-mail: (b) (6)

Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- A Statement of Compliance
- A QA Statement
- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

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PIs at Sponsor or Sponsor-designated Test Site(s)

Anti-Therapeutic Antibody Analysis

(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

PBMC Analysis

(b) (6)
Southern Research - Cell Biology and Immunology
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

Each PI is required to report any deviations or other circumstances that could affect the quality or integrity of the study to the Study Director in a timely manner. Each PI will provide a report addressing their assigned phase of the study, which will be included as an appendix to the Final Report. The phase report will include the following:

- The archive site for all records, samples, specimens and reports generated from the phase or segment (alternatively, details regarding the retention of the materials may be provided to the Study Director for inclusion in the Final Report)
- A listing of critical computerized systems used in the conduct and/or interpretation of the assigned study phase

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1647
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17015
Concentration:	2.7 / 2.4*mg/mL
Retest Date:	An end-of-use analysis of the bulk Test Item will be performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanoparticle dispersion

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Storage Conditions: Kept in a freezer set to maintain -20°C

* Concentration based on SoA released on 16 March 2017 /Concentration based on SoA released on 31 May 2017

8.2. Reference Item

Identification: Phosphate-buffered Saline (PBS) pH 7.2

Supplier: Will be included in the Final Report

Batch (Lot) Number: Will be included in the Final Report

Expiration Date: Will be included in the Final Report

Physical Description: Liquid

Storage Conditions: Kept in a controlled temperature area set to maintain 21°C

8.3. Test Item Characterization

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity and composition for the Test Item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report. The Sponsor will also provide information concerning the regulatory standard that was followed for these evaluations.

The Sponsor has appropriate documentation on file concerning the method of synthesis, fabrication or derivation of the Test Item, and this information is available to the appropriate regulatory agencies should it be requested.

8.4. Analysis of Test Item

A sample (2 vials) of the Test Item will be taken on the completion of the dosing period. Analysis of bulk Test Item for concentration, particle size and purity will be performed.

The first vial will be transferred (on dry ice) to the analytical laboratory at the Test Facility for concentration and particle size analysis.

The second vial will be transferred (on dry ice) to the analytical laboratory laboratory at the Test Facility for purity analysis.

Concentration, Purity and Particle size analysis will be performed by IEX- HPLC, Differential Light Scattering (DLS) and rHPLC using validated or qualified analytical procedures.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 mL or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

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8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned on dry ice to the Sponsor (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
800 Technology Sq, 8th Floor
Cambridge MA 02476
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

The safety precautions for the Test Item and dose formulations will be documented in a Test Material Safety Data Sheet (TMSDS) based on the information provided by the Sponsor either by an MSDS or similar document.

10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

The Reference Item, Phosphate-buffered Saline (PBS) pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15, 29 and 43) for administration to Group 1 control animals and will be used as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots will be stored in a refrigerator set to maintain 4°C until use. They will be removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

Any residual volumes will be discarded unless otherwise requested by the Study Director.

10.2. Preparation of Test Item

Dose formulation preparations will be performed under a laminar flow hood using clean procedures.

Test Item formulations will be diluted with PBS pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15, 29 and 43) and will be stored in a refrigerator set to maintain 4°C. The dose formulations will be allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots can be transferred directly to room temperature. When possible, stock vials will be used only once.

Any residual volumes of formulated Test Item and stock test item will be stored in a refrigerator set at 4°C and discarded prior to report finalization.

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10.3. Sample Collection and Analysis

Dose formulation samples will be collected for analysis as indicated in the following table. Additional samples may be collected and analyzed at the discretion of the Study Director.

Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 43	N/A	All groups	Dosing container

N/A = Not applicable.

[a] The homogeneity results obtained from the top, middle and bottom preparations will be averaged and utilized as the concentration results.

[b] Samples will be collected on the first preparation of the study and on the last preparation of the study.

Samples to be analyzed will be submitted as soon as possible following collection.

All samples to be analyzed will be transferred (on ice pack) to the analytical laboratory.

Any residual/retained analytical samples (and Test Item used in analysis) will be discarded before issue of the Final Report.

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No.1802050).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis:	Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Backup Samples:	Triplicate top, middle, and bottom samples (Triplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Sampling Containers:	Appropriate sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for

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acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study however, end of use stability analysis of the bulk test item will be performed at the end of the dosing period.

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

The actual age, weight, and number of animals received will be listed in the Final Report.

11.1. Justification of Test System and Number of Animals

The Sprague Dawley rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies.

The total number of animals to be used in this study is considered to be the minimum required to properly characterize the effects of the Test Item. This study has been designed such that it does not require an unnecessary number of animals to accomplish its objectives.

At this time, studies in laboratory animals provide the best available basis for extrapolation to humans and are required to support regulatory submissions. Acceptable models which do not use live animals currently do not exist.

11.2. Animal Identification

Each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 14 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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11.4. Selection, Assignment, Replacement, and Disposition of Animals

Animals will be assigned to groups by a stratified randomization scheme designed to achieve similar group mean body weights. Males and females will be randomized separately. Animals in poor health or at extremes of body weight range will not be assigned to groups.

Before the initiation of dosing, any assigned animals considered unsuitable for use in the study will be replaced by alternate animals obtained from the same shipment and maintained under the same environmental conditions.

After initiation of dosing, study animals may be replaced during the replacement period with alternate animals in the event of accidental injury, non-Test Item-related health issues, or similar circumstances.

The alternate animals may be used as replacements on the study within 3 days.

The disposition of all animals will be documented in the study records.

12. HUSBANDRY

12.1. Housing

Animals will be group housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions will be maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room(s) in which the animals will be kept will be documented in the study records.

Animals will be separated during designated procedures/activities. Each cage will be clearly labeled with a color-coded cage card indicating study, group, animal number(s), and sex. Cages will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the Test Item treated animals.

12.2. Environmental Conditions

The targeted conditions for animal room environment will be as follows:

Temperature:	19°C to 25°C
Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

12.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 will be provided ad libitum throughout the study, except during designated procedures. The same diet in meal form may be provided to individual animals as warranted by clinical signs (e.g., broken/damaged incisors or other health changes).

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The feed is analyzed by the supplier for nutritional components and environmental contaminants. Results of the analysis are provided by the supplier and are on file at the Test Facility.

It is considered that there are no known contaminants in the feed that would interfere with the objectives of the study.

12.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation will be freely available to each animal via an automatic watering system (except during designated procedures). Water bottles can be provided, if required.

Periodic analysis of the water is performed, and results of these analyses are on file at the Test Facility.

It is considered that there are no known contaminants in the water that could interfere with the outcome of the study.

12.5. Animal Enrichment

Animals will be socially housed for psychological/environmental enrichment and will be provided with items such as a hiding tube and a chewing object, except during study procedures/activities.

12.6. Veterinary Care

Veterinary care will be available throughout the course of the study and animals will be examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations and recommended therapeutic treatments, if any, will be documented in the study records.

In the event that animals show signs of illness or distress, the responsible veterinarian may make initial recommendations about treatment of the animal(s) and/or alteration of study procedures, which must be approved by the Study Director or Scientific designate. All such actions will be properly documented in the study records and, when appropriate, by study plan amendment. Treatment of the animal(s) for minor injuries or ailments may be approved without prior consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or clinical veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10/8.9	200	0.05/0.045	10	10	-	-
3	mRNA-1647	30/27	200	0.15/0.14	10	10	-	-
4	mRNA-1647	100/89	200	0.5/0.45	10	10	5	5

- : Not applicable
[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, 29 and 43, the injection site will be alternated on each dosing occasion (site 1= left; site 2= right). The volume for each dose will be administered using a syringe/needle within the demarcated area. The first day of dosing will be designated as Day 1 (exception: alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

The injection area will be marked as frequently as required to allow appropriate visualization of administration sites. Hair may be clipped or shaved if required to improve visualization of the injection sites. The injection site will be documented in the raw data for each dose administered.

13.2. Justification of Route and Dose Levels

The intramuscular route of exposure was selected because this is the intended route of human exposure.

The dose levels for this toxicology study were chosen to approximate a substantial multiple of the anticipated clinical starting dose and top clinical dose. The highest dose to be tested is expected to represent the intended maximum human clinical dose and volume and will be administered by the clinical route (intramuscular). At this dose level, minimal systemic toxicity is expected, but it is possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below including Laboratory Investigations listed in section below will be performed for all main study and recovery animals, unless otherwise indicated in the respective section. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or

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Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

Frequency: Twice daily, once in the morning and once in the afternoon, throughout the study.

Procedure: Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 43 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 44.

Procedure: All animals will have the dose injection site examined for signs of erythema/edema. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

Erythema (Redness)	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Mild erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness to slight eschar formation, injury in depth)	4
Notable dermal lesion (maximized)	M
Edema (Swelling)	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema	2
Moderate edema	3

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Severe edema	4

Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

Frequency: Weekly during the dosing and recovery periods, and at least every two weeks during the predosing period.

Procedure: Animals will be individually weighed. A fasted weight will be recorded on the day of necropsy. Terminal body weights will not be collected from animals found dead or euthanized moribund.

14.5. Food Consumption

Frequency: Weekly, starting Day -7, throughout the dosing and recovery periods.

Procedure: Food consumption will be quantitatively measured except for on the day of scheduled euthanasia.

14.6. Ophthalmic Examinations

Frequency: Once prestudy and again toward the end of Week 6 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.

Procedure: All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.

Evaluation: A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency: On Day 1 and Day 43 at predose, and 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0°C to 38.0°C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes measurements may be taken at the discretion of the Study Director.

Procedure: Rectal body temperature will be recorded on un-sedated animals.

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15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

Blood will be collected from the abdominal aorta following isoflurane anesthesia. After collection, samples will be transferred to the appropriate laboratory for processing.

Animals will be fasted overnight before blood sampling (for clinical chemistry). Samples will be collected according to the following table.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	α1-acid glycoprotein/ α2-macroglubulin
1 to 4[a]	Day 44	X	X	X	X
1 and 4	Day 57	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X	X

X = Sample to be collected

[a] Samples will only be collected from those animals scheduled for euthanasia on Day 44.

Any residual/retained clinical pathology samples will be discarded before issue of the Final Report.

15.1.2. Hematology

Target Volume: 0.5 mL

Anticoagulant: EDTA

Hematology Parameters

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Red Blood Cell Distribution Width Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute) Platelet count	White blood cell count Neutrophil count (absolute) Lymphocyte count (absolute) Monocyte count (absolute) Eosinophil count (absolute) Basophil count (absolute) Large unstained cells (absolute)

A blood smear will be prepared from each hematology sample. Blood smears will be labeled, stained, and stored. Blood smears may be read to investigate results. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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15.1.3. Coagulation

Target Volume: 1.2 mL (in a 1.3 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tube

Processing: To serum

Clinical Chemistry Parameters

Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine Kinase Total bilirubin[a] Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample Quality

[a] When total bilirubin is > 0.5 mg/dL, indirect and direct bilirubin will also be measured.

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.1.6. α1-acid Glycoprotein and α2-macroglobulin Analysis

Blood will be collected via the abdominal aorta following isoflurane anesthesia before scheduled and unscheduled euthanasia for all animals.

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: Blood samples to clot at ambient room temperature. Centrifugation for (b) (4) set at (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)). Samples will be processed to

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serum by the Immunology Department. Serum will be aliquoted into 1 x 75 µL aliquot for α2-macroglobulin and 2 x 75 µL aliquot and a leftover (if available) for α1-acid glycoprotein.

Storage conditions: Stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin will be conducted using a qualified ELISA method by the Immunology Department. The procedure to be followed along with the assay acceptance criteria will be detailed in the appropriate analytical procedure.

Samples will be analyzed in duplicate. Any residual/retained samples will be discarded prior to report finalization.

15.2. Laboratory Investigations (Cytokine Analysis)

Blood will be collected from the jugular vein of all recovery animals and preterminally euthanized animals (recovery animals only). After collection, blood samples for serum will be allowed to clot at ambient room temperature and blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hrs**	**No. of Males/ Females**	IFN-α*	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	5/5	X	X
15	6	5/5	X	X
29	6	5/5	X	X
43	6	5/5	X	X
57	N / A	5/5	X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR-SHB	CR-SHB

X = Sample to be collected; N/A = not applicable

*** The assay validation of IFN-α did not work appropriately and serum samples analysis will not be conducted.**

The number of aliquots and volumes are targets that may be adjusted based on sample volume availability.

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The samples will be analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 will be conducted using a multiplex Luminex method. ~~**An ELISA method will be used for the analysis of IFN-α.**~~ The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.

Following Study Director approval, any residual/retained samples will be discarded prior to report finalization.

An Immunology Report for cytokine analysis will be included as an appendix to the Final Report.

15.3. Anti Therapeutic Antibody (ATA) Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	Before initiation of dosing, Day 29 (before dosing), Day 43 (main animals only) and Day 57 (recovery animals).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and allow to clot at ambient room temperature until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at -80°C.

The samples will be analyzed for rat anti-CMV antibodies using a qualified ELISA method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the

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Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Anti-therapeutic Antibody Report will be included as an appendix to the Final Report.

15.4. PBMC Analysis

Blood will be collected by jugular venipuncture from the appropriate animals.

Time Points:	On Day 44 (main animals only).
Target Volume:	0.5 mL
Anticoagulant:	Sodium Heparin
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

Samples will be shipped at controlled temperature set to maintain 21°C via overnight courier to the Immunology laboratory, for whole blood stimulation and cytokine analysis, to:

Shipping Contact
(b) (6)
Cell Biology and Immunology
Southern Research
2000 Ninth Ave S
Birmingham Alabama 35205
Tel: (b) (6)
E-mail: (b) (6)

The Test Site will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored at room temperature.

The PBMC samples will be analyzed using a qualified method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the Audited Draft Report after which samples will be discarded. Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period. An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

An Immunology Report for PBMC analysis will be included as an appendix to the Final Report.

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	44	X	X	X	Full Tissue[a]	Full Tissue[a]
2	10	10					Full Tissue[a]	Gross Lesions Target Tissues
3	10	10					Full Tissue[a]	Gross Lesions Target Tissues
4	10	10					Full Tissue[a]	Full Tissue[a]
1	5	5	57	X	X	X	Full Tissue[a]	Full Tissue[a]
4	5	5					Full Tissue[a]	Full Tissue[a]
Unscheduled Deaths				X	X	-	Full Tissue[a]	Full Tissue[a]
Replaced animals (prestudy)[b]				X	Standard Diagnostic List	-	-	-
Replaced animals (after dosing start)				X	X	-	-	-

X = Procedure to be conducted; - = Not applicable.
[a] See Tissue Collection and Preservation table for listing of tissues.
[b] Animals found dead or euthanized before the initiation of dosing.

16.1. Unscheduled Deaths

If a main study or recovery animal dies on study, a complete necropsy examination will be conducted and specified tissues will be saved. If necessary, the animal will be refrigerated to minimize autolysis.

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of laboratory evaluation will be obtained if possible as specified in Section 15. These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

Animals found dead or euthanized before the initiation of dosing will be subject to complete necropsy examination and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to complete necropsy examination and tissues will be retained (as per Tissue Collection and Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

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16.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia will have a terminal body weight recorded, samples for laboratory evaluation will be collected (as appropriate), and will be euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. When possible, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day. Animals will be fasted overnight before their scheduled necropsy.

16.3. Necropsy

Main and recovery animals will be subjected to a complete necropsy examination, which will include evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

Necropsy procedures will be performed by qualified personnel with appropriate training and experience in animal anatomy and gross pathology. A veterinary pathologist, or other suitably qualified person, will be available.

At the discretion of the necropsy supervising pathologist, images may be generated for illustration of or consultation on gross observations. Generation of such images will be documented and communicated to the Study Director. Images and associated documentation will be retained and archived.

16.4. Organ Weights

The organs identified for weighing in the Tissues Collection and Preservation table will be weighed at necropsy for all scheduled euthanasia animals. Organ weights will not be recorded for animals found dead or euthanized in poor condition or in extremis. Paired organs will be weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight will be calculated.

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

Appendix 1

17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

Tissues in the Tissue Collection and Preservation table from animals identified in the Terminal Procedures table will be embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. Target tissues identified by the study pathologist during microscopic evaluation will be communicated to the study Director; tissues will be evaluated and reported. Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by study plan amendment following discussion with the Study Director and in consultation the Sponsor.

At the discretion of the study pathologist and after acknowledgement by the Study Director, images may be captured for consultation purposes.

The appropriate Charles River Laboratories, Pathology Associates Test Site will be contacted for the slide shipping address.

17.3. Pathology Peer Review

A pathology peer review will be conducted by a Sponsor-designated pathologist:

(b) (6)
Experimental Pathology Laboratories, Inc.
PO Box 12766
Research Triangle Park, NC 27709
Tel.: (b) (6)
Fax: (b) (6)
Email: (b) (6)

The peer review statement or equivalent documentation will be included as an appendix to the Final Report.

18. CONSTRUCTED VARIABLES

Body Weight Gains	Calculated between at least each interval as well as between the beginning and end of each phase
Organ Weight relative to Body Weight	Calculated against the Terminal body weight for scheduled intervals
Organ Weight relative to Brain Weight	Calculated against the brain weight for scheduled intervals

Appendix 1

19. STATISTICAL ANALYSIS

All statistical tests will be conducted at the 5% significance level. All pairwise comparisons will be conducted using two sided tests and will be reported at the 0.1%, 1%, and 5% levels.

Numerical data collected on scheduled occasions for the listed variables will be analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) will be reported whenever possible. Values may also be expressed as a percentage of predose or control values when deemed appropriate. Inferential statistics will be performed according to the matrix below when possible, but will exclude semi-quantitative data, and any group with less than 3 observations.

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
α2-macroglobulin	X
α1-acid glycoprotein	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

Levene's test will be used to assess the homogeneity of group variances.

Datasets with at least 3 groups will be compared using an overall one-way ANOVA *F*-test if Levene's test is not significant or the Kruskal-Wallis test if it is. If the overall *F*-test or Kruskal-Wallis test is found to be significant, then the above pairwise comparisons will be conducted using Dunnett's or Dunn's test, respectively.

Datasets with 2 groups (the designated control group and 1 other group) will be compared using a *t*-test if Levene's test is not significant or Wilcoxon Rank-Sum test if it is.

Appendix 1

20. COMPUTERIZED SYSTEMS

The following critical computerized systems may be used in the study. The actual critical computerized systems used will be specified in the Final Report.

Data for parameters not required by study plan, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are generated by the program but are not required by study plan and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
BioPlex Manager	Cytokine data collection
Softmax Pro GxP	Elisa data collection
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS

21. AMENDMENTS AND DEVIATIONS

Changes to the approved study plan shall be made in the form of an amendment, which will be signed and dated by the Study Director. Every reasonable effort will be made to discuss any necessary study plan changes in advance with the Sponsor.

All study plan and SOP deviations will be documented in the study records. Deviations from the study plan and/or SOP related to the phase(s) of the study conducted at a Test Site shall be documented, acknowledged by the PI/IS, and reported to the Study Director for authorization/acknowledgement. The Study Director will notify the Sponsor of deviations that may result in a significant impact on the study as soon as possible.

Appendix 1

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Records to be maintained will include, but will not be limited to, documentation and data for the following:

- Study Plan, study plan amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Test and Reference Item receipt, identification, preparation, and analysis
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

A comprehensive Draft Report will be prepared following completion of the study and will be finalized following consultation with the Sponsor. The report will include all information necessary to provide a complete and accurate description of the experimental methods and results and any circumstances that may have affected the quality or integrity of the study.

The Sponsor will receive an electronic version of the Draft and Final Report provided in Adobe Acrobat PDF format (hyperlinked and searchable at final) along with a Microsoft Word version of the text. The PDF document will be created from native electronic files to the extent possible, including text and tables generated by the Test Facility. Report components not available in native electronic files and/or original signature pages will be scanned and converted to PDF image files for incorporation. An original copy of the report with the Test Facility's handwritten signatures will be retained.

Reports should be finalized within 6 months of issue of the Draft Report. If the Sponsor has not provided comments to the report within 6 months of draft issue, the report will be finalized by the Test Facility unless other arrangements are made by the Sponsor.

Appendix 1

24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

The study plan and any amendment(s) or procedures involving the care and use of animals in this study will be reviewed and approved by CR SHB Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

Appendix 1

AMENDMENT APPROVAL

(b) (6) Date: 08 Sep 2017

As authorized by the Sponsor on 08 Sep 2017

Appendix 1

ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	-	Level 4 processed to slide for evaluation of olfactory bulb. Nasal structures will not be examined.
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

Appendix 1

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for last injection
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

X = Procedure to be conducted; - = Not applicable.

[a] At the discretion of the Study Pathologist, findings for extraneous tissues (nonspecified tissues in the Study Plan that may be present on a slide as a result of collection of Study Plan tissues) will be recorded when observed.

Appendix 1

DEVIATIONS

All deviations that occurred during the study have been authorized/acknowledged by the Study Director, assessed for impact, and documented in the study records. All study plan deviations and those SOP deviations that could have impacted the quality or integrity of the study are listed below.

None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

In-life Observations, Measurements, and Evaluations

- Given that the study dosing initiation was changed, the food consumption assessment was initiated on Day -9 and was also performed on Day 1, although specified otherwise in the study plan. These deviations were considered to have no impact on the study outcome.

Other

- A reserve sample (1 mL) of the Reference Item, Phosphate-buffered Saline (PBS) pH 7.2 (Lot No. 1830677) was not collected as there were none remaining after dispensing for dosing the control animals. As this Reference Item is commercially available and well characterized, this deviation was considered to have no impact on the study outcome.

Appendix 2

moderna
messenger therapeutics

500 Tech Square • Cambridge, MA 02139
Phone 617-714-6500 • fax 617-583-1998

Summary of Analysis

Document number	DPAD-SOA-0002
Date of Document Generation	30 May 2017
Revision	002
Product\Test Article	mRNA-1647 (CVM 1-6) in 100 mM TRIS 60 mM NaCl 7% (w/v PG) 2.4 mg/mL , 0.5mL Fill volume
Lot No.	MTDP17015
Moderna Protocol	DPAD-PRO-0003
Drug Substance (API)	See Table Below
Date of Manufacture	24 Feb 2017
Stability Initiation Date	13 Mar 2017
Stability Time Point	T=0, Release

CMV Construct #	CX Number	Drug Substance Lot	Construct Name
1	CX000667	MTDS16019	gB
2	CX000359	MTDS16020	UL128
3	CX000594	MTDS16034	gL
4	CX000712	MTDS16035	UL130
5	CX005282	MTDS16033	gH
6	CX005128	MTDS16027	UL131A

Test	Method	Testing Reference	Target Attributes	Results
mRNA Content	(b) (4) (DPTM-024.2)	2017_03_12-003	(b) (4)	
Endotoxin	USP <85>	0317-022 (ACCI)		
Bioburden	USP <61>	949975-S01 (Nelson Labs)		

Author: (b) (6) (b) (6) Date: 30 May 2017

Data reviewed: (b) (6) (b) (6) Date: 31-MAY-17

Data generated in accordance with standard Moderna Therapeutics laboratory Practices and have been verified for accuracy

Appendix 2

Number: DPAD-00018 Version: 4.0 Effective Date: 8/30/2017
DPAD-SOA-0002.4_mRNA-1647 MTDP17015

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phone 617-714-6500 • fax 617-583-1998

Summary of Analysis

Document number	DPAD-SOA-0002
Date of Document Generation	30 Aug 2017
Revision	004
Product name	**mRNA-1647 Test Article**
Product description	mRNA-1647 LNP in 93 mM Tris, 60 mM NaCl, 7% PG
Lot No.	**MTDP 17015**
Drug Substance (API)	CX005128 Lot MTDS16027 (UL131) CX000359 Lot MTDS16020 (UL128) CX000712 Lot MTDS16035 (UL130) CX000594 Lot MTDS16034 (gL) CX005282 Lot MTDS16033 (gH) CX000667 Lot MTDS16019 (gB)
Date of Manufacture	24-Feb-2017
Re-test Date	24-Feb-2018
Time Point	T = Initial

Test	Method	Testing Reference	Target Attributes	Results	
Appearance	Visual	2017_03_16-005	White to off-white dispersion, no visible particulates	Conforms	
Identity	qRT-PCR	Study ID Q032417P1RQ	(b) (4)	CX005128 CX000359 CX000712 CX000594 CX005282 CX000667	(b) (4)
Total RNA Content	(b) (4)	2017_03_12-003	(b) (4)		
mRNA ratio	qRT-PCR	Study ID Q032417P1RQ	Report $\Delta\Delta C_T$	CX005128 CX000359 CX000712 CX000594 CX005282 CX000667	(b) (4)
mRNA Purity	RP-IP-HPLC (Length-based)	2017_03_15-015	Report Result (mg/mL)	Construct CX005128 CX000359 CX000712 CX000594	Conc (mg/mL) (b) (4)

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				CX005282	(b) (4)
				CX000667	
	RP-IP-HPLC (Length-based)	2017_03_15-015	Report % Area of Impurity Regions	Impurity group	%Area
	RP-HPLC (% Poly A Tail)	2017_03_15-015	Report main peak % area	(b) (4)	
			Report pre-main peak % area		
% Encapsulation	(b) (4)	2017_03_12-007	(b) (4)		
Particle Size	Dynamic Light Scattering	2017_03_12-005			
Polydispersity	Dynamic Light Scattering	2017_03_12-005	Report results		
Lipid ID	UPLC-CAD	2017_03_12-002	Lipid	Criteria	Result
			SM-102	Matches Retention time of standard	Conforms
			Cholesterol		Conforms
			DSPC		Conforms
			PEG-DMG		Conforms
Lipid Content	UPLC-CAD	2017_03_12-002	Lipid	Conc (mg/mL)	Conc (mg/mL)
			SM102	(b) (4)	
			Cholesterol		
			DSPC		
			PEG-DMG		
Lipid Impurities	UPLC-CAD	2017_03_12-002	Report Result RRT and %Area	(b) (4)	

Appendix 2

Number: DPAD-00018 Version: 4.0 Effective Date: 8/30/2017
DPAD-SOA-0002.4_mRNA-1647 MTDP17015

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phone 617-714-6500 • fax 617-583-1998

pH	USP <791>	2017_03_16-005	(b) (4)
Osmolality	USP <785>	2017_03_16-005	Report result
Bacterial Endotoxin	USP 85 (b) (4)	IC Number 0317-022	(b) (4)
Particulate Matter	USP 85	Study Number 949974-S01	
Bioburden	USP <61>	Study Number 949975-S01	

*Reported value is a pooled result with MTDP17017. The analytical lab provider assumed these lots were to be combined for this test.

Revision #	Change Details	Author
1.0	Introduction of a New Document	(b) (6)
2.0	Updated drug product concentration to reflect the most current Drug Substance SoA (used for drug product calculation of concentration)	(b) (6)
3.0	Updated to include all other release test data	(b) (6)
4.0	Corrected the formulation buffer concentration from 100 mM Tris 60 mM NaCl 7% PG to 93 mM Tris 60 mM NaCl 7% PG. Added lipid and RNA Impurity Data. Updated qPCR data to conform to new practices.	(b) (6)

Appendix 2

Number: DPAD-00020 Version: 4.0 Effective Date: 8/30/2017
mRNA-1647 MTDP17015 Concentration Adjustment Memo

Memorandum

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To: (b) (6)
From: (b) (6)
Cc: (b) (6)
Date: 30 Aug 2017
Subject: Revised mRNA concentration determination for mRNA-1647 reference standard lot MTDS16027, and subsequent revised final concentration of mRNA-1647 drug product lot MTDP17015.

(b) (4)

Appendix 2

Memorandum

moderna

(b) (4)

Appendix 2

Number: DPAD-00020 Version: 4.0 Effective Date: 8/30/2017
mRNA-1647 MTDP17015 Concentration Adjustment Memo

Memorandum

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Reference	Description
1	CX-005128 MTDS16027 SOA Version 1
2	CX-005128 MTDS16027 SOA Version 2
3	CX-005128 MTDS16027 SOA Version 3
4	Drug Product Target Adjustment Memo: DPAD-TM-045 Version 1
5	Drug Product SOA: DP-AD-SOA-0002.2
6	Drug Product Target Adjustment Memo DPAD-TM-055 Version 1
7	"Revised mRNA Concentration Determination for mRNA-1647 reference standard Lot MTDS16027, and subsequent revised final concentration of mRNA-1647 drug product lot MTDP17015," (b) (6)

3 of 3

Appendix 2

Memorandum
moderna

To: (b) (6), Charles River Laboratory, Montréal ULC

From: (b) (6)

Date: 13Jun17

Subject: Revised mRNA concentration determination for mRNA-1647 reference standard lot MTDS16027, and subsequent revised final concentration of mRNA-1647 drug product lot MTDP17015

The revised mRNA concentration reported in the revised SoA dated 30May17 and described in memo (reference[1]) directly impacts the effective doses for the GLP toxicology study referenced 5002034. Both the original and revised Summary of Analysis documents reporting the concentration of MTDP17015 will be reported in the toxicology report such that all doses are presented as a pre- and post-method change. The change in the reported RNA content for the mRNA-1647 is -11%, and this percentage difference in reported RNA content was used to revise the calculated doses.

The original doses calculated for dose groups 2, 3 and 4 in study 5002034 were revised based on the updated concentration reported for the mRNA-1647 lot MTDP17015 (Table 2). All calculations and projected margins derived from the GLP toxicology studies should utilize the new effective doses described herein.

Table 2. Revised mRNA-1647 Dose Levels based on Ref Standard MTDS16027(reference[2]) **and drug product lot MTDP17015** (reference[3])

Dose Group	Original Dose (ug)	Revised Dose (ug)
2	10	8.9
3	30	27
4	100	89

References

1. mRNA-1647 MTDP17015 DPAD-TM-00055.1 30May17
2. mRNA-1647 MTDS16027 DSAD-SOA-0025 13Apr17
3. mRNA-1647 MTDP17017 0.5ml Fill, T0, DPAD-SOA-0002v002 30May17

Approvals

Appendix 2

Memorandum

moderna

Name/Title/Company/Role	Signature	Date
(b) (6) Non-Clinical Sciences Moderna Therapeutics *Indicates authorship of memo*	(b) (6)	20 June 2017
(b) (6) Non-Clinical Sciences Moderna Therapeutics *Indicates second person review of verifiable facts and calculations*	(b) (6)	20 June 2017

Appendix 3

FINAL REPORT

Study Phase: Analytical Chemistry

Test Facility Study No. 5002034

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)

Page 1 of 37

Appendix 3

TABLE OF CONTENTS

Appendix 3

LIST OF TABLES

LIST OF APPENDICES

Appendix 3

1. SUMMARY

Dose formulation samples have been analyzed by Ion Exchange High Performance Liquid Chromatography (IEX-HPLC) for the determination of mRNA-1647.

In addition, at the end of the study dosing phase, the bulk test item was analyzed by Ion Exchange High Performance Liquid Chromatography (IEX-HPLC) for concentration analysis, by Reversed Phase High Performance Liquid Chromatography (RP-HPLC) for purity analysis and by Dynamic Light Scattering (DLS) for particle size analysis.

The dose formulations were within specification. Homogeneity testing showed that the formulation technique used produced homogeneous preparations.

The end of use bulk Test Item analysis demonstrated that the test item was suitable for use during the study period.

2. INTRODUCTION

This report describes the analytical evaluation of mRNA-1647 in dose formulations (phosphate-buffered saline (PBS) pH 7.2) and in the bulk test item from Study 5002034.

For the work detailed in this report, the analytical phase experimental start date was 24 Mar 2017, and the analytical phase experimental completion date was 17 Jun 2017.

3. EXPERIMENTAL DESIGN

3.1. Dose Formulation Analysis

Analysis of dose formulations was carried out with regard to concentration and homogeneity.

On Day 1 of the study, duplicate samples were collected from the top, middle and bottom strata of the test item Groups for concentration and homogeneity verification while duplicate samples were collected from the middle strata of the control group. Duplicate samples were also collected from the middle strata of all Groups for concentration verification on Day 43 of the study. The samples were shipped on ice packs, stored refrigerated upon receipt and analyzed within the established stability.

3.2. Bulk Test Item Analysis

Analysis of the bulk test item was carried out with regard to concentration, purity and particle size analysis.

At the end of the study dosing phase, unopened vials of test item were transferred for concentration, purity and particle size analysis.

Appendix 3

4. MATERIALS AND METHODS

4.1. Materials

4.1.1. Reference Standard

Identification:	CX-0005128 mRNA
Physical Description:	Clear, colorless solution
Batch/Lot No.:	MTDS16027
Concentration:	2.22 mg/mL / 1.95 mg/mL (used for calculations) *
Retest Date:	Oct 2017
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

* Corrected concentration as per SoA issued on 12 Apr 2017.

4.1.2. Reference Material (Bulk Test Item)

Identification:	mRNA-1647
Physical Description:	0.5 mL per vial, white to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP17015
Concentration:	2.7 mg/mL / 2.4 mg/mL (used for calculations) **
Purity (RP-HPLC):	96.9%
Particle Size:	63 nm
Date of Manufacture:	24 Feb 2017
Retest Date:	24 Feb 2018
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

** Re-calculated concentration as per SoA issued on 31 May 2017.

4.1.3. Characterization of Reference Standard and Reference Material

The Sponsor provided the documentation for the identity, strength, purity, composition, and stability for the reference standard and reference material. Copies of the supplied Summary of Analysis (SoA) or equivalent documentation are presented in Appendix 2.

Appendix 3

4.1.4. Inventory and Disposition of Reference Standard and Reference Material

Records of the receipt, distribution, and storage of the reference standard and reference material were maintained. All unused Sponsor-supplied reference standard and reference material were retained for use on subsequent studies for the Sponsor.

4.2. Methods

4.2.1. Analytical Procedures

The method for concentration analysis is documented in Analytical Procedure AP.5002034.SP.02 (Appendix 1) and was previously validated under Study Nos. 1802050. Concentration stability data were generated by the department of Analytical Chemistry, Charles River, CR MTL for 1 day, 6 days, and 8 days, for formulation samples stored at ambient temperature, in a refrigerator set to maintain 4°C and in a freezer set to maintain a temperature of -20°C, respectively, over the concentration range of 0.00888 – 2.40 mg/mL, under Study No. 1802050.

The methods for purity analysis and particle size analysis are documented in Analytical Procedures AP.5002034.PU.03 and AP.5002034.DLS.02 (Appendix 1), respectively.

4.3. Computerized Systems

Critical computerized systems used in this study phase are listed below (see Text Table 1).

Text Table 1
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Empower 3 (Waters Corporation)	Build 3471 SR1	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
Dynamics (Wyatt)	7.1.9.3	Data acquisition for particle size analysis for the test item using DLS
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

5. RESULTS AND DISCUSSIONS

All results presented in the tables of the report are calculated using non-rounded values as per the raw data rounding procedure and may not be exactly reproduced from the individual data presented.

Appendix 3

5.1. Dose Formulation Analysis

All study samples analyzed had mean concentrations within or equal to the acceptance criteria of ± 15% (individual values within or equal to ± 20%) of their theoretical concentrations. Results are presented in Table 1.

For homogeneity, the RSD of concentrations for all samples in each group tested was within the acceptance criteria of ≤ 5%. Results are presented in Table 1.

5.2. Bulk Test Item Analysis

The concentration, purity and particle size was measured. Concentration, purity and particle size results were consistent with the initial Certificate of Analysis provided by the Sponsor. Results are presented in Table 2, Table 3 and Table 4.

6. CONCLUSION

The dose formulations were within specification. Homogeneity testing showed that the formulation technique used produced homogeneous preparations.

The bulk Test Item analysis demonstrated that the test item was suitable for use during the study period.

Appendix 3

7. REPORT APPROVAL

(b) (6)

(b) (6)

Date: 11 Sep 2017

Appendix 3

Table 1 Study Samples - Concentration and Homogeneity

Occasion (Sampling Date)	Group	Theoretical Concentration (mg/mL)	Sampling Location	Measured Concentration (mg/mL)	Percent of Theoretical	RSD (%)
Day 1 (22 Mar 2017)	1	(b) (4)	Middle	ND	-	-
				ND	-	
			Mean	ND	-	-
	2		Top	(b) (4)		
			Middle			
			Bottom			
			Mean			
	3		Top			
			Middle			
			Bottom			
			Mean			
	4		Top			
			Middle			
			Bottom			
			Mean			
Day 43 (04 May 2017)	1		Middle	ND	-	-
				ND	-	
			Mean	ND	-	
	2		Middle	(b) (4)		-
			Mean			
	3		Middle			-
			Mean			
	4		Middle			-
			Mean			

ND = None detected.
[a] Re-calculated theoretical dose concentration as per SoA issued on 31 May 2017.

Appendix 3

Table 2 Bulk Test Item - Concentration

Occasion (Analysis Date)	Theoretical Concentration	Measured Concentration	Percent of	Mean Measured Concentration
End of study (09 May 2016)	(b) (4)			

Table 3 Bulk Test Item - Particle Size Analysis

Occasion (Analysis Date)	Theoretical Diameter (nm)	Measured Diameter (nm)	PD Index	% Difference Between Duplicate	Mean Measured Diameter (nm)
End of study (09 May 2017)	(b) (4)				

Appendix 3

Table 4 Bulk Test Item - Purity Analysis

Occasion (Analysis Date)	Theoretical Purity (%)	Replicate	Peak Id	Peak area (%)	Total Peak Area (%)	Mean Purity (%)
End of study (16 Jun 2017)	96.9	1	CX-005128	(b) (4)		
			CX-000359			
			CX-000712			
			CX-000594			
			CX-005282			
			CX-000667			
		2	CX-005128			
			CX-000359			
			CX-000712			
			CX-000594			
			CX-005282			
			CX-000667			
		3	CX-005128			
			CX-000359			
			CX-000712			
			CX-005282			
			CX-000667			
			CX-005128			

Appendix 3

Appendix 1
Analytical Procedures

Appendix 3

Analytical Procedure (AP.5002034.SP.02)

Determination of mRNA-1647 in Dose Formulations by Ion Exchange High Performance Chromatography Using Ultraviolet/Visible Detection

Reference Standard, Reference Material and Vehicle

Reference Standard	CX-0005128 mRNA (API)
Lot number	MTDS16027
Concentration (actual)	1.95 mg/mL
Reference Material	mRNA-1647
Description	White dispersion in lipid nanoparticles
Lot number	MTDP17015
Concentration (nominal)	2.4 mg/mL (to be used for calculations)
Vehicle	Phosphate-buffered Saline (PBS) pH 7.2

For storage conditions for reference standard and reference material supplied by the Sponsor, refer to the corresponding log sheets.

NOTES:

- ❑ Modifications may be made to the chromatographic conditions in order to optimize the chromatography.
- ❑ Solution volumes throughout this AP (including reagent solutions, blanks, standard stocks, standards and spiked samples) may be scaled up or down as long as the final concentration remains the same as specified in the procedure.
- ❑ Any changes made are to be documented in the raw data of the run.
- ❑ Unless otherwise indicated, information relating to the time of mixing/stirring, temperature or mixing method used in the preparation of solutions, diluents, mobile phases and vehicle will be considered non-critical. If a step is deemed critical, it will be noted within the procedure, and a positive entry will be made in the raw data
- ❑ **The compound is a mRNA, benchwork and handling should be performed under clean conditions to limit RNase contamination. When possible use RNase free tubes, pipette and repeater tips for reference standard/test item dilutions. DO NOT VORTEX, mix manually by inversion.**
- ❑ The method was previously validated under study 1802050.

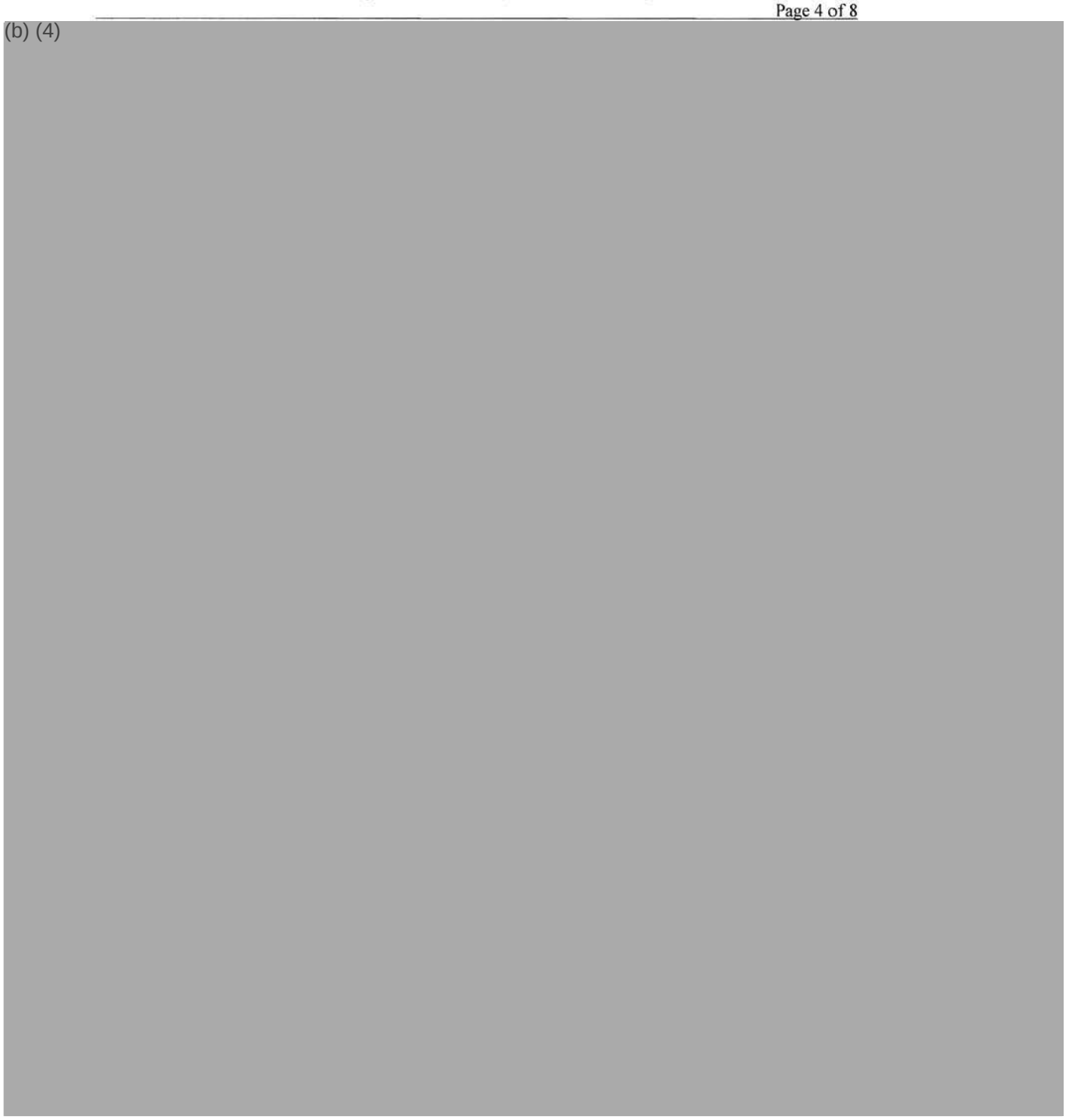
Appendix 3

(b) (4)

Appendix 3

Appendix 3

(b) (4)

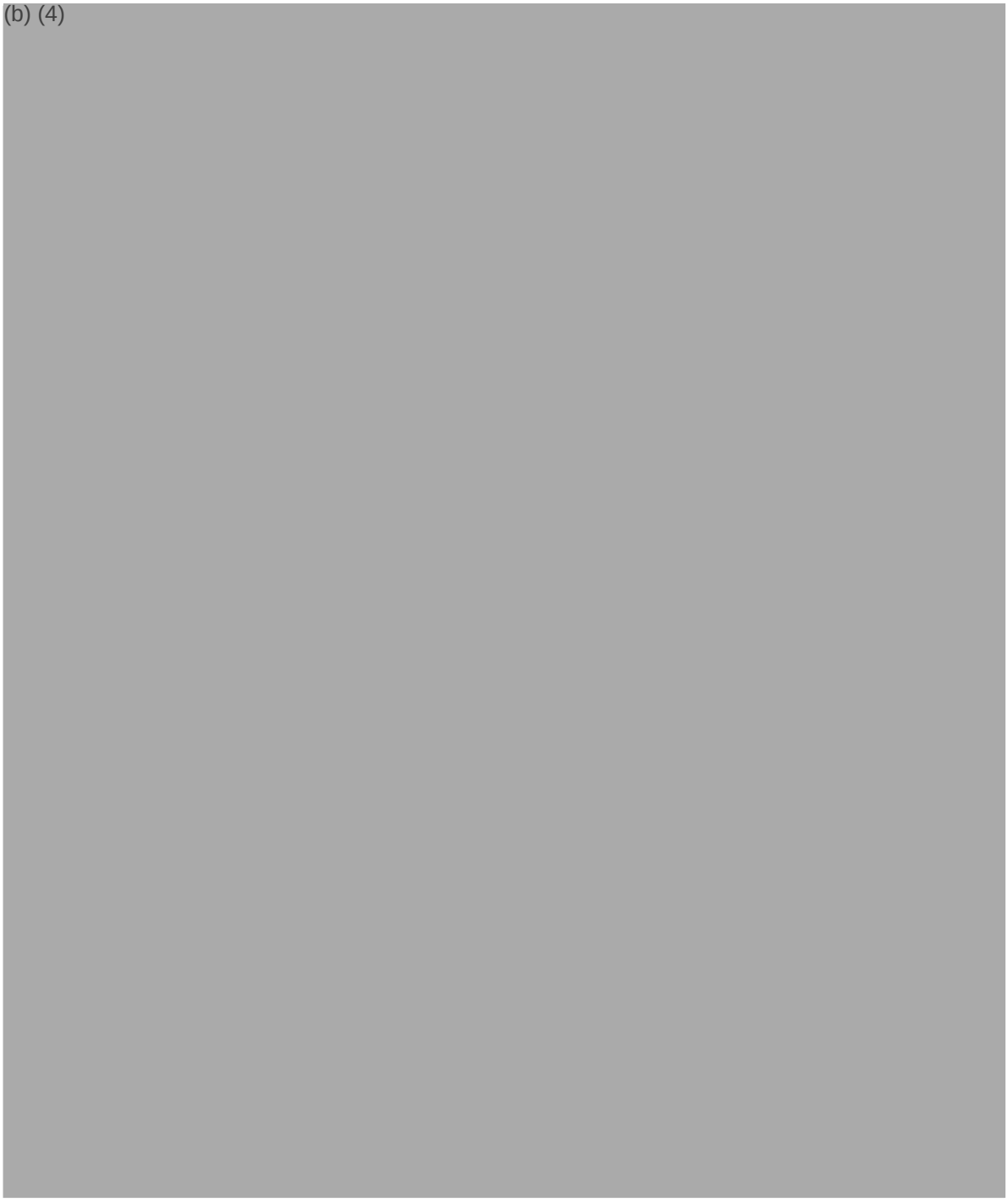


Appendix 3

(b) (4)

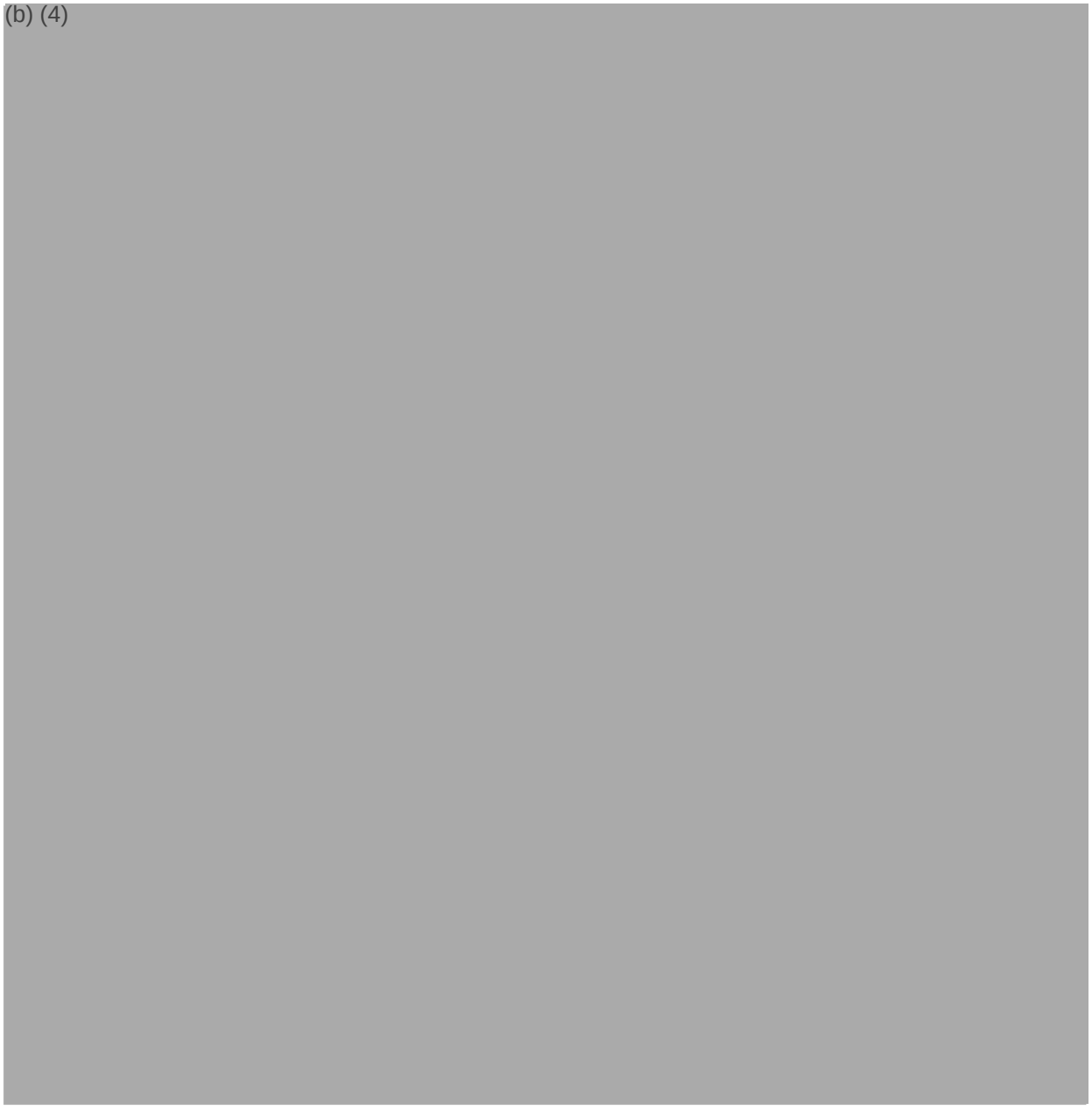
Appendix 3

(b) (4)



Appendix 3

(b) (4)



Appendix 3

Analytical Procedure (AP.5002034.SP.02)

AP Version Control

First update:
- Updated actual concentration of the reference standard and reference material as per latest summary of analysis (SoA); updated concentrations throughout the AP accordingly.
- Updated sample concentrations in Table 3 and 4 as per Study Plan amendment 05.
- Included all missing expiry periods.
- Updated wording of "test item" for "reference material" in the spike preparation.

Verified by (b) (6) Date 28 Jun 2017

Approved by Date 28 Jun 2017

Authorized by Date 28 Jun 2017

Scientific Director ☑

Appendix 3

Analytical Procedure (AP.5002034.PU.03)

Determination of the Purity of mRNA-1647 Drug Product by Reversed Phase High Performance Chromatography Using Ultraviolet/Visible Detection

Reference Standards

Reference Standard 1	CX-005128 mRNA
Lot number	MTDS16027
Concentration (actual)	1.95 mg/mL
Reference Standard 2	CX-000359 mRNA
Lot number	MTDS16020
Concentration (actual)	2.28 mg/mL
Reference Standard 3	CX-000712 mRNA
Lot number	MTDS16035
Concentration (actual)	2.33 mg/mL
Reference Standard 4	CX-000594 mRNA
Lot number	MTDS16034
Concentration (actual)	2.40 mg/mL
Reference Standard 5	CX-005282 mRNA
Lot number	MTDS16033
Concentration (actual)	2.29 mg/mL
Reference Standard 6	CX-000667 mRNA
Lot number	MTDS16019
Concentration (actual)	2.28 mg/mL

Bulk Test Item

Identity	mRNA-1647
Description	White dispersion in lipid nanoparticles, 0.5 mL/vial
Lot number	MTDP17015
Concentration (nominal)	2.4 mg/mL (to be used for calculations)
Vehicle	Phosphate-buffered Saline (PBS) pH 7.2

For storage conditions for reference standard and reference material supplied by the Sponsor, refer to the corresponding log sheets.

Appendix 3

Analytical Procedure (AP.5002034.PU.03)

HPLC Conditions

(b) (4)

Representative Chromatogram

(b) (4)

Appendix 3

Analytical Procedure (AP.5002034.PU.03)

Page 3 of 7

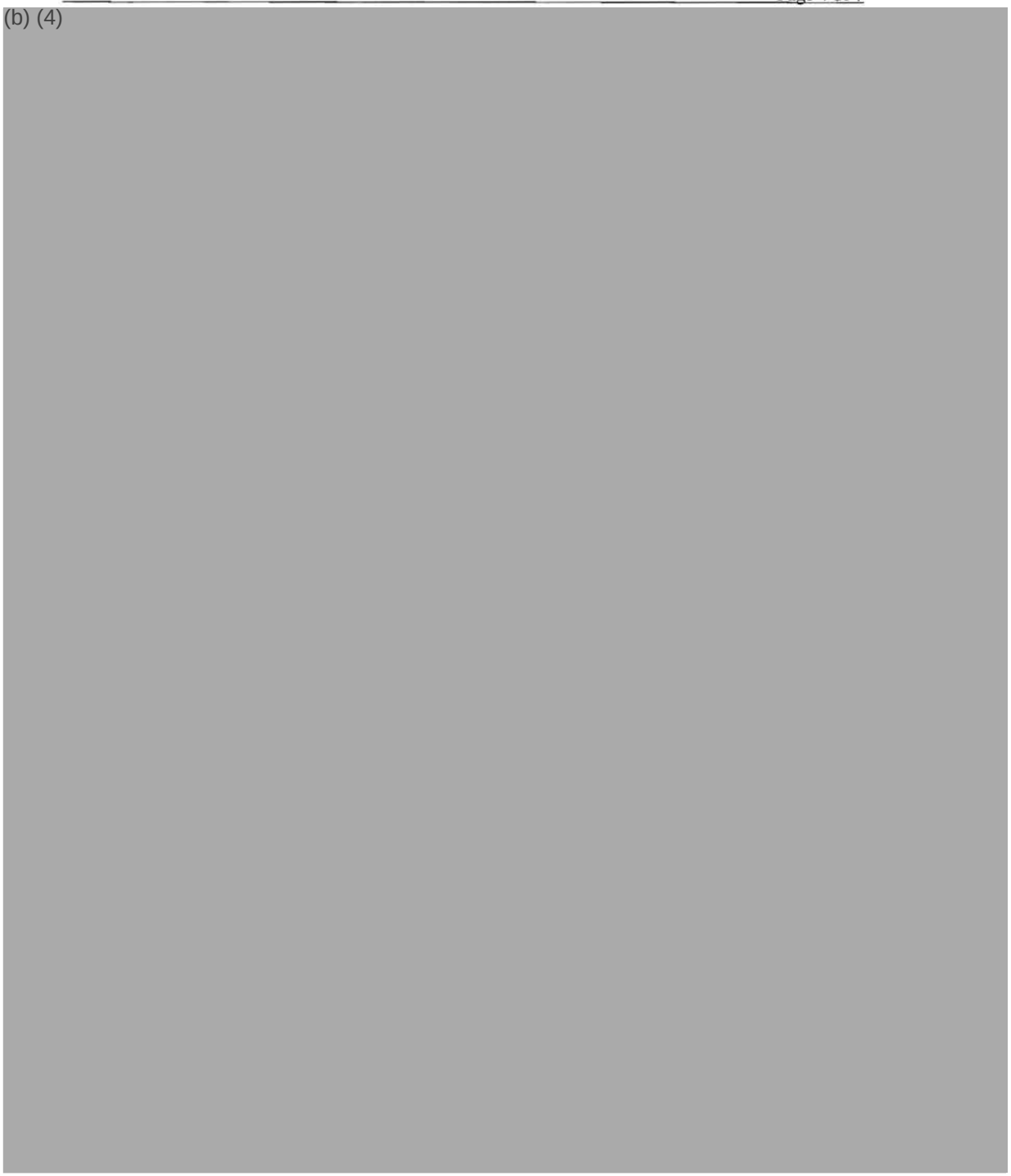
NOTES:

- Modifications may be made to the chromatographic conditions in order to optimize the chromatography.
- Solution volumes throughout this AP (including reagent solutions, blanks, standard stocks, standards and spiked samples) may be scaled up or down as long as the final concentration remains the same as specified in the procedure.
- Any changes made are to be documented in the raw data of the run.
- Unless otherwise indicated, information relating to the time of mixing/stirring, temperature or mixing method used in the preparation of solutions, diluents, mobile phases and vehicle will be considered non-critical. If a step is deemed critical, it will be noted within the procedure, and a positive entry will be made in the raw data
- **The compound is a mRNA, benchwork and handling should be performed under clean conditions to limit RNase contamination. When possible use RNase free tubes, pipette and repeater tips for reference standard/test item dilutions. DO NOT VORTEX, mix manually by inversion.**
- The method was previously qualified under study 1802160.

(b) (4)

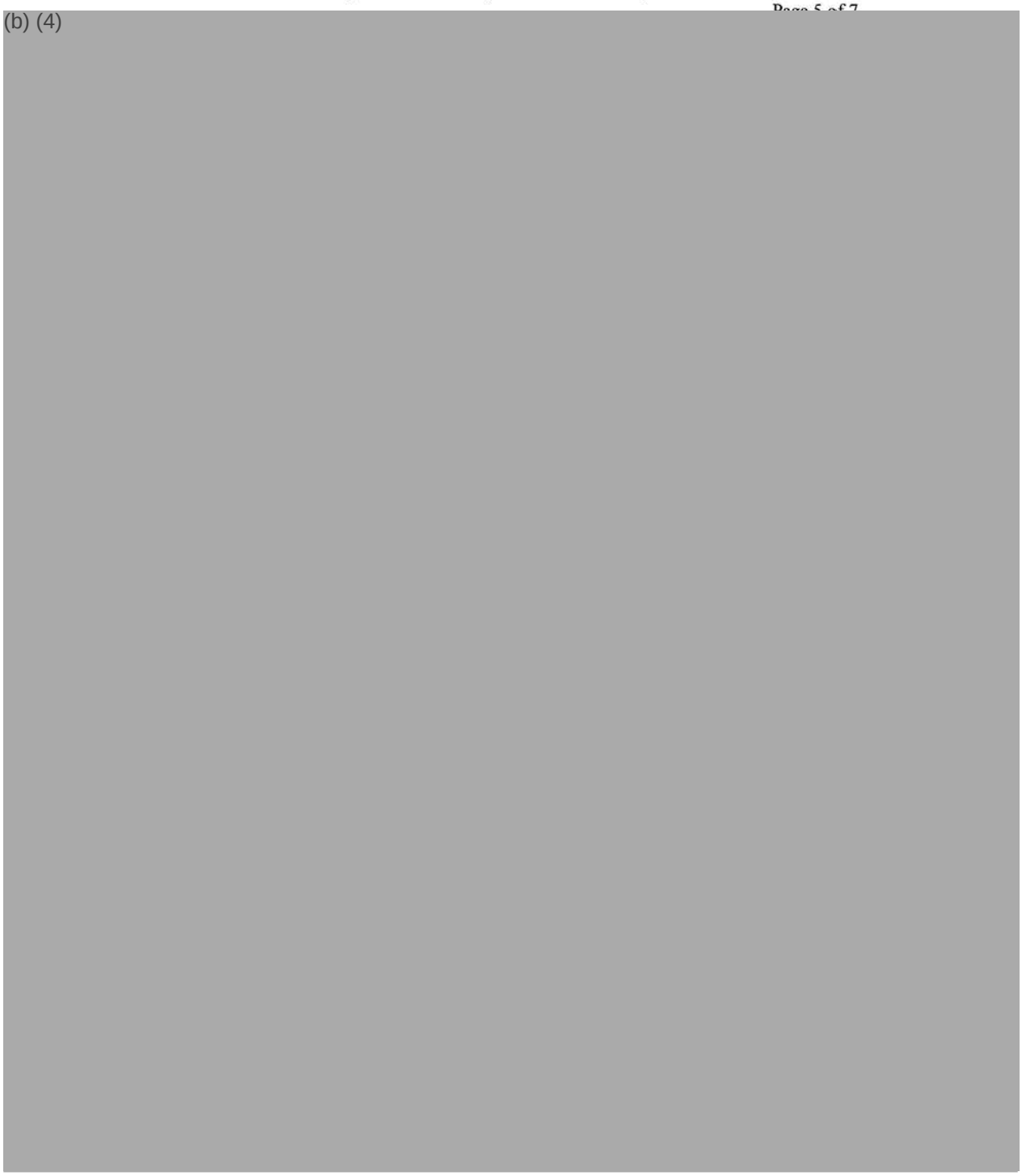
Appendix 3

(b) (4)



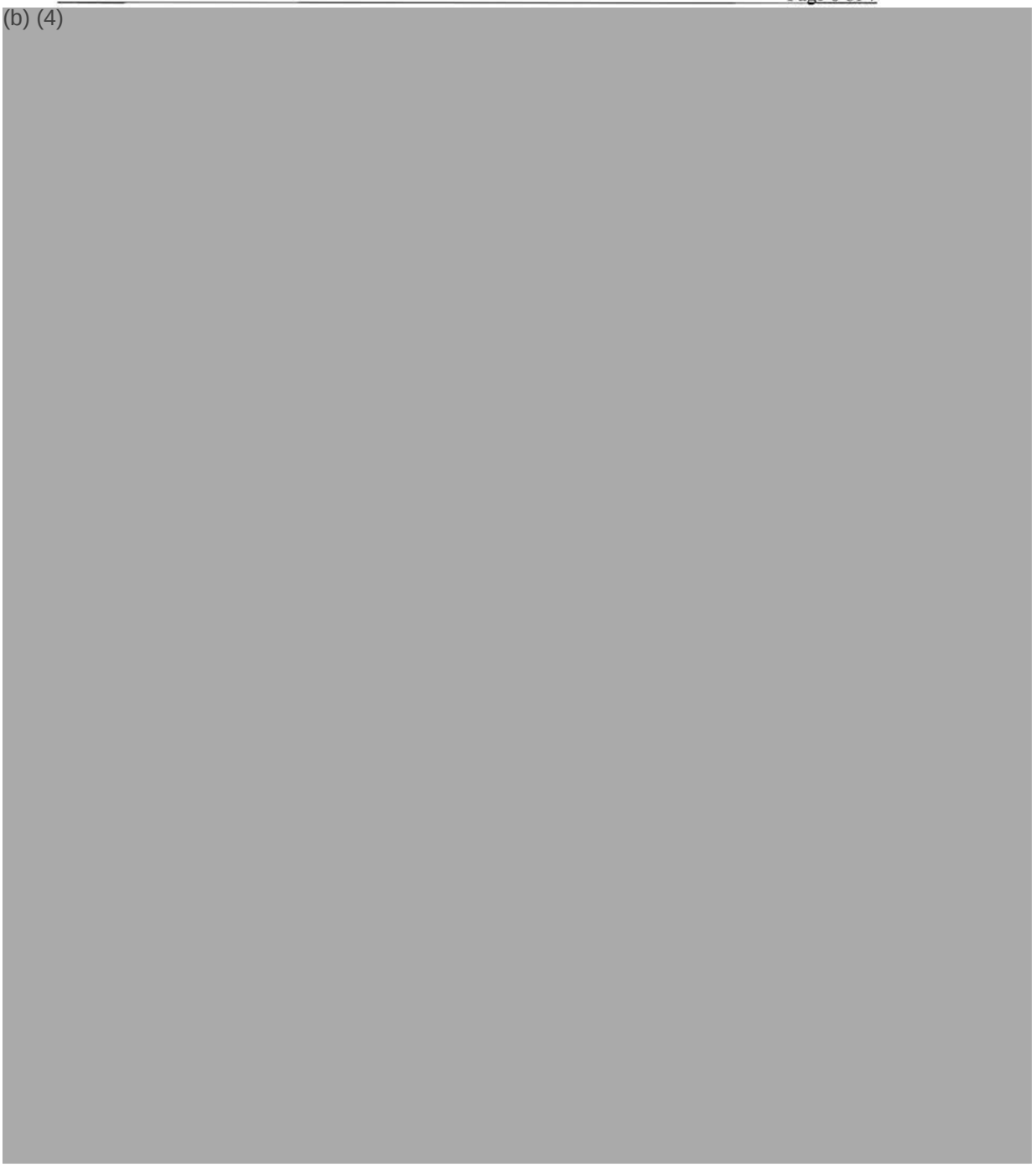
Appendix 3

(b) (4)



Appendix 3

(b) (4)



Appendix 3

Analytical Procedure (AP.5002034.PU.03)

AP Version Control

First update:
- Updated the gradient to optimize the chromatography.
- Updated the preparation of Mobile phase B (removal of sodium phosphate).
- Updated the expiry period of the diluent.

Second update:
- Updated concentration of the bulk test item throughout the AP.
- Updated concentration for CX-005128.
- Included the "blank" in the injection sequence.
- Corrected some reference standard names on Page 1.
- Updated the RSD criteria for system suitability with CX-005128 for consistency with sample variability criteria.

Verified by (b) (6) Date 22 Aug 2017

Approved by (b) (6) Date 22 Aug 2017

Authorized by (b) (6) Date 22 Aug. 2017

Scientific Director

Appendix 3

Analytical Procedure (AP.5002034.DLS.02)

Determination of the Particle Size Distribution of mRNA-1647 Drug Product by Dynamic Light Scattering (DLS) using Wyatt DynaPro NanoStar.

Bulk Test Item

Identity	mRNA-1647
Description	White dispersion in lipid nanoparticles
Lot number	MTDP17015
Concentration (nominal)	2.4 mg/mL (to be used for calculations)

For storage conditions for test item supplied by the Sponsor, refer to the corresponding log sheets.

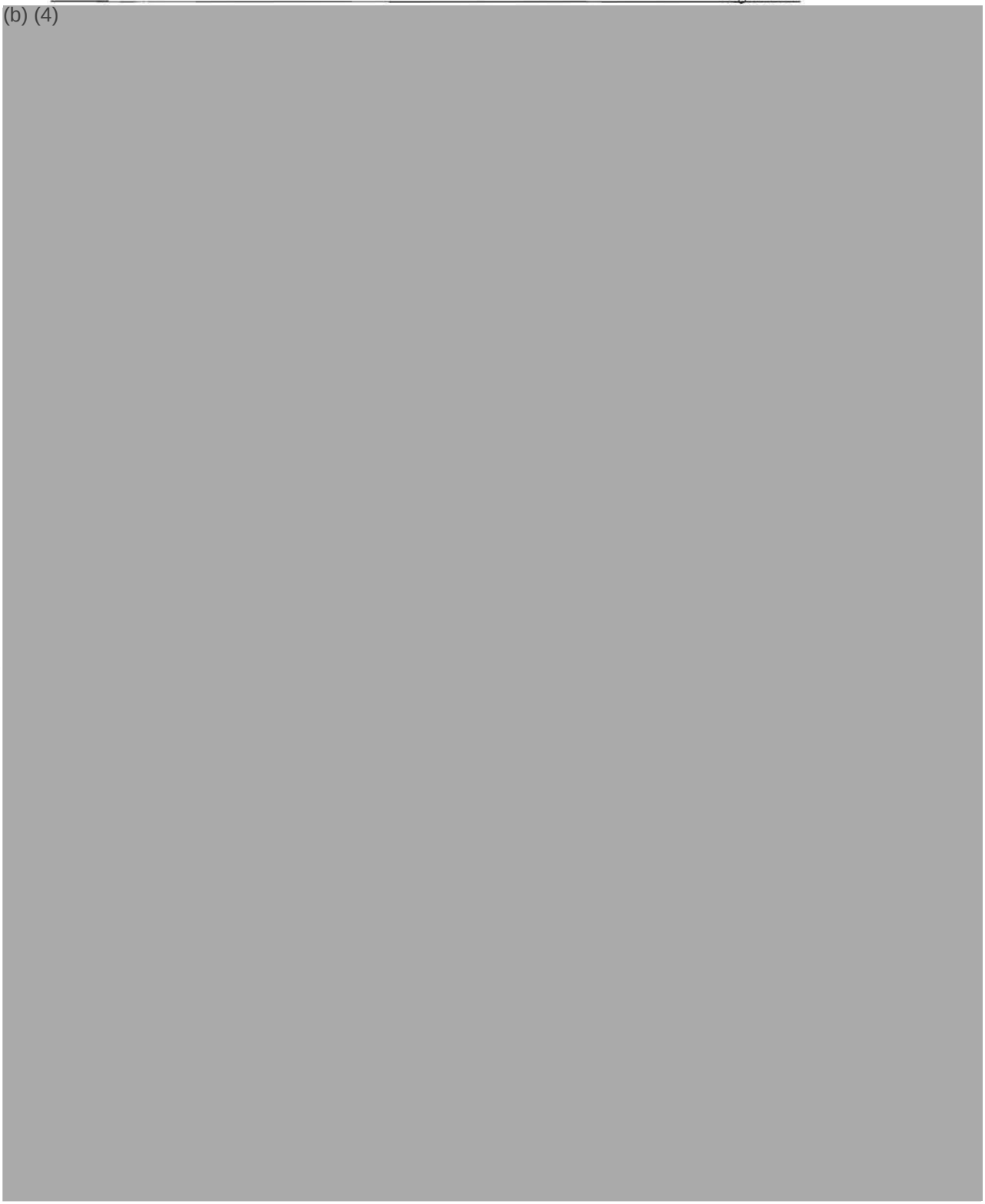
NOTES:

- ❑ Solution volumes throughout this AP may be scaled up or down as long as the final concentration remains the same as specified in the procedure.
- ❑ Any changes made are to be documented in the raw data of the run.
- ❑ Unless otherwise indicated, information relating to the time of mixing/stirring, temperature or mixing method used in the preparation of solutions will be considered non-critical. If a step is deemed critical, it will be noted within the procedure, and a positive entry will be made in the raw data
- ❑ **The compound is a mRNA, benchwork and handling should be performed under clean conditions to limit RNase contamination. When possible use RNase free tubes, pipette and repeater tips for test item dilutions. DO NOT VORTEX, mix manually by inversion.**
- ❑ Refer to SOP CAE-238 for operation of the Dynapro Nanostar DLS instrument with Dynamics software.

(b) (4)

Appendix 3

(b) (4)

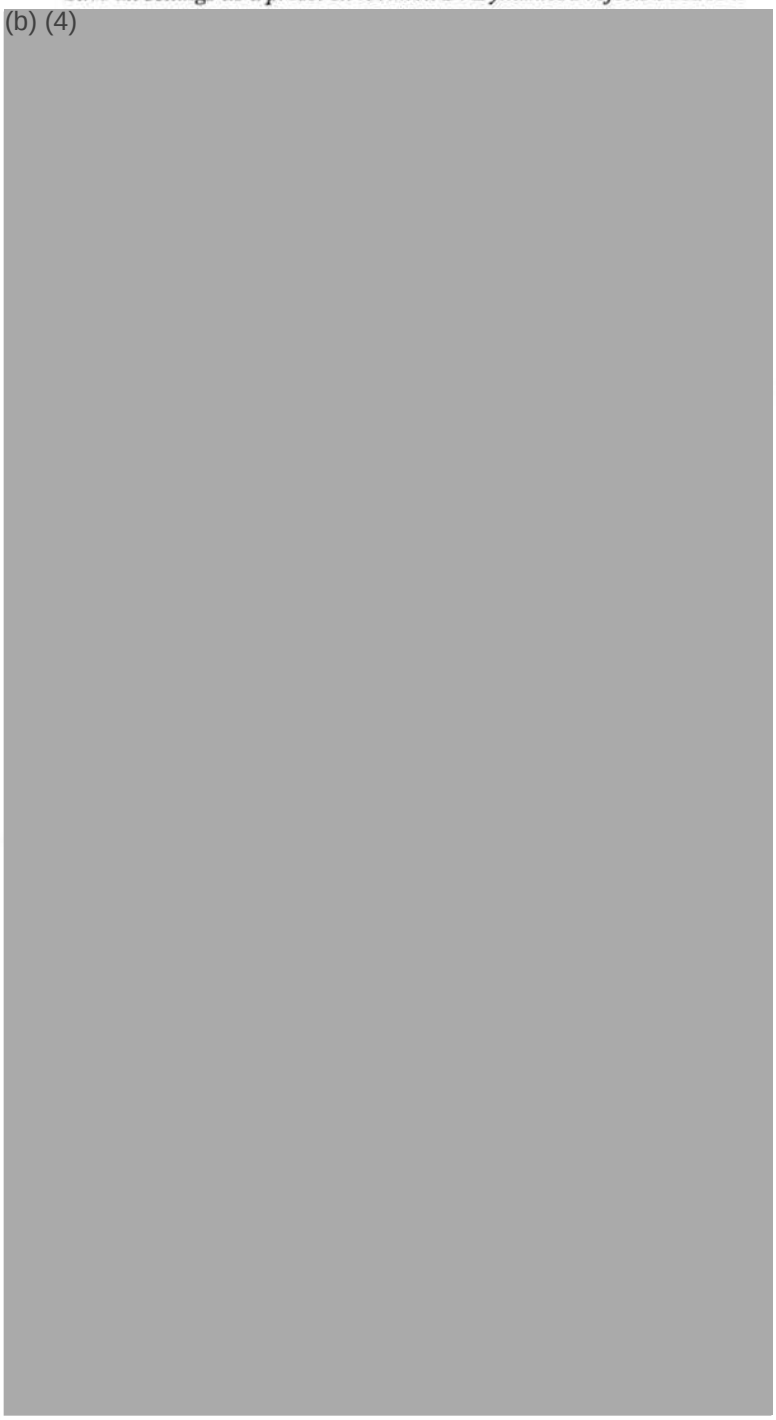


Appendix 3

Instrument Parameters for Sample Reading

Save all settings as a preset on location D:\Dynamics\Projects\5002034.

(b) (4)



Appendix 3

(b) (4)

[redacted]

AP Version Control

First update:

• Updated the concentration of the Test Item throughout the AP and reading concentration in Table 2.

Verified by [redacted] (b) (6) Date 10 August

Approved by [redacted] Date 10 Aug 2017

Authorized by [redacted] Date 10 Aug. 2017

Scientific Director

Appendix 3

Appendix 2
Certificates of Analysis

Appendix 3

Document Number: DSAD-SOA-0025 Version: 3.0 Final Date: 13 Apr 2017
CX-005128 MTDS16027 SoA

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Phone 617.714.6500 • Fax 617.583.1998

SUMMARY OF ANALYSIS

Sample Description:	CX-005128 mRNA (mRNA API)
mRNA length:	(b)
SCC:	32.60 µg/mL
Plasmid ID:	PL-011212
Lot or Batch No:	**MTDS16027**
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	October 2016
Date of Analysis:	October 2016
Storage:	Shipping Temperature: ≤ -15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	October 2017

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Identity	RT/Sanger Sequencing TSOP134.03	Sequence matches 100% description of the coding region	Sequence matches 100% description of the coding region	209-TSOP134-145.00
Appearance	SOP-0045, v1.0	Clear, colorless solution, no visible particulates	Clear, colorless solution, no visible particulates	2016_10_13-103-(b) (6)
Total RNA content	DSAD-TM-0019*	(b) (4)		2016_10_13-103-(b) (6)
Purity	DSAD-TM-0010			2016_10_13-103-(b) (6)
Product related impurities	DSAD-TM-0010	Report % Pre-main peak and % Post-main areas	(b) (4)	2016_10_13-103-(b) (6)
pH	SOP-0046, v1.0	(b) (4)		2016_10_13-103-(b) (6)
Residual DNA template	qPCR TSOP344.01			209-TSOP344-146.00
Residual total protein	SOP-0182, v0.1			2016_11_07-020-(b) (6)

CX-005128 Page 1 of 2 version 03

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Appendix 3

Document Number: DSAD-SOA-0025 Version: 3.0 Final Date: 13 Apr 2017
CX-005128 MTDS16027 SoA

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Residual solvents TEA IPA Ethanol Hexylene glycol	 SOP-0185, v0.1 SOP-0183, v0.1 SOP-0183, v0.1 SOP-0184, v0.1	Report results	(b) (4) 2016_12_13-029-(b) (6) 2016_10_21-018-(b) (6) 2016_10_21-018-(b) (6) 2016_12_13-031-(b) (6)
% Poly A tailed RNA (% Tailless RNA)	DSAD-TM-0013	Report % main peak area	2016_10_13-103-(b) (6)
% 5' Capped	DSAD-TM-0021	(b) (4)	2016_10_13-103-(b) (6)
Bacterial Endotoxins	USP<85>		PD Batch Record MTDS16027
Bioburden	USP<61>		) (4)

(b) (4) (Reference: 2016_10_13-103 (b) (6)

Signatures:

(b) (6)
Generated by: (b) (6) Date: 12 April 17

(b) (6)
Reviewed by: (b) (6) Date: 12 APR 2017

Appendix 3

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Summary of Analysis

Document number	DPAD-SOA-0002
Date of Document Generation	30 May 2017
Revision	002
Product\Test Article	mRNA-1647 (CVM 1-6) in 100 mM TRIS 60 mM NaCl 7% (w/v PG) 2.4 mg/mL , 0.5mL Fill volume
Lot No.	MTDP17015
Moderna Protocol	DPAD-PRO-0003
Drug Substance (API)	See Table Below
Date of Manufacture	24 Feb 2017
Stability Initiation Date	13 Mar 2017
Stability Time Point	T=0, Release

CMV Construct #	CX Number	Drug Substance Lot	Construct Name
1	CX000667	MTDS16019	gB
2	CX000359	MTDS16020	UL128
3	CX000594	MTDS16034	gL
4	CX000712	MTDS16035	UL130
5	CX005282	MTDS16033	gH
6	CX005128	MTDS16027	UL131A

Test	Method	Testing Reference	Target Attributes	Results
mRNA Content	(b) (4) (DPTM-024.2)	2017_03_12-003	(b) (4)	
Endotoxin	USP <85>	0317-022 (ACCI)		
Bioburden	USP <61>	949975-S01 (Nelson Labs)		

Author: (b) (6) (b) (6) Date: 30 May 2017

Data reviewed: (b) (6) Date: 31-MAY-17

Data generated in accordance with standard Moderna Therapeutics laboratory Practices and have been verified for accuracy

Appendix 3

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Summary of Analysis

Document number	DPAD-SOA-0002
Date of Document Generation	15 Jun 2017
Revision	003
Product name	**mRNA-1647 Test Article**
Product description	mRNA-1647 LNP in 100 mM Tris, 60 mM NaCl, 7% PG
Lot No.	**MTDP 17015**
Drug Substance (API)	CX005128 Lot MTDS16027 (UL131) CX000359 Lot MTDS16020 (UL128) CX000712 Lot MTDS16035 (UL130) CX000594 Lot MTDS16034 (gL) CX005282 Lot MTDS16033 (gH) CX000667 Lot MTDS16019 (gB)
Date of Manufacture	24-Feb-2017
Re-test Date	24-Feb-2018
Time Point	T = Initial

Test	Method	Testing Reference	Target Attributes	Results
Appearance	Visual	2017_03_16-005	White to off-white dispersion, no visible particulates	Conforms
mRNA Identification	qPCR	Outsourced	Matches target sequences	Conforms
mRNA Content	(b) (4)	2017_03_12-003	(b) (4)	
mRNA ratio	qPCR	Outsourced	Report results	CX005128 Lot MTDS16027 (UL131)(b) CX000359 Lot MTDS16020 (UL128)(4) CX000712 Lot MTDS16035 (UL130) CX000594 Lot MTDS16034 (gL)(b) CX005282 Lot MTDS16033 (gH(4) CX000667 Lot MTDS16019 (gB)
mRNA Purity	RP-IP-HPLC (Length-based)	2017_03_15-015	Report gB and gH Concentrations	(b) (4)
	RP-HPLC (% Poly A Tail)	2017_03_15-015	Report results	
% Encapsulation	(b) (4)	2017_03_12-007	(b) (4)	
Particle Size	Dynamic Light Scattering	2017_03_12-005		

Doc: DPAD-SOA-0001.4 *Page 1 of 2*

Appendix 3

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Polydispersity	Dynamic Light Scattering	2017_03_12-005	Report results	(b) (4)
Lipid	UPLC-CAD	2017_03_12-002	Lipid / Target Concentration (mg/mL): SM102, Cholesterol, DSPC, PEG-DMG, Total Impurity (% Area) — (b) (4); Report	Lipid / Concentration (mg/mL): SM102, Cholesterol, DSPC, PEG-DMG, Total Impurity (% Area) — (b) (4)
pH	USP <791>	2017_03_16-005	Report result	(b) (4)
Osmolality	USP <785>	2017_03_16-005	Report result	
Bacterial Endotoxin	USP 85 (b) (4)	IC Number 0317-022	(b) (4)	
Particulate Matter	USP 85	Study Number 949974-S01	Size / Target Number of Particles/mL — (b) (4)	Size / *Number of Particles/mL — (b) (4)
Bioburden	USP <61>	Study Number 949975-S01	TAMC, TYMC / Target CFU/10 mL — (b) (4)	TAMC, TYMC / Target CFU/10 mL — (b) (4)

*Reported value is a pooled result with MTDP17017. The analytical lab provider assumed these lots were to be combined for this test.

Data Approved: (b) (6) (b) (6) **Date:** 22 Jun 2017

Doc: DPAD-SOA-0001.4 *Page 2 of 2*

Appendix 4

Individual Animal Mortality Explanation Page

Abbreviation	Description	Abbreviation	Description
AD or ACCD	Accidental death	REC	Recovery euthanasia
FD	Found dead	REL	Released
INTM	Interim	TE or TERM	Terminal euthanasia
NR	Not recorded	UE or UNSC	Unscheduled euthanasia
		Unsc	Unscheduled examination

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Removal Time represents the time the removal was entered into the Provantis system and may not be representative of the time of death.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 4

Individual Animal Mortality

5002034

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
1	0 ug/dose	Male	1001	1001	44	7	04MAY2017	12:09	.	.	TERM
			1002	1001	44	7	04MAY2017	12:08	.	.	TERM
			1003	1001	44	7	04MAY2017	13:16	.	.	TERM
			1004	1004	44	7	04MAY2017	13:26	.	.	TERM
			1005	1004	44	7	04MAY2017	14:23	.	.	TERM
			1006	1004	44	7	04MAY2017	14:37	.	.	TERM
			1007	1007	44	7	04MAY2017	15:35	.	.	TERM
			1008	1007	44	7	04MAY2017	16:54	.	.	TERM
			1009	1009	44	7	04MAY2017	17:52	.	.	TERM
			1010	1009	44	7	04MAY2017	17:59	.	.	TERM
			1011	1011	57	9	17MAY2017	8:47	.	.	REC
			1012	1011	57	9	17MAY2017	10:17	.	.	REC
			1013	1011	57	9	17MAY2017	12:45	.	.	REC
			1014	1014	43	7	03MAY2017	18:09	Unsc	FD	FD
			1015	1014	57	9	17MAY2017	13:46	.	.	REC
1	0 ug/dose	Female	1501	1501	44	7	05MAY2017	11:46	.	.	TERM
			1502	1501	44	7	05MAY2017	11:47	.	.	TERM
			1503	1501	44	7	05MAY2017	12:56	.	.	TERM
			1504	1504	44	7	05MAY2017	12:58	.	.	TERM
			1505	1504	44	7	05MAY2017	13:58	.	.	TERM
			1506	1504	44	7	05MAY2017	14:04	.	.	TERM
			1507	1507	44	7	05MAY2017	14:59	.	.	TERM
			1508	1507	44	7	05MAY2017	16:24	.	.	TERM
			1509	1509	44	7	05MAY2017	17:12	.	.	TERM
			1510	1509	44	7	05MAY2017	17:27	.	.	TERM
			1511	1511	57	9	18MAY2017	8:55	.	.	REC
			1612	1511	57	9	18MAY2017	9:31	.	.	REC
			1513	1511	57	9	18MAY2017	10:06	.	.	REC
			1514	1514	57	9	18MAY2017	10:41	.	.	REC
			1515	1514	57	9	18MAY2017	11:18	.	.	REC
2	8.9 ug/dose	Male	2001	2001	44	7	04MAY2017	12:59	.	.	TERM
			2102	2001	44	7	04MAY2017	13:08	.	.	TERM
			2003	2001	44	7	04MAY2017	14:04	.	.	TERM
			2004	2004	44	7	04MAY2017	14:20	.	.	TERM
			2005	2004	44	7	04MAY2017	15:14	.	.	TERM

Appendix 4

Individual Animal Mortality

5002034

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
2	8.9 ug/dose	Male	2006	2004	44	7	04MAY2017	16:39	.	.	TERM
			2007	2007	44	7	04MAY2017	17:33	.	.	TERM
			2008	2007	44	7	04MAY2017	17:43	.	.	TERM
			2009	2009	44	7	04MAY2017	18:49	.	.	TERM
			2010	2009	44	7	04MAY2017	18:44	.	.	TERM
2	8.9 ug/dose	Female	2501	2501	44	7	05MAY2017	12:41	.	.	TERM
			2502	2501	44	7	05MAY2017	12:41	.	.	TERM
			2503	2501	44	7	05MAY2017	13:42	.	.	TERM
			2504	2504	44	7	05MAY2017	13:48	.	.	TERM
			2505	2504	44	7	05MAY2017	14:43	.	.	TERM
			2506	2504	44	7	05MAY2017	14:55	.	.	TERM
			2507	2507	44	7	05MAY2017	16:54	.	.	TERM
			2508	2507	44	7	05MAY2017	17:11	.	.	TERM
			2509	2509	44	7	05MAY2017	18:01	.	.	TERM
			2510	2509	44	7	05MAY2017	18:13	.	.	TERM
3	27 ug/dose	Male	3001	3001	44	7	04MAY2017	12:43	.	.	TERM
			3002	3001	44	7	04MAY2017	12:50	.	.	TERM
			3103	3001	44	7	04MAY2017	13:49	.	.	TERM
			3004	3004	44	7	04MAY2017	14:01	.	.	TERM
			3005	3004	44	7	04MAY2017	14:57	.	.	TERM
			3006	3004	44	7	04MAY2017	16:22	.	.	TERM
			3007	3007	44	7	04MAY2017	17:15	.	.	TERM
			3008	3007	44	7	04MAY2017	17:28	.	.	TERM
			3009	3009	44	7	04MAY2017	18:29	.	.	TERM
			3010	3009	44	7	04MAY2017	18:29	.	.	TERM
3	27 ug/dose	Female	3501	3501	44	7	05MAY2017	12:24	.	.	TERM
			3502	3501	44	7	05MAY2017	12:24	.	.	TERM
			3503	3501	44	7	05MAY2017	13:27	.	.	TERM
			3604	3604	44	7	05MAY2017	13:31	.	.	TERM
			3505	3604	44	7	05MAY2017	14:28	.	.	TERM
			3506	3604	44	7	05MAY2017	14:39	.	.	TERM
			3507	3507	44	7	05MAY2017	16:33	.	.	TERM
			3508	3507	44	7	05MAY2017	16:55	.	.	TERM
			3509	3509	44	7	05MAY2017	17:45	.	.	TERM

Appendix 4

Individual Animal Mortality

5002034

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
3	27 ug/dose	Female	3510	3509	44	7	05MAY2017	17:58	.	.	TERM
4	89 ug/dose	Male	4001	4001	44	7	04MAY2017	12:26	.	.	TERM
			4002	4001	44	7	04MAY2017	12:29	.	.	TERM
			4003	4001	44	7	04MAY2017	13:32	.	.	TERM
			4004	4004	44	7	04MAY2017	13:43	.	.	TERM
			4005	4004	44	7	04MAY2017	14:40	.	.	TERM
			4006	4004	44	7	04MAY2017	14:59	.	.	TERM
			4007	4007	44	7	04MAY2017	16:58	.	.	TERM
			4008	4007	44	7	04MAY2017	17:11	.	.	TERM
			4009	4009	44	7	04MAY2017	18:09	.	.	TERM
			4010	4009	44	7	04MAY2017	18:14	.	.	TERM
			4011	4011	57	9	17MAY2017	9:11	.	.	REC
			4012	4011	57	9	17MAY2017	10:40	.	.	REC
			4013	4011	57	9	17MAY2017	13:09	.	.	REC
			4014	4014	57	9	17MAY2017	13:28	.	.	REC
			4015	4014	57	9	17MAY2017	14:13	.	.	REC
4	89 ug/dose	Female	4501	4501	44	7	05MAY2017	12:06	.	.	TERM
			4502	4501	44	7	05MAY2017	12:06	.	.	TERM
			4503	4501	44	7	05MAY2017	13:11	.	.	TERM
			4504	4504	44	7	05MAY2017	13:14	.	.	TERM
			4505	4504	44	7	05MAY2017	14:12	.	.	TERM
			4506	4504	44	7	05MAY2017	14:21	.	.	TERM
			4507	4507	44	7	05MAY2017	16:17	.	.	TERM
			4508	4507	44	7	05MAY2017	16:40	.	.	TERM
			4509	4509	44	7	05MAY2017	17:30	.	.	TERM
			4510	4509	44	7	05MAY2017	17:42	.	.	TERM
			4511	4511	57	9	18MAY2017	9:16	.	.	REC
			4512	4511	57	9	18MAY2017	9:50	.	.	REC
			4513	4511	57	9	18MAY2017	10:22	.	.	REC
			4514	4514	57	9	18MAY2017	10:58	.	.	REC
			4515	4514	57	9	18MAY2017	11:36	.	.	REC

Appendix 5

Individual Clinical Observations Explanation Page

Abbreviation	Description	Abbreviation	Description
AM SIRT	Signs of ill health or reaction to treatment check in the morning	PM SIRT	Signs of ill health or reaction to treatment check in the afternoon
CSO	Cage side observation	PostRx #	Observation post dosing
DE	Detailed examination	PreRx #	Observation predosing
During Rx/R #	Observation during dosing	Unsc #	Unscheduled examination
Vet Aid	Anything observed by Vet Aid	#	Number to avoid using the same timeslot/animal/day

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Only animals with findings are presented in this appendix.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	7 DE	28 DE	35 DE	42 DE	44 DE
1	m	1005	Skin, Scab	Pinna, Left	.	.	.	.	X
		1006	Skin, Red	Pinna, Right	.	.	.	.	X
			Skin, Red	Pinna, Left	.	.	.	.	X
			Skin, Scab	Pinna, Right	.	.	.	.	X
			Skin, Scab	Pinna, Left	.	.	.	.	X
		1014	Fur, Thin Cover	Forepaw, Right	.	X	X	X	.
			Fur, Thin Cover	Forepaw, Left	.	X	X	X	.
		1015	Skin, Red	Tail	X	.	.	.	.
			Skin, Scab	Tail	X	.	.	.	.

Severity Codes: X = Present

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	14 DE	21 DE	28 DE	35 DE	42 DE	44 DE
2	m	2001	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	1
			Fur, Staining, Red	Muzzle	.	.	.	X	X	X	.
			Fur, Staining, Red	Cranium	.	.	.	X	X	X	.
		2102	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	1
			Skin, Red	Pinna, Right	.	.	.	X	.	.	.
			Fur, Erected		.	.	.	.	.	.	X
		2003	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	1
			Skin, Scab	Lumbar	.	.	.	.	X	X	.
		2004	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	1
			Fur, Staining, Red	Cranium	.	.	.	.	.	X	X
		2005	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
			Skin, Scab	Hindlimb, Right	.	.	.	X	X	.	.
			Skin, Scab	Abdominal	.	.	.	X	.	.	.
		2006	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	1
		2007	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	1
			Fur, Erected		.	.	.	.	.	.	X
			Testis, Enlarged	Right	.	.	.	X	.	.	.
		2008	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	1
		2009	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	1
			Skin, Red	Pinna, Right	.	X	X	X	X	X	X
			Skin, Red	Pinna, Left	.	.	.	X	X	X	X
			Skin, Red	Forepaw, Left	.	.	.	.	.	X	X
			Skin, Scab	Pinna, Right	.	X	X	X	X	X	X
			Skin, Scab	Pinna, Left	.	.	.	X	X	X	X
			Skin, Scab	Forepaw, Left	.	.	.	.	.	X	X
			Skin, Scab	Forelimb, Left	.	.	.	.	.	.	X
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	X
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	X
		2010	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
			Skin, Lesion w/ Discharge	Lumbar	1	.	.	.	.	.	.
			Skin, Scab	Lumbar	X	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 8.9 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	7 DE	14 DE	21 DE	28 DE	35 DE	42 DE	44 DE
3	m	3001	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
		3002	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	1
		3103	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
			Swollen Soft	Abdominal	.	.	.	1	1	1	1
			Fur, Erected		.	.	.	.	.	.	X
		3004	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
			Digit Bent	Digit Forepaw, Left	.	.	.	.	.	.	X
		3005	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
		3006	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
			Malocclusion		X	X	X	X	X	X	X
		3007	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
		3008	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
		3009	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3
			Skin, Red	Hindlimb, Right	.	X	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	X	.	.	.	.	.
		3010	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	2
			Fur, Erected		.	.	.	.	.	.	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 3 - 27 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	14 DE	21 DE	28 DE	31 Unsc	35 DE	42 DE	44 DE	45 Unsc	49 DE	56 DE
4	m	4001	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
			Swollen Soft	Hindlimb, Left	.	.	.	3	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	X	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	X	.	.	.	.	.	.
			Skin, Red	Hindlimb, Right	.	.	.	.	.	.	X	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	X	.	.	.	.	.	.
		4002	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
		4003	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	X	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	X	.	.	.
		4004	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
		4005	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
		4006	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
		4007	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	X	.	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	X	.	.	.	.	.	.
			Fur, Staining, Red	Periorbital, Left	X	X	.	.	.	.	.	.	.	.
		4008	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
			Fur, Erected		.	.	.	.	.	.	X	.	.	.
		4009	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	X	.	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	X	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	X	X	.	.	.	.	.	.
		4010	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	3	.	.	.
			Swollen Firm	Hindlimb, Right	.	.	.	.	.	.	1	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	X	.	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	X	.	.	.	.	.	.
		4011	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Right	.	.	.	.	.	.	.	X	.	.

Severity Codes: X = Present; 1 = Slight; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	57 DE
4	m	4001	Swollen Soft	Hindlimb, Right	.
			Swollen Soft	Hindlimb, Left	.
			Skin, Red	Treatment Site No.02	.
			Skin, Red	Treatment Site No.01	.
			Skin, Red	Hindlimb, Right	.
			Skin, Red	Hindlimb, Left	.
		4002	Swollen Soft	Hindlimb, Right	.
		4003	Swollen Soft	Hindlimb, Right	.
			Fur, Staining, Red	Cranium	.
			Fur, Thin Cover	Forelimb, Left	.
		4004	Swollen Soft	Hindlimb, Right	.
		4005	Swollen Soft	Hindlimb, Right	.
		4006	Swollen Soft	Hindlimb, Right	.
		4007	Swollen Soft	Hindlimb, Right	.
			Swollen Firm	Hindlimb, Left	.
			Skin, Red	Treatment Site No.01	.
			Skin, Red	Hindlimb, Left	.
			Fur, Staining, Red	Periorbital, Left	.
		4008	Swollen Soft	Hindlimb, Right	.
			Fur, Erected		.
		4009	Swollen Soft	Hindlimb, Right	.
			Swollen Firm	Hindlimb, Left	.
			Skin, Red	Treatment Site No.01	.
			Skin, Red	Hindlimb, Left	.
			Skin, Scab	Hindlimb, Right	.
		4010	Swollen Soft	Hindlimb, Right	.
			Swollen Firm	Hindlimb, Right	.
			Swollen Firm	Hindlimb, Left	.
			Skin, Red	Treatment Site No.01	.
			Skin, Red	Hindlimb, Left	.
		4011	Swollen Soft	Hindlimb, Right	.
			Skin, Red	Treatment Site No.02	.
			Skin, Red	Hindlimb, Right	.

Severity Codes: X = Present; 1 = Slight; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	14 DE	21 DE	28 DE	31 Unsc	35 DE	42 DE	44 DE	45 Unsc	49 DE	56 DE
4	m	4014	Skin, Scab	Hindlimb, Right	.	.	X	.	X	.	.	.	.	.
		4015	Swollen Soft	Hindlimb, Left	.	.	.	3	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	X	.	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	X	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	X	X	X	.	.	X	X

Severity Codes: X = Present; 1 = Slight; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	57 DE
4	m	4014	Skin, Scab	Hindlimb, Right	.
		4015	Swollen Soft	Hindlimb, Left	.
			Skin, Red	Treatment Site No.01	.
			Skin, Red	Hindlimb, Left	.
			Fur, Staining, Red	Dorsal Cervical	X

Severity Codes: X = Present; 1 = Slight; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	7 DE	21 DE	28 DE	35 DE	38 Unsc	42 DE	44 DE	49 DE	56 DE
1	f	1503	Fur, Thin Cover	Forepaw, Right	.	.	.	X	X	.	X	X	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	X	X	.	X	X	.	.
		1506	Skin, Scab	Pinna, Right	.	.	.	.	X	.	X	X	.	.
			Skin, Scab	Pinna, Left	.	.	.	.	X	.	X	X	.	.
		1509	Fur, Staining, Red	Ventral Cervical	.	.	.	.	X	.	X	X	.	.
		1510	Skin, Red	Treatment Site No.02	.	.	X	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	X	.	.	.	.	.	.	.
			Skin, Red	Hindlimb, Right	.	.	X	.	X	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	X	.	X	.	.	.	.	.
			Skin, Dry	Hindlimb, Right	.	.	X	X	X	.	.	.	.	.
			Skin, Dry	Hindlimb, Left	.	.	X	X	X	.	.	.	.	.
			Skin, Scab	Treatment Site No.02	.	.	X	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	X	.	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	X	X	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Left	.	.	X	X	.	.	.	.	.	.
		1511	Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	X	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	X	.	.	.	X	X
		1612	Skin, Lesion	Tail	2	.	.	.	.	.	.	.	.	.
			Skin, Scab	Tail	X	X	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	.	.	.
		1513	Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Hindpaw, Right	.	.	.	.	X	.	X	.	X	X

Severity Codes: X = Present; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	57 DE
1	f	1503	Fur, Thin Cover	Forepaw, Right	.
			Fur, Thin Cover	Forepaw, Left	.
		1506	Skin, Scab	Pinna, Right	.
			Skin, Scab	Pinna, Left	.
		1509	Fur, Staining, Red	Ventral Cervical	.
		1510	Skin, Red	Treatment Site No.02	.
			Skin, Red	Treatment Site No.01	.
			Skin, Red	Hindlimb, Right	.
			Skin, Red	Hindlimb, Left	.
			Skin, Dry	Hindlimb, Right	.
			Skin, Dry	Hindlimb, Left	.
			Skin, Scab	Treatment Site No.02	.
			Skin, Scab	Treatment Site No.01	.
			Skin, Scab	Hindlimb, Right	.
			Skin, Scab	Hindlimb, Left	.
		1511	Fur, Staining, Red	Ventral Cervical	X
			Fur, Staining, Red	Muzzle	.
			Fur, Staining, Red	Cranium	X
		1612	Skin, Lesion	Tail	.
			Skin, Scab	Tail	.
			Fur, Staining, Red	Ventral Cervical	X
		1513	Fur, Staining, Red	Ventral Cervical	X
			Fur, Thin Cover	Hindpaw, Right	.

Severity Codes: X = Present; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	7 DE	21 DE	28 DE	35 DE	38 Unsc	42 DE	44 DE	49 DE	56 DE
1	f	1514	Skin, Red	Treatment Site No.02	.	.	.	.	.	X	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	X	.	.	.	.
			Skin, Red	Hindlimb, Right	.	.	.	.	X	X	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	X	X	.	.	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	.	X	X	X	.	X	.
			Skin, Dry	Hindlimb, Left	.	.	.	.	X	X	X	.	X	.
			Skin, Scab	Treatment Site No.02	.	.	.	.	.	X	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	X	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	X	X	X	.	X	.
			Skin, Scab	Hindlimb, Left	.	.	.	.	X	X	X	.	X	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	.	.	X	X
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	.	.	X	X
		1515	Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	X	.	X	.	X	X
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	X	.	X	.	X	X

Severity Codes: X = Present; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	57 DE
1	f	1514	Skin, Red	Treatment Site No.02	.
			Skin, Red	Treatment Site No.01	.
			Skin, Red	Hindlimb, Right	.
			Skin, Red	Hindlimb, Left	.
			Skin, Dry	Hindlimb, Right	.
			Skin, Dry	Hindlimb, Left	.
			Skin, Scab	Treatment Site No.02	.
			Skin, Scab	Treatment Site No.01	.
			Skin, Scab	Hindlimb, Right	.
			Skin, Scab	Hindlimb, Left	.
			Fur, Staining, Red	Ventral Cervical	X
			Fur, Thin Cover	Forelimb, Right	X
			Fur, Thin Cover	Forelimb, Left	X
		1515	Fur, Staining, Red	Ventral Cervical	X
			Fur, Thin Cover	Forepaw, Right	X
			Fur, Thin Cover	Forepaw, Left	X

Severity Codes: X = Present; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	14 DE	21 DE	28 DE	35 DE	42 DE	44 DE
2	f	2501	Swollen Soft	Hindlimb, Right	.	.	.	.	.	1
		2502	Swollen Soft	Hindlimb, Right	.	.	.	.	.	1
			Fur, Staining, Red	Cranium	X	X	X	X	X	X
		2503	Swollen Soft	Hindlimb, Right	.	.	.	.	.	1
		2504	Swollen Soft	Hindlimb, Right	.	.	.	.	.	1
		2505	Swollen Soft	Hindlimb, Right	.	.	.	.	.	1
		2506	Swollen Soft	Hindlimb, Right	.	.	.	.	.	1
		2507	Swollen Soft	Hindlimb, Right	.	.	.	.	.	1
		2508	Hyperreactive		.	.	.	X	X	X
			Swollen Soft	Hindlimb, Right	.	.	.	.	.	2
		2509	Swollen Soft	Hindlimb, Right	.	.	.	.	.	1
		2510	Swollen Soft	Hindlimb, Right	.	.	.	.	.	1

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 8.9 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-14 Vet Aid	7 DE	21 DE	28 DE	35 DE	42 DE
3	f	3501	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	X	.
			Skin, Scab	Hindlimb, Left	.	.	.	.	X	.
		3502	Caught in Cage	Tail	.	.	.	X	.	.
			Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
			Skin, Lesion	Tail	.	.	.	.	1	.
			Skin, Lesion w/ Discharge	Tail	.	.	.	1	.	.
			Skin, Scab	Tail	.	.	.	.	X	X
			Skin Staining	Tail	.	.	.	.	.	.
		3503	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	X	.	.	.
			Skin, Red	Pinna, Left	.	.	X	.	.	.
			Skin, Red	Hindlimb, Left	.	X	.	.	.	.
			Skin, Scab	Pinna, Right	.	.	X	.	.	.
			Skin, Scab	Pinna, Left	.	.	X	.	.	.
			Skin, Scab	Hindlimb, Left	.	X	.	.	.	.
		3604	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
		3505	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	X
			Skin, Scab	Hindlimb, Left	.	.	.	.	.	X
		3506	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
		3507	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
		3508	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	X	X	X	X
			Fur, Staining, Red	Cranium	.	.	X	X	X	X
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	X	X
		3509	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
			Skin, Scab	Digit Forepaw, Right	.	.	X	.	.	.
			Fur, Thin Cover	Lumbar	X	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	X	X	X	X
			Fur, Thin Cover	Forepaw, Left	.	.	X	X	X	X
		3510	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.
			Swollen Soft	Hindlimb, Left	.	1	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 6 = Brown

Group 3 - 27 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	44 DE
3	f	3501	Swollen Soft	Hindlimb, Right	2
			Skin, Red	Hindlimb, Left	.
			Skin, Scab	Hindlimb, Left	.
		3502	Caught in Cage	Tail	.
			Swollen Soft	Hindlimb, Right	2
			Skin, Lesion	Tail	.
			Skin, Lesion w/ Discharge	Tail	.
			Skin, Scab	Tail	X
			Skin Staining	Tail	6
		3503	Swollen Soft	Hindlimb, Right	2
			Skin, Red	Pinna, Right	.
			Skin, Red	Pinna, Left	.
			Skin, Red	Hindlimb, Left	.
			Skin, Scab	Pinna, Right	.
			Skin, Scab	Pinna, Left	.
			Skin, Scab	Hindlimb, Left	.
		3604	Swollen Soft	Hindlimb, Right	2
		3505	Swollen Soft	Hindlimb, Right	2
			Skin, Scab	Hindlimb, Right	.
			Skin, Scab	Hindlimb, Left	.
		3506	Swollen Soft	Hindlimb, Right	2
		3507	Swollen Soft	Hindlimb, Right	2
		3508	Swollen Soft	Hindlimb, Right	2
			Fur, Staining, Red	Dorsal Cervical	X
			Fur, Staining, Red	Cranium	X
			Fur, Thin Cover	Forepaw, Left	X
		3509	Swollen Soft	Hindlimb, Right	2
			Skin, Scab	Digit Forepaw, Right	.
			Fur, Thin Cover	Lumbar	.
			Fur, Thin Cover	Forepaw, Right	X
			Fur, Thin Cover	Forepaw, Left	X
		3510	Swollen Soft	Hindlimb, Right	2
			Swollen Soft	Hindlimb, Left	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 6 = Brown

Group 3 - 27 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	7 DE	14 DE	17 Unsc	21 DE	28 DE	31 Unsc	35 DE	42 DE
4	f	4501	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	.	X	X	.	.	.
		4502	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.02	.	.	.	X	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	.	X	X	.	.	.
		4503	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Skin, Red	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	.	.	.	.	.	.
		4504	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	X	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	X	X
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	X	X
		4505	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Warm to Touch		.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	X	X
			Skin, Red	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	X	X
		4506	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.	X
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.	X
			Teeth, Broken		X	X	X	.	X	X	.	X	X

Severity Codes: X = Present; 2 = Moderate; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	44 DE	45 Unsc	49 DE	56 DE	57 DE
4	f	4501	Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	.	.
		4502	Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	.	.
		4503	Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Skin, Red	Hindlimb, Right	X	.	.	.	.
			Skin, Dry	Hindlimb, Right	X	.	.	.	.
		4504	Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	X	.	.	.	.
		4505	Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Warm to Touch		X	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Right	X	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	X	.	.	.	.
		4506	Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	X	.	.	.	.
			Teeth, Broken		X	.	.	.	.

Severity Codes: X = Present; 2 = Moderate; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	7 DE	14 DE	17 Unsc	21 DE	28 DE	31 Unsc	35 DE	42 DE
4	f	4507	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
		4508	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.02	.	.	.	X	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
		4509	Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.02	.	.	.	X	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
		4510	Hypersensitive		.	X	X	.	X	X	X	X	X
			Vocalization Increased		.	X	X	.	X	X	X	X	X
			Swollen Soft	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Warm to Touch		.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	X	X	X	X	X
		4511	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
			Skin, Scab	Sacral	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 2 = Moderate; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	44 DE	45 Unsc	49 DE	56 DE	57 DE
4	f	4507	Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
		4508	Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Right	X	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
		4509	Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
		4510	Hypersensitive		X	.	.	.	.
			Vocalization Increased		X	.	.	.	.
			Swollen Soft	Hindlimb, Right	3	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Warm to Touch		X	.	.	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Right	X	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	X	.	.	.	.
		4511	Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
			Skin, Scab	Sacral	.	.	.	.	X
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	X

Severity Codes: X = Present; 2 = Moderate; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	7 DE	14 DE	17 Unsc	21 DE	28 DE	31 Unsc	35 DE	42 DE
4	f	4512	Skin, Red	Treatment Site No.02	.	.	.	X	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	.	.
		4513	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	.	.
		4514	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Swollen Soft	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.02	.	.	.	X	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Right	.	.	.	.	.	.	.	.	X
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	X
			Skin, Dry	Treatment Site No.02	.	.	.	.	X	.	.	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Skin, Dry	Hindlimb, Left	.	.	.	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	.	.	.	X
			Skin, Scab	Hindlimb, Left	.	.	.	.	.	.	.	.	X
		4515	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	X	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Periorbital, Right	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Periorbital, Left	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 2 = Moderate; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Clinical Observations

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	44 DE	45 Unsc	49 DE	56 DE	57 DE
4	f	4512	Skin, Red	Treatment Site No.02	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	X
		4513	Swollen Soft	Treatment Site No.02	.	2	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	X	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	X
		4514	Swollen Soft	Treatment Site No.02	.	2	.	.	.
			Swollen Soft	Hindlimb, Left	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	X	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Right	.	.	.	X	.
			Skin, Red	Hindlimb, Left	.	.	.	X	.
			Skin, Dry	Treatment Site No.02	.	.	.	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	X	X
			Skin, Dry	Hindlimb, Left	.	.	.	X	.
			Skin, Scab	Hindlimb, Right	.	.	X	X	.
			Skin, Scab	Hindlimb, Left	.	.	.	X	.
		4515	Swollen Soft	Treatment Site No.02	.	2	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	X	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.
			Skin, Dry	Hindlimb, Right	.	.	X	.	.
			Skin, Scab	Hindlimb, Right	.	.	X	.	.
			Fur, Thin Cover	Periorbital, Right	.	.	.	.	X
			Fur, Thin Cover	Periorbital, Left	.	.	.	.	X

Severity Codes: X = Present; 2 = Moderate; 3 = Severe

Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment Explanation Page

Score	Erythema (Redness) Description
0	No erythema
1	Very slight erythema (barely perceptible)
2	Mild erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness to slight eschar formation, injuries in depth)
M	Notable dermal lesions (maximized)

Score	Edema (Swelling) Description
0	No edema
1	Very slight edema (barely perceptible)
2	Slight edema
3	Moderate edema
4	Severe edema

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
AVS	Suspected aberrant value	Post Rx	Observation Post dosing
NR	Not recorded	PreRx	Observation predosing
OA	Omitted activity	DE	Detailed examination
		Unsc	Unscheduled examination

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
1	m	1001	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	1	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1002	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1003	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1004	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	1	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1005	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1006	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	1
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1007	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	1	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1008	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
1	m	1001	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1002	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1003	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1004	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1005	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1006	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1007	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1008	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
1	m	1009	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1010	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1011	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	1	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1012	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1013	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	1	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
		1014	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	.
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	.
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	.
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	.
		1015	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
1	m	1009	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1010	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1011	Erythema	Treatment Site No.02	0	0	.	0
			Erythema	Treatment Site No.01	.	0	.	0
			Edema	Treatment Site No.02	2	0	.	0
			Edema	Treatment Site No.01	.	0	.	0
		1012	Erythema	Treatment Site No.02	0	0	.	0
			Erythema	Treatment Site No.01	.	0	.	0
			Edema	Treatment Site No.02	0	0	.	0
			Edema	Treatment Site No.01	.	0	.	0
		1013	Erythema	Treatment Site No.02	0	0	.	0
			Erythema	Treatment Site No.01	.	0	.	0
			Edema	Treatment Site No.02	0	0	.	0
			Edema	Treatment Site No.01	.	0	.	0
		1014	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1015	Erythema	Treatment Site No.02	0	0	.	0
			Erythema	Treatment Site No.01	.	0	.	0
			Edema	Treatment Site No.02	0	0	.	0
			Edema	Treatment Site No.01	.	0	.	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
2	m	2001	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	1	1	0	0	.	0	3
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	2	1	0	0
		2102	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	1	0	0	.	0	3
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	1	1	0	0
		2003	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	0	0	0	.	0	2
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	2	1	0	0
		2004	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	1	0	0	.	0	1
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	2	1	0	0
		2005	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	0	0	.	0	1
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	2	1	0	0
		2006	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	2	0	0	.	0	2
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	2	1	0	0
		2007	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	1	0	0	.	0	2
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	2	1	0	0
		2008	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	1	0	0	.	0	2
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	1	1	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
2	m	2001	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2102	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2003	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2004	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2005	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2006	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2007	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2008	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
2	m	2009	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	1	0	0	.	0	3
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	2	1	0	0
		2010	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	0	0	0	.	0	3
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	2	1	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
2	m	2009	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2010	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
3	m	3001	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	2	2	0	0	.	0	3
			Edema	Treatment Site No.01	.	3	0	0	0	.	0	3	2	0	0
		3002	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	3	2	0	0	.	0	2
			Edema	Treatment Site No.01	.	3	0	0	0	.	0	4	2	0	0
		3103	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	3	0	0	.	0	2
			Edema	Treatment Site No.01	.	3	1	0	0	.	0	2	2	0	0
		3004	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	3	2	0	3	.	0	2
			Edema	Treatment Site No.01	.	3	0	0	0	.	0	3	1	0	0
		3005	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	3	2	0	0	.	0	2
			Edema	Treatment Site No.01	.	3	1	0	0	.	0	3	2	0	0
		3006	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	3	2	0	0	.	0	2
			Edema	Treatment Site No.01	.	3	0	0	0	.	0	3	1	0	0
		3007	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	3	2	0	0	.	0	3
			Edema	Treatment Site No.01	.	3	1	0	0	.	0	3	2	0	0
		3008	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	3	1	0	0	.	0	3
			Edema	Treatment Site No.01	.	3	1	0	0	.	0	3	2	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
3	m	3001	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3002	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3103	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3004	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3005	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3006	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3007	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3008	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
3	m	3009	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	2	0	0	.	0	3
			Edema	Treatment Site No.01	.	3	0	0	0	.	0	3	2	0	0
		3010	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	1	0	0
			Edema	Treatment Site No.02	.	0	.	0	3	2	0	0	.	0	2
			Edema	Treatment Site No.01	.	3	1	0	0	.	0	3	2	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
3	m	3009	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3010	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
4	m	4001	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	1	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	3	0	0	.	0	3
			Edema	Treatment Site No.01	.	4	2	0	0	.	0	4	2	0	0
		4002	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	1	0	.	0	4	3	0	0
		4003	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	1	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	2	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0
		4004	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	2	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0
		4005	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	2	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	2	3	0	0
		4006	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	1	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	3	0	0	.	0	3
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0
		4007	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	2	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0
		4008	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	1	0	0	0	.	0	0	1	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
4	m	4001	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4002	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4003	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4004	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4005	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4006	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4007	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4008	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
4	m	4009	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	1	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	2	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0
		4010	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	1	2	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	4	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0
		4011	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0
		4012	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0
		4013	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	1	0	0
			Edema	Treatment Site No.02	.	0	.	0	3	3	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0
		4014	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	2	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	2	0	0
		4015	Erythema	Treatment Site No.02	.	0	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	0	0	2	0	0
			Edema	Treatment Site No.02	.	0	.	0	4	4	0	0	.	0	4
			Edema	Treatment Site No.01	.	4	1	0	0	.	0	4	3	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
4	m	4009	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4010	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4011	Erythema	Treatment Site No.02	0	0	.	0
			Erythema	Treatment Site No.01	.	0	.	0
			Edema	Treatment Site No.02	2	0	.	0
			Edema	Treatment Site No.01	.	0	.	0
		4012	Erythema	Treatment Site No.02	0	0	.	0
			Erythema	Treatment Site No.01	.	0	.	0
			Edema	Treatment Site No.02	3	0	.	0
			Edema	Treatment Site No.01	.	0	.	0
		4013	Erythema	Treatment Site No.02	0	0	.	0
			Erythema	Treatment Site No.01	.	0	.	0
			Edema	Treatment Site No.02	3	0	.	0
			Edema	Treatment Site No.01	.	0	.	0
		4014	Erythema	Treatment Site No.02	0	0	.	0
			Erythema	Treatment Site No.01	.	0	.	0
			Edema	Treatment Site No.02	2	0	.	0
			Edema	Treatment Site No.01	.	0	.	0
		4015	Erythema	Treatment Site No.02	0	0	.	0
			Erythema	Treatment Site No.01	.	0	.	0
			Edema	Treatment Site No.02	3	0	.	0
			Edema	Treatment Site No.01	.	0	.	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
1	f	1501	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	1	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1502	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1503	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1504	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1505	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1506	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	1	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1507	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1508	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
1	f	1501	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1502	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1503	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1504	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1505	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1506	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1507	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1508	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
1	f	1509	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1510	Erythema	Treatment Site No.02	0	.	.	0	0	0	4	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	4	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1511	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1612	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1513	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1514	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
		1515	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
1	f	1509	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1510	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		1511	Erythema	Treatment Site No.02	0	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	0	0	0	.
			Edema	Treatment Site No.01	.	0	0	.
		1612	Erythema	Treatment Site No.02	0	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	0	0	0	.
			Edema	Treatment Site No.01	.	0	0	.
		1513	Erythema	Treatment Site No.02	0	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	0	0	0	.
			Edema	Treatment Site No.01	.	0	0	.
		1514	Erythema	Treatment Site No.02	0	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	0	0	0	.
			Edema	Treatment Site No.01	.	0	0	.
		1515	Erythema	Treatment Site No.02	0	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	0	0	0	.
			Edema	Treatment Site No.01	.	0	0	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
2	f	2501	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	2	0	0	.	0	1
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	1	0	0	0
		2502	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	1	1	0	0	.	0	1
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	1	1	0	0
		2503	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	1	2	0	0	.	0	2
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	1	0	0	0
		2504	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	1	1	0	0	.	0	2
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	1	1	0	0
		2505	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	1	1	0	0	.	0	2
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	1	1	0	0
		2506	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	1	1	0	0	.	0	1
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	1	0	0	0
		2507	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	1	0	0	.	0	1
			Edema	Treatment Site No.01	1	.	0	0	0	.	0	1	1	0	0
		2508	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	2	0	0	.	0	2
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	1	0	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
2	f	2501	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2502	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2503	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2504	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2505	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2506	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2507	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2508	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
2	f	2509	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	1	2	0	0	.	0	2
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	1	1	0	0
		2510	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	1	1	0	0	.	0	2
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	1	1	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
2	f	2509	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		2510	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
3	f	3501	Erythema	Treatment Site No.02	0	.	.	0	1	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	0	0	.	0	3
			Edema	Treatment Site No.01	3	.	0	0	0	.	0	3	1	0	0
		3502	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	0	0	.	0	2
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	2	1	0	0
		3503	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	2	0	0	.	0	3
			Edema	Treatment Site No.01	3	.	0	0	0	.	0	2	1	0	0
		3604	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	1	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	0	0	.	0	4
			Edema	Treatment Site No.01	3	.	0	0	0	.	0	3	2	0	0
		3505	Erythema	Treatment Site No.02	0	.	.	0	0	1	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	3	0	0	.	0	3
			Edema	Treatment Site No.01	3	.	0	0	0	.	0	2	2	0	0
		3506	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	1	0	0	.	0	3
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	2	1	0	0
		3507	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	2	0	0	.	0	3
			Edema	Treatment Site No.01	3	.	0	0	0	.	0	3	2	0	0
		3508	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	0	0	.	0	3
			Edema	Treatment Site No.01	3	.	1	0	0	.	0	3	2	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
3	f	3501	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3502	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3503	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3604	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3505	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3506	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3507	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3508	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
3	f	3509	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	0	0	.	0	3
			Edema	Treatment Site No.01	3	.	0	0	0	.	0	2	1	0	0
		3510	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	2	2	0	0	.	0	3
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	3	2	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
3	f	3509	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		3510	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
4	f	4501	Erythema	Treatment Site No.02	0	.	.	0	0	1	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	3
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	3	1	0
		4502	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	3	0	0	.	0	3
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	2	0	0
		4503	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	1	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	2	0	0
		4504	Erythema	Treatment Site No.02	0	.	.	0	0	1	0	0	.	1	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	3	4	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	1	0	0	.	0	3	2	2	0
		4505	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	3	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	1	1	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	3	1	0
		4506	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	1	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	3
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	3	3	1	0
		4507	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	1	1	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	3	2	0
		4508	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	1	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	4	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	1	0	0	.	0	4	3	1	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
4	f	4501	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4502	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4503	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4504	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4505	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4506	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4507	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4508	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 Unsc	4	8	16	18	22	30	32	36	44
4	f	4509	Erythema	Treatment Site No.02	0	.	.	0	1	1	0	0	.	0	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	3
			Edema	Treatment Site No.01	2	.	0	0	0	.	0	4	2	0	0
		4510	Erythema	Treatment Site No.02	0	.	.	0	0	1	0	0	.	0	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	1	2	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	4	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	3	1	0
		4511	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	2	1	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	3
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	1	0	0
		4512	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	4	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	2	0	0
		4513	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	1	1	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	3	0	0
		4514	Erythema	Treatment Site No.02	0	.	.	0	1	2	0	0	.	0	1
			Erythema	Treatment Site No.01	1	.	0	0	0	.	0	2	2	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	4	3	1	0
		4515	Erythema	Treatment Site No.02	0	.	.	0	0	0	0	0	.	0	1
			Erythema	Treatment Site No.01	0	.	0	0	0	.	0	0	0	0	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	0	0	.	0	4
			Edema	Treatment Site No.01	4	.	0	0	0	.	0	3	2	0	0

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 5

Individual Local Irritation Assessment

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	46	50	57	57 DE
4	f	4509	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4510	Erythema	Treatment Site No.02	.	.	.	.
			Erythema	Treatment Site No.01	.	.	.	.
			Edema	Treatment Site No.02	.	.	.	.
			Edema	Treatment Site No.01	.	.	.	.
		4511	Erythema	Treatment Site No.02	0	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	2	0	0	.
			Edema	Treatment Site No.01	.	0	0	.
		4512	Erythema	Treatment Site No.02	1	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	3	0	0	.
			Edema	Treatment Site No.01	.	0	0	.
		4513	Erythema	Treatment Site No.02	2	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	3	0	0	.
			Edema	Treatment Site No.01	.	0	0	.
		4514	Erythema	Treatment Site No.02	0	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	2	0	0	.
			Edema	Treatment Site No.01	.	0	0	.
		4515	Erythema	Treatment Site No.02	1	0	0	.
			Erythema	Treatment Site No.01	.	0	0	.
			Edema	Treatment Site No.02	3	0	0	.
			Edema	Treatment Site No.01	.	0	0	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 6

Individual Body Weights Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	TERR	Technical error
AVS	Suspected aberrant value	UPTD	Unable to perform due to technical difficulty
OA	Omitted activity	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day -12	-1	7	14	21	28	35	42
1M	1001	153	264	329	402	453	491	534	564
	1002	154	254	314	371	422	463	496	519
	1003	166	269	332	387	443	475	509	532
	1004	165	267	337	407	456	498	535	570
	1005	159	277	352	430	474	520	550	581
	1006	157	264	330	401	451	501	534	562
	1007	154	235	291	349	399	434	464	486
	1008	163	261	321	381	432	473	509	542
	1009	164	284	357	434	501	544	589	623
	1010	165	278	346	411	470	516	558	591
	1011	151	268	328	383	438	478	505	528
	1012	156	275	347	426	482	541	582	619
	1013	162	272	339	400	445	486	522	556
	1014	162	288	369	456	524	579	625	672
	1015	161	286	354	428	475	509	539	567

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
1M	1001	--	--
	1002	--	--
	1003	--	--
	1004	--	--
	1005	--	--
	1006	--	--
	1007	--	--
	1008	--	--
	1009	--	--
	1010	--	--
	1011	551	564
	1012	657	674
	1013	585	607
	1014	--	--
	1015	592	606

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day -12	-1	7	14	21	28	35	42
2M	2001	154	254	309	368	408	442	471	492
	2102	148	264	325	387	432	473	508	525
	2003	158	263	323	384	432	476	503	536
	2004	162	263	313	363	403	431	452	459
	2005	164	292	355	409	457	496	522	547
	2006	155	259	308	362	404	432	457	487
	2007	165	282	335	398	436	473	498	525
	2008	159	262	321	381	428	465	495	521
	2009	156	255	300	360	397	422	449	479
	2010	162	273	347	432	496	569	615	647

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
2M	2001	--	--
	2102	--	--
	2003	--	--
	2004	--	--
	2005	--	--
	2006	--	--
	2007	--	--
	2008	--	--
	2009	--	--
	2010	--	--

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day -12	-1	7	14	21	28	35	42
3M	3001	156	267	320	382	428	454	481	504
	3002	164	259	302	352	389	418	445	466
	3103	144	250	295	353	392	426	451	475
	3004	158	262	306	368	406	439	473	507
	3005	162	260	310	374	415	453	482	508
	3006	159	255	305	366	408	448	474	506
	3007	163	276	330	395	436	474	503	524
	3008	154	255	321	392	444	498	536	573
	3009	159	255	321	388	446	486	524	567
	3010	164	254	310	371	412	447	480	511

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
3M	3001	--	--
	3002	--	--
	3103	--	--
	3004	--	--
	3005	--	--
	3006	--	--
	3007	--	--
	3008	--	--
	3009	--	--
	3010	--	--

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day -12	-1	7	14	21	28	35	42
4M	4001	163	262	309	378	414	453	481	513
	4002	157	281	343	420	464	518	553	596
	4003	156	266	316	379	414	462	484	525
	4004	153	268	310	392	429	484	507	556
	4005	153	276	336	411	455	501	529	559
	4006	164	269	311	371	397	436	454	483
	4007	152	245	300	364	406	457	493	527
	4008	159	267	315	375	411	454	480	516
	4009	161	273	324	400	435	498	522	564
	4010	161	269	323	389	426	472	495	530
	4011	162	289	332	415	449	491	525	564
	4012	166	281	325	399	430	472	496	536
	4013	164	297	355	424	467	520	543	571
	4014	155	241	293	361	397	443	476	510
	4015	166	284	326	395	428	469	496	530

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
4M	4001	--	--
	4002	--	--
	4003	--	--
	4004	--	--
	4005	--	--
	4006	--	--
	4007	--	--
	4008	--	--
	4009	--	--
	4010	--	--
	4011	586	609
	4012	551	591
	4013	596	631
	4014	531	567
	4015	551	575

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day -13	-1	7	14	21	28	35	42
1F	1501	158	238	265	290	312	334	346	366
	1502	157	229	243	275	292	307	317	337
	1503	150	239	260	269	289	306	318	326
	1504	163	241	264	284	306	326	341	345
	1505	144	210	228	240	261	277	290	294
	1506	146	248	272	308	306	337	350	365
	1507	161	245	267	287	315	337	351	366
	1508	149	209	226	257	273	286	300	314
	1509	147	202	228	244	255	260	276	283
	1510	149	210	236	256	270	273	294	307
	1511	159	205	221	225	242	257	250	262
	1612	164	232	253	273	279	304	319	332
	1513	156	236	255	273	299	320	334	335
	1514	145	224	261	290	304	314	327	341
	1515	161	221	258	285	302	311	334	355

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
1F	1501	--	--
	1502	--	--
	1503	--	--
	1504	--	--
	1505	--	--
	1506	--	--
	1507	--	--
	1508	--	--
	1509	--	--
	1510	--	--
	1511	277	285
	1612	332	350
	1513	353	364
	1514	349	348
	1515	350	352

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day -13	-1	7	14	21	28	35	42
2F	2501	149	218	233	257	263	277	286	288
	2502	157	230	249	267	287	296	306	312
	2503	145	231	265	308	333	362	366	373
	2504	146	195	207	224	227	242	247	251
	2505	154	243	275	317	333	338	363	369
	2506	158	226	249	274	291	315	322	330
	2507	148	209	233	255	268	280	294	301
	2508	156	229	265	291	293	309	321	314
	2509	159	225	243	266	287	319	328	339
	2510	152	233	246	274	292	306	317	329

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
2F	2501	--	--
	2502	--	--
	2503	--	--
	2504	--	--
	2505	--	--
	2506	--	--
	2507	--	--
	2508	--	--
	2509	--	--
	2510	--	--

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day -13	-1	7	14	21	28	35	42
3F	3501	147	209	224	248	264	283	295	305
	3502	149	224	240	259	276	291	290	306
	3503	156	222	246	262	291	305	312	323
	3604	141	226	259	296	319	353	374	384
	3505	158	234	263	284	311	338	347	353
	3506	154	209	234	259	270	290	306	315
	3507	160	202	234	259	279	280	296	312
	3508	150	229	248	265	285	310	323	327
	3509	152	238	278	331	326	345	357	369
	3510	145	209	221	241	245	258	269	276

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
3F	3501	--	--
	3502	--	--
	3503	--	--
	3604	--	--
	3505	--	--
	3506	--	--
	3507	--	--
	3508	--	--
	3509	--	--
	3510	--	--

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day -13	-1	7	14	21	28	35	42
4F	4501	161	230	243	271	290	306	322	341
	4502	155	208	225	245	254	271	280	291
	4503	151	230	253	279	287	309	323	336
	4504	159	218	238	258	262	283	280	296
	4505	157	234	249	281	297	306	328	339
	4506	150	214	229	263	266	288	291	302
	4507	145	219	235	268	280	298	306	319
	4508	153	239	267	302	319	339	357	365
	4509	161	232	248	268	295	313	316	325
	4510	143	225	251	284	295	309	328	341
	4511	160	235	246	274	273	296	299	317
	4512	161	225	246	273	284	302	315	325
	4513	148	233	261	304	312	323	341	363
	4514	145	221	233	254	279	294	299	316
	4515	147	213	216	235	241	255	256	270

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
4F	4501	--	--
	4502	--	--
	4503	--	--
	4504	--	--
	4505	--	--
	4506	--	--
	4507	--	--
	4508	--	--
	4509	--	--
	4510	--	--
	4511	322	330
	4512	329	353
	4513	382	378
	4514	332	340
	4515	279	287

Appendix 7

Individual Body Weight Gains Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	TERR	Technical error
AVS	Suspected aberrant value	UPTD	Unable to perform due to technical difficulty
NC	Not calculable	X	Excluded from mean
OA	Omitted activity		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day							
		Change -12 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
1M	1001	111	65	73	51	38	43	30	--
	1002	100	60	57	51	41	33	23	--
	1003	103	63	55	56	32	34	23	--
	1004	102	70	70	49	42	37	35	--
	1005	118	75	78	44	46	30	31	--
	1006	107	66	71	50	50	33	28	--
	1007	81	56	58	50	35	30	22	--
	1008	98	60	60	51	41	36	33	--
	1009	120	73	77	67	43	45	34	--
	1010	113	68	65	59	46	42	33	--
	1011	117	60	55	55	40	27	23	23
	1012	119	72	79	56	59	41	37	38
	1013	110	67	61	45	41	36	34	29
	1014	126	81	87	68	55	46	47	--
	1015	125	68	74	47	34	30	28	25

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
1M	1001	--
	1002	--
	1003	--
	1004	--
	1005	--
	1006	--
	1007	--
	1008	--
	1009	--
	1010	--
	1011	13
	1012	17
	1013	22
	1014	--
	1015	14

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day Change -12 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
2M	2001	100	55	59	40	34	29	21	--
	2102	116	61	62	45	41	35	17	--
	2003	105	60	61	48	44	27	33	--
	2004	101	50	50	40	28	21	7	--
	2005	128	63	54	48	39	26	25	--
	2006	104	49	54	42	28	25	30	--
	2007	117	53	63	38	37	25	27	--
	2008	103	59	60	47	37	30	26	--
	2009	99	45	60	37	25	27	30	--
	2010	111	74	85	64	73	46	32	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
2M	2001	--
	2102	--
	2003	--
	2004	--
	2005	--
	2006	--
	2007	--
	2008	--
	2009	--
	2010	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day							
		Change -12 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
3M	3001	111	53	62	46	26	27	23	--
	3002	95	43	50	37	29	27	21	--
	3103	106	45	58	39	34	25	24	--
	3004	104	44	62	38	33	34	34	--
	3005	98	50	64	41	38	29	26	--
	3006	96	50	61	42	40	26	32	--
	3007	113	54	65	41	38	29	21	--
	3008	101	66	71	52	54	38	37	--
	3009	96	66	67	58	40	38	43	--
	3010	90	56	61	41	35	33	31	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
3M	3001	--
	3002	--
	3103	--
	3004	--
	3005	--
	3006	--
	3007	--
	3008	--
	3009	--
	3010	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day							
		Change -12 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
4M	4001	99	47	69	36	39	28	32	--
	4002	124	62	77	44	54	35	43	--
	4003	110	50	63	35	48	22	41	--
	4004	115	42	82	37	55	23	49	--
	4005	123	60	75	44	46	28	30	--
	4006	105	42	60	26	39	18	29	--
	4007	93	55	64	42	51	36	34	--
	4008	108	48	60	36	43	26	36	--
	4009	112	51	76	35	63	24	42	--
	4010	108	54	66	37	46	23	35	--
	4011	127	43	83	34	42	34	39	22
	4012	115	44	74	31	42	24	40	15
	4013	133	58	69	43	53	23	28	25
	4014	86	52	68	36	46	33	34	21
	4015	118	42	69	33	41	27	34	21

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
4M	4001	--
	4002	--
	4003	--
	4004	--
	4005	--
	4006	--
	4007	--
	4008	--
	4009	--
	4010	--
	4011	23
	4012	40
	4013	35
	4014	36
	4015	24

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day							
		Change -13 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
1F	1501	80	27	25	22	22	12	20	--
	1502	72	14	32	17	15	10	20	--
	1503	89	21	9	20	17	12	8	--
	1504	78	23	20	22	20	15	4	--
	1505	66	18	12	21	16	13	4	--
	1506	102	24	36	-2	31	13	15	--
	1507	84	22	20	28	22	14	15	--
	1508	60	17	31	16	13	14	14	--
	1509	55	26	16	11	5	16	7	--
	1510	61	26	20	14	3	21	13	--
	1511	46	16	4	17	15	-7	12	15
	1612	68	21	20	6	25	15	13	0
	1513	80	19	18	26	21	14	1	18
	1514	79	37	29	14	10	13	14	8
	1515	60	37	27	17	9	23	21	-5

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
1F	1501	--
	1502	--
	1503	--
	1504	--
	1505	--
	1506	--
	1507	--
	1508	--
	1509	--
	1510	--
	1511	8
	1612	18
	1513	11
	1514	-1
	1515	2

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day							
		Change -13 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
2F	2501	69	15	24	6	14	9	2	--
	2502	73	19	18	20	9	10	6	--
	2503	86	34	43	25	29	4	7	--
	2504	49	12	17	3	15	5	4	--
	2505	89	32	42	16	5	25	6	--
	2506	68	23	25	17	24	7	8	--
	2507	61	24	22	13	12	14	7	--
	2508	73	36	26	2	16	12	-7	--
	2509	66	18	23	21	32	9	11	--
	2510	81	13	28	18	14	11	12	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
2F	2501	--
	2502	--
	2503	--
	2504	--
	2505	--
	2506	--
	2507	--
	2508	--
	2509	--
	2510	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day							
		Change -13 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
3F	3501	62	15	24	16	19	12	10	--
	3502	75	16	19	17	15	-1	16	--
	3503	66	24	16	29	14	7	11	--
	3604	85	33	37	23	34	21	10	--
	3505	76	29	21	27	27	9	6	--
	3506	55	25	25	11	20	16	9	--
	3507	42	32	25	20	1	16	16	--
	3508	79	19	17	20	25	13	4	--
	3509	86	40	53	-5	19	12	12	--
	3510	64	12	20	4	13	11	7	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
3F	3501	--
	3502	--
	3503	--
	3604	--
	3505	--
	3506	--
	3507	--
	3508	--
	3509	--
	3510	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day							
		Change -13 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
4F	4501	69	13	28	19	16	16	19	--
	4502	53	17	20	9	17	9	11	--
	4503	79	23	26	8	22	14	13	--
	4504	59	20	20	4	21	-3	16	--
	4505	77	15	32	16	9	22	11	--
	4506	64	15	34	3	22	3	11	--
	4507	74	16	33	12	18	8	13	--
	4508	86	28	35	17	20	18	8	--
	4509	71	16	20	27	18	3	9	--
	4510	82	26	33	11	14	19	13	--
	4511	75	11	28	-1	23	3	18	5
	4512	64	21	27	11	18	13	10	4
	4513	85	28	43	8	11	18	22	19
	4514	76	12	21	25	15	5	17	16
	4515	66	3	19	6	14	1	14	9

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Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
4F	4501	--
	4502	--
	4503	--
	4504	--
	4505	--
	4506	--
	4507	--
	4508	--
	4509	--
	4510	--
	4511	8
	4512	24
	4513	-4
	4514	8
	4515	8

Appendix 8

Individual Food Consumption Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	OA	Omitted activity
AFE	Animal found with no food during measurement interval-Exclude	ONEG	Original value negative, animal did not eat
AFNF	Animal found with no food during measurement interval	POWF	Powdered food
ANH	Animal found with no hopper during measurement interval	REHO	Animal rehoused during measurement interval
ANIC	Animal not in cage or in incorrect cage during measurement	REPL	Animal replaced during measurement interval
ANW	Animal found with no water access during measurement intervals	SPIL	Spilled food (by animal)
ANWB	Animal found with no water bottle during measurement interval	TERR	Technical error
AVS	Suspected aberrant value	UPTD	Unable to perform due to technical difficulty
AWE	Animal found with no water in bottle during measurement interval-Exclude	WAFE	Water added to food during measurement interval
FSG	Food supplementation given during interval, included in feed weight	WAFI	Water added to food during measurement interval, included
FSNC	Food supplementation given during interval, value not calculable	WETF	Wet or contaminated food (in container)
NC	Not calculable	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) -9/1	1/8	8/15	15/22	22/29	29/36	36/43
1M	1001	28.9	30.8	31.3	33.9	34.1	34.2	35.1
	1002	28.9	30.8	31.3	33.9	34.1	34.2	35.1
	1003	28.9	30.8	31.3	33.9	34.1	34.2	35.1
	1004	29.9	33.3	33.2	34.5	35.2	35.5	36.1
	1005	29.9	33.3	33.2	34.5	35.2	35.5	36.1
	1006	29.9	33.3	33.2	34.5	35.2	35.5	36.1
	1007	25.8	28.7	30.8	30.9	32.1	31.9	32.5
	1008	25.8	28.7	30.8	30.9	32.1	31.9	32.5
	1009	31.2	34.4	35.6	36.8	37.4	37.3	38.7
	1010	31.2	34.4	35.6	36.8	37.4	37.3	38.7
	1011	30.2	31.9	31.9	33.3	35.2	34.3	35.2
	1012	30.2	31.9	31.9	33.3	35.2	34.3	35.2
	1013	30.2	31.9	31.9	33.3	35.2	34.3	35.2
	1014	32.9	36.2	39.1	37.6	38.6	37.9	37.9
	1015	32.9	36.2	39.1	37.6	38.6	37.9	37.9

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
1M	1001	--	--
	1002	--	--
	1003	--	--
	1004	--	--
	1005	--	--
	1006	--	--
	1007	--	--
	1008	--	--
	1009	--	--
	1010	--	--
	1011	34.8	34.9
	1012	34.8	34.9
	1013	34.8	34.9
	1014	--	--
	1015	33.6	32.2

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) -9/1	1/8	8/15	15/22	22/29	29/36	36/43
2M	2001	--REPL	31.5	32.8	33.1	34.8	33.8	33.6
	2102	--REPL	31.5	32.8	33.1	34.8	33.8	33.6
	2003	--REPL	31.5	32.8	33.1	34.8	33.8	33.6
	2004	31.0	30.7	31.0	32.1	33.4	32.5	31.9
	2005	31.0	30.7	31.0	32.1	33.4	32.5	31.9
	2006	31.0	30.7	31.0	32.1	33.4	32.5	31.9
	2007	29.5	31.1	34.1	33.4	34.3	31.9	34.9
	2008	29.5	31.1	34.1	33.4	34.3	31.9	34.9
	2009	29.9	32.2	35.3	36.4	36.4	36.4	36.1
	2010	29.9	32.2	35.3	36.4	36.4	36.4	36.1

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Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
2M	2001	--	--
	2102	--	--
	2003	--	--
	2004	--	--
	2005	--	--
	2006	--	--
	2007	--	--
	2008	--	--
	2009	--	--
	2010	--	--

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) -9/1	1/8	8/15	15/22	22/29	29/36	36/43
3M	3001	--REPL	28.6	30.3	31.0	31.7	30.3	31.2
	3002	--REPL	28.6	30.3	31.0	31.7	30.3	31.2
	3103	--REPL	28.6	30.3	31.0	31.7	30.3	31.2
	3004	27.2	26.6	30.5	31.0	32.8	31.6	34.1
	3005	27.2	26.6	30.5	31.0	32.8	31.6	34.1
	3006	27.2	26.6	30.5	31.0	32.8	31.6	34.1
	3007	28.8	30.4	33.1	33.0	34.5	34.0	34.8
	3008	28.8	30.4	33.1	33.0	34.5	34.0	34.8
	3009	27.3	29.6	31.6	32.6	33.2	32.6	34.8
	3010	27.3	29.6	31.6	32.6	33.2	32.6	34.8

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Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
3M	3001	--	--
	3002	--	--
	3103	--	--
	3004	--	--
	3005	--	--
	3006	--	--
	3007	--	--
	3008	--	--
	3009	--	--
	3010	--	--

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) -9/1	1/8	8/15	15/22	22/29	29/36	36/43
4M	4001	30.5	30.0	34.2	33.3	37.0	34.2	37.7
	4002	30.5	30.0	34.2	33.3	37.0	34.2	37.7
	4003	30.5	30.0	34.2	33.3	37.0	34.2	37.7
	4004	31.6	30.5	35.1	32.6	36.0	32.3	34.2
	4005	31.6	30.5	35.1	32.6	36.0	32.3	34.2
	4006	31.6	30.5	35.1	32.6	36.0	32.3	34.2
	4007	29.7	28.9	33.4	31.3	35.1	33.2	35.6
	4008	29.7	28.9	33.4	31.3	35.1	33.2	35.6
	4009	30.7	29.7	36.7	33.9	38.7	34.5	38.3
	4010	30.7	29.7	36.7	33.9	38.7	34.5	38.3
	4011	31.9	31.9	36.6	34.9	37.7	33.8	37.6
	4012	31.9	31.9	36.6	34.9	37.7	33.8	37.6
	4013	31.9	31.9	36.6	34.9	37.7	33.8	37.6
	4014	29.5	28.6	33.9	32.9	36.0	34.2	36.0
	4015	29.5	28.6	33.9	32.9	36.0	34.2	36.0

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Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
4M	4001	--	--
	4002	--	--
	4003	--	--
	4004	--	--
	4005	--	--
	4006	--	--
	4007	--	--
	4008	--	--
	4009	--	--
	4010	--	--
	4011	35.2	36.7
	4012	35.2	36.7
	4013	35.2	36.7
	4014	34.4	37.9
	4015	34.4	37.9

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Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) -9/1	1/8	8/15	15/22	22/29	29/36	36/43
1F	1501	24.3	23.4	23.6	25.4	25.1	24.8	24.0
	1502	24.3	23.4	23.6	25.4	25.1	24.8	24.0
	1503	24.3	23.4	23.6	25.4	25.1	24.8	24.0
	1504	22.4	22.6	22.6	23.0	23.6	23.7	22.0
	1505	22.4	22.6	22.6	23.0	23.6	23.7	22.0
	1506	22.4	22.6	22.6	23.0	23.6	23.7	22.0
	1507	22.2	22.9	23.4	25.1	24.4	24.4	24.8
	1508	22.2	22.9	23.4	25.1	24.4	24.4	24.8
	1509	20.7	21.1	21.4	21.6	20.7	22.0	22.4
	1510	20.7	21.1	21.4	21.6	20.7	22.0	22.4
	1511	--REPL	22.3	22.3	22.8	23.7	23.3	21.5
	1612	--REPL	22.3	22.3	22.8	23.7	23.3	21.5
	1513	--REPL	22.3	22.3	22.8	23.7	23.3	21.5
	1514	24.7	26.2	26.2	26.4	24.9	25.7	25.4
	1515	24.7	26.2	26.2	26.4	24.9	25.7	25.4

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Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
1F	1501	--	--
	1502	--	--
	1503	--	--
	1504	--	--
	1505	--	--
	1506	--	--
	1507	--	--
	1508	--	--
	1509	--	--
	1510	--	--
	1511	22.4	24.7
	1612	22.4	24.7
	1513	22.4	24.7
	1514	24.6	25.9
	1515	24.6	25.9

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Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) -9/1	1/8	8/15	15/22	22/29	29/36	36/43
2F	2501	21.7	24.0	25.3	25.7	25.3	24.9	24.0
	2502	21.7	24.0	25.3	25.7	25.3	24.9	24.0
	2503	21.7	24.0	25.3	25.7	25.3	24.9	24.0
	2504	22.6	22.6	23.4	23.6	22.9	24.1	23.9
	2505	22.6	22.6	23.4	23.6	22.9	24.1	23.9
	2506	22.6	22.6	23.4	23.6	22.9	24.1	23.9
	2507	20.8	23.2	23.4	21.9	21.9	22.9	21.5
	2508	20.8	23.2	23.4	21.9	21.9	22.9	21.5
	2509	24.0	23.8	24.4	26.0	27.2	26.1	25.8
	2510	24.0	23.8	24.4	26.0	27.2	26.1	25.8

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
2F	2501	--	--
	2502	--	--
	2503	--	--
	2504	--	--
	2505	--	--
	2506	--	--
	2507	--	--
	2508	--	--
	2509	--	--
	2510	--	--

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) -9/1	1/8	8/15	15/22	22/29	29/36	36/43
3F	3501	22.3	22.7	23.3	23.7	25.4	22.9	24.2
	3502	22.3	22.7	23.3	23.7	25.4	22.9	24.2
	3503	22.3	22.7	23.3	23.7	25.4	22.9	24.2
	3604	--REPL	23.8	24.2	25.8	26.0	26.6	26.0
	3505	--REPL	23.8	24.2	25.8	26.0	26.6	26.0
	3506	--REPL	23.8	24.2	25.8	26.0	26.6	26.0
	3507	21.8	23.0	23.7	23.3	23.6	24.2	24.6
	3508	21.8	23.0	23.7	23.3	23.6	24.2	24.6
	3509	22.2	24.1	25.7	23.4	22.9	23.8	23.3
	3510	22.2	24.1	25.7	23.4	22.9	23.8	23.3

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
3F	3501	--	--
	3502	--	--
	3503	--	--
	3604	--	--
	3505	--	--
	3506	--	--
	3507	--	--
	3508	--	--
	3509	--	--
	3510	--	--

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) -9/1	1/8	8/15	15/22	22/29	29/36	36/43
4F	4501	21.4	22.2	23.0	23.3	23.3	23.4	24.4
	4502	21.4	22.2	23.0	23.3	23.3	23.4	24.4
	4503	21.4	22.2	23.0	23.3	23.3	23.4	24.4
	4504	19.7	18.9	21.3	21.8	21.3	20.8	21.2
	4505	19.7	18.9	21.3	21.8	21.3	20.8	21.2
	4506	19.7	18.9	21.3	21.8	21.3	20.8	21.2
	4507	23.9	22.9	25.3	25.4	27.3	25.5	27.5
	4508	23.9	22.9	25.3	25.4	27.3	25.5	27.5
	4509	23.4	24.4	28.0	27.9	26.6	27.6	27.5
	4510	23.4	24.4	28.0	27.9	26.6	27.6	27.5
	4511	21.7	22.8	23.9	23.7	23.2	23.4	24.2
	4512	21.7	22.8	23.9	23.7	23.2	23.4	24.2
	4513	21.7	22.8	23.9	23.7	23.2	23.4	24.2
	4514	20.9	21.0	21.2	23.5	23.2	22.7	21.6
	4515	20.9	21.0	21.2	23.5	23.2	22.7	21.6

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
4F	4501	--	--
	4502	--	--
	4503	--	--
	4504	--	--
	4505	--	--
	4506	--	--
	4507	--	--
	4508	--	--
	4509	--	--
	4510	--	--
	4511	23.6	25.4
	4512	23.6	25.4
	4513	23.6	25.4
	4514	22.3	24.0
	4515	22.3	24.0

Appendix 9

Individual Body Temperature Values Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	TERR	Technical error
AVS	Suspected aberrant value	X	Excluded from mean
NR	Not recorded	p	6 hours post dose
pr	Predose		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 43 pr	Day 43 p	Day 44
1M	1001	35.6	34.7	37.4	36.5	36.2	36.5
	1002	36.2	35.8	38.1	36.1	36.0	36.6
	1003	35.6	34.7	38.1	35.7	36.0	36.0
	1004	36.0	35.0	38.0	36.6	36.2	37.5
	1005	35.9	34.2	37.5	36.0	36.3	36.6
	1006	36.1	35.1	38.2	36.0	37.8	37.6
	1007	36.9	34.6	37.5	36.3	37.0	36.3
	1008	37.0	35.1	37.0	36.0	36.9	38.0
	1009	36.0	36.5	36.6	35.8	37.1	36.7
	1010	36.3	34.3	36.8	36.0	36.6	36.0
	1011	36.0	37.1	37.3	36.4	36.7	37.4
	1012	36.5	36.2	37.5	36.0	37.1	37.5
	1013	36.1	34.2	37.7	36.1	37.3	36.6
	1014	36.8	35.7	37.0	36.7	37.3	--
	1015	36.6	35.7	37.1	37.3	37.4	37.5

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 43 pr	Day 43 p	Day 44
2M	2001	36.9	36.3	37.1	36.1	36.6	36.1
	2102	37.2	35.7	36.5	37.2	36.4	36.9
	2003	36.7	36.0	36.9	36.1	36.9	35.7
	2004	37.0	35.2	37.0	36.2	36.2	36.5
	2005	36.6	35.5	37.4	36.6	36.4	36.8
	2006	37.2	36.2	37.0	36.6	36.6	36.9
	2007	36.6	35.6	37.0	37.3	37.1	36.9
	2008	36.7	36.7	36.8	36.3	37.8	36.4
	2009	36.5	35.9	36.7	38.0	36.3	36.3
	2010	36.8	36.8	36.8	38.5	36.3	36.2

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 43 pr	Day 43 p	Day 44
3M	3001	36.5	37.0	37.3	38.4	36.3	37.2
	3002	37.0	37.5	37.3	38.7	37.9	37.1
	3103	36.6	37.0	36.9	37.6	37.7	37.0
	3004	36.8	35.3	36.8	37.9	37.3	36.8
	3005	36.8	36.2	37.4	36.9	38.4	36.9
	3006	37.0	35.3	37.4	37.8	38.2	37.5
	3007	36.2	36.3	36.8	38.4	37.7	36.7
	3008	36.6	38.8	36.3	37.2	36.9	36.7
	3009	36.4	37.1	37.5	38.2	37.3	36.7
	3010	36.5	36.1	37.6	38.6	38.3	37.3

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 43 pr	Day 43 p	Day 44
4M	4001	35.9	38.8	37.7	37.6	36.4	37.0
	4002	36.3	39.4	38.2	36.5	37.7	35.2
	4003	36.0	38.3	37.6	36.0	37.9	37.4
	4004	36.8	37.2	37.8	36.7	38.1	38.1
	4005	35.7	38.5	37.1	36.7	38.2	37.1
	4006	36.9	39.2	36.7	37.8	38.1	36.9
	4007	36.5	38.1	37.3	36.6	37.3	37.3
	4008	37.2	38.4	37.7	36.8	37.4	37.7
	4009	37.2	38.6	37.4	36.4	37.1	37.1
	4010	36.7	38.2	38.3	36.5	38.0	37.5
	4011	36.9	38.2	37.3	36.7	36.8	36.8
	4012	36.5	35.0	38.1	36.5	37.3	38.4
	4013	36.2	38.3	36.3	36.5	37.9	37.8
	4014	36.8	37.7	37.0	36.9	37.5	37.5
	4015	37.5	36.8	37.6	38.0	37.3	37.5

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 43 pr	Day 43 p	Day 44
1F	1501	37.1	36.4	37.3	--	37.2	37.2	36.8
	1502	37.9	36.1	37.5	--	37.5	36.2	36.7
	1503	37.0	35.6	37.4	--	37.0	37.0	37.7
	1504	37.0	36.6	38.2	--	37.7	36.4	37.3
	1505	37.0	36.0	37.8	--	37.9	36.5	37.7
	1506	37.5	36.5	37.5	--	38.6	36.4	36.9
	1507	36.9	36.0	37.5	--	38.5	36.7	36.0
	1508	37.1	36.8	37.3	--	38.4	36.4	36.4
	1509	38.2	36.3	38.3	--	39.0	37.0	38.4
	1510	37.1	36.2	37.7	--	39.0	37.7	37.8
	1511	37.6	35.3	37.8	--	38.1	37.5	37.6
	1612	37.2	36.9	37.8	--	37.3	37.9	37.2
	1513	37.8	37.2	37.6	--	37.9	37.9	37.9
	1514	36.9	35.8	37.1	--	38.0	37.5	38.2
	1515	37.5	36.1	37.5	--	38.0	37.3	38.2

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 43 pr	Day 43 p	Day 44
2F	2501	38.0	37.2	37.5	--	38.1	36.5	37.0
	2502	38.3	37.2	37.3	--	38.0	36.9	36.8
	2503	37.4	36.5	37.1	--	37.8	36.4	36.8
	2504	37.1	36.8	37.6	--	38.6	37.8	38.4
	2505	37.5	37.1	37.0	--	38.6	37.4	37.7
	2506	36.9	36.2	37.0	--	37.8	37.1	37.8
	2507	37.9	36.4	37.2	--	38.1	38.0	37.8
	2508	37.5	37.4	37.4	--	38.7	37.2	37.7
	2509	37.5	36.4	38.0	--	37.1	38.1	38.3
	2510	37.8	36.7	37.6	--	37.0	37.7	37.5

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 43 pr	Day 43 p	Day 44
3F	3501	38.1	36.8	37.7	--	38.4	38.0	37.4
	3502	37.6	37.0	37.5	--	38.0	38.5	37.4
	3503	37.6	35.9	37.3	--	38.6	38.2	37.7
	3604	37.4	37.0	37.3	--	38.8	37.9	37.8
	3505	36.7	37.7	37.5	--	37.0	37.5	36.9
	3506	37.2	37.0	38.3	--	38.4	37.2	37.4
	3507	38.1	37.2	37.4	--	38.6	38.0	38.8
	3508	37.1	37.3	37.7	--	38.7	37.9	37.8
	3509	37.2	36.7	37.8	--	38.8	37.6	38.2
	3510	38.0	36.1	38.2	--	39.0	37.0	39.4

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 43 pr	Day 43 p	Day 44
4F	4501	36.7	37.9	38.0	36.6	37.2	39.1	37.6
	4502	37.0	37.6	38.7	37.0	37.0	38.9	37.2
	4503	37.3	37.7	38.0	37.1	37.2	38.7	38.3
	4504	38.0	38.5	38.8	37.2	38.5	39.2	37.7
	4505	38.5	37.8	38.7	37.9	38.2	38.2	39.1
	4506	37.1	38.0	38.9	37.5	37.7	38.3	37.6
	4507	37.3	37.3	39.4	37.9	37.7	38.9	38.2
	4508	37.5	36.9	39.3	37.5	37.7	38.7	38.3
	4509	38.0	37.3	38.2	37.7	38.7	38.0	38.1
	4510	38.1	37.7	38.5	38.2	39.5	38.4	38.7
	4511	38.1	36.8	37.6	37.9	38.0	38.4	38.3
	4512	37.5	37.6	38.3	38.3	38.0	38.3	38.5
	4513	37.5	37.7	38.8	37.1	37.2	38.6	37.9
	4514	38.2	37.2	39.2	37.6	37.0	38.6	39.0
	4515	37.8	37.3	38.0	37.8	36.9	38.5	37.3

Appendix 10

Individual Hematology Values Explanation Page

ADVIA 120 Analyzer
Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Hematocrit	HCT	%	Calculated
Hemoglobin	HGB	g/dL	Colorimetric
Mean Corpuscular Hemoglobin	MCH	pg	Calculated
Mean Corpuscular Hemoglobin Concentration	MCHC	g/dL	Calculated
Mean Corpuscular Volume	MCV	fL(μm^3)	Calculated
Mean Platelet Volume	MPV	fL(μm^3)	Calculated
Platelet Count	PLT	$x10^3/\mu L$	Light scatter
Red Blood Cell Count	RBC	$x10^6/\mu L$	Light scatter
Red Blood Cell Distribution Width	RDW	%	Calculated
Reticulocytes	RETIC	$x10^9/L$	Calculated
Reticulocytes Percent	RETIC	%	Light scatter
White Blood Cell Count	WBC	$x10^3/\mu L$	Light scatter
White Blood Cell Differential Count			
Neutrophils Percent	NEUT	%	Light scatter
Lymphocytes Percent	LYMPH	%	Light scatter
Monocytes Percent	MONO	%	Light scatter
Eosinophils Percent	EOS	%	Light scatter
Basophils Percent	BASO	%	Light scatter
Large Unstained Cells Percent	LUC	%	Light scatter
Neutrophils	NEUT	$x10^3/\mu L$	Calculated
Lymphocytes	LYMPH	$x10^3/\mu L$	Calculated
Monocytes	MONO	$x10^3/\mu L$	Calculated
Eosinophils	EOS	$x10^3/\mu L$	Calculated
Basophils	BASO	$x10^3/\mu L$	Calculated
Large Unstained Cells	LUC	$x10^3/\mu L$	Calculated

Manual and Visual

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Count		% and/or $x10^3/\mu L$	Microscopic enumeration (100 white cells)
- Immature Neutrophils Count	IMM NEUT		
- Immature Neutrophils Percent	IMM NEUT		
- Immature Cells Percent	IMM CELL		
- Immature Cells Count	IMM CELL		
- Large Platelets	LPLT		
- Neutrophils Band Form	NEUT BAND		
- Neutrophils Band Form Percent	NEUT BAND		
- Packed Cell Volume	PCV		
- Neutrophils	NEUT		

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- Lymphocytes	LYMPH		
- Monocytes	MONO		
- Eosinophils	EOS		
- Basophils	BASO		
Others			
- Nucleated Red Blood Cells/100 Leukocytes	RBCNUCLE	#/100 WBC	Microscopic enumeration (100 white cells) Reported as Number but not included in WBC Differential
CELL MORPHOLOGY			
- Cytoplasmic Basophilia Neutrophil	CYTO BASO NEUT	1+ (Minimal) 2+ (Mild)	Microscopic Examination
- Polychromasia	POLY	3+ (Moderate)	
- Anisocytosis	ANISO	4+ (Marked)	
- Hypochromasia	HYPOCHROMIA		
- Reactive Lymphocytes	REACTIVE LYMPH		
- Megakaryocytes	MEGAK		
- Smudge Cells	SMUDGE CELL		
- Microcytes	MICROCYTES		
- Macrocytes	MACROCYTES		
- Poikilocytosis	POIK		
- Rouleaux Formation	ROULEAUX		
- Agglutination	AGGL		
- Red Blood Cell Clumping	RBC Clumping		
- Acanthocytes	ACAN		
- Codocytes	TARGET CELLS		
- Dacryocytes	DACR		
- Platelet Clumps	PLATELET CLUMPS		
- Eccentrocytes	ECCENTCY		
- Schistocytes	SCHZ		
- Spherocytes	SPHR		
- Stomatocytes	STOM		
- Howell Jolly Bodies	HJB		
- Basophilic Stippling	BASO STIP RBC		
- Echinocytes	ECHINO		
- Vacuolated Neutrophils	NEUTVAC		
- Vacuolated Lymphocyted	LYMVAC		
- Döhle Bodies	DOHLE		
- Degenerated Cells	DEG CELL		
- Ovalocytes	OVAL		
- Large Platelets Alpha	LARGE PLATELETS		
- Immature Neutrophils Morphology	IMM NEUT MORPH		
- Heinz Bodies	HEINZ BODY		
- Plasmodium	PLASMOD		

Appendix 10

- Kurloff Cell	KURL		
- Burr Cells	BURR		
- Neutrophils Band Form Morphology	NEUT BAND MORPH		
- Nuclear Swelling	NUC SWELL NEUT		
- Red Blood Cell Morphology	RBC MORPH		
- White Blood Cell Morphology	WBC MORPH		
- Toxic Granulation	TOXG		
- Platelet Morphology	PLT MORPH		
Heinz Bodies Percent	HEINZ BODY	%	Microscopic examination. Methyl violet in physiological saline
Reticulocyte Percent	RETIC	%	Microscopic enumeration, (b) (4)
Bone Marrow Stain		None	n
Bone Marrow Slide Fixation		None	Manual, Fixative

Aerospray Automated Slide Stainer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Stain		None	2 parts aqueous stain (Eosin-Thiazin)

Midas III Slide Stainer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Stain		None	Wright-Giemsa stain
Bone Marrow Stain		None	Wright-Giemsa stain
Bone Marrow Slide Fixation		None	Fixative

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
--	Not required for veterinary monitoring / No findings / Not scheduled to be performed/Dead	QNS	Quantity not sufficient
ADQ	Adequate	RSV	Refer to source data
AVS	Suspected aberrant value	SAMU	Large number of smudge cells
CLOT	Sample clotted	SND	Stability not documented
COMM	Comment added	SNR	Sample not received
DEC	Decreased	UDPC	Results not confirmed by smear review
INC	Increased	Unsc	Unscheduled bleed
MDIFF	Manual differential	UPTD	Unable to perform due to technical difficulty
NAF	No abnormal findings	UTD	Unable to determine
NRBC	WBC corrected for presence of nucleated RBC	UTDM	Unable to determine, not confirmed by microscopy
NSCH	Not scheduled to be performed	UTDR	Unable to determine, results not reproducible

Appendix 10

OA	Omitted activity	Vet	Bleed for veterinary monitoring
OOS	Sample analysed outside of established stability, results for information only	VNC	Value not calculable
		X	Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Note: Additional morphology for flagged samples has been reported for the following animals: 1013, 1015, 4008, 4010.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 10

Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1M	1001	8.38	1.11	6.76	0.26	0.12	0.01	0.10
	1002	10.95	2.29	7.98	0.32	0.21	0.02	0.13
	1003	7.32	0.85	6.04	0.27	0.08	0.01	0.08
	1004	7.71	1.91	5.40	0.24	0.06	0.01	0.08
	1005	15.19	3.11	11.29	0.41	0.11	0.03	0.23
	1006	18.31	2.44	15.13	0.41	0.10	0.05	0.18
	1007	8.34	1.17	6.53	0.32	0.13	0.01	0.17
	1008	6.96	0.81	5.82	0.21	0.06	0.01	0.05
	1009	9.65	1.31	7.82	0.27	0.10	0.02	0.13
	1010	12.89	0.95	11.25	0.32	0.11	0.03	0.23
2M	2001	11.12	2.74	7.47	0.34	0.22	0.02	0.32
	2102	11.56	4.19	6.70	0.23	0.23	0.02	0.18
	2003	9.45	3.98	4.62	0.20	0.32	0.02	0.32
	2004	12.39	4.16	7.13	0.25	0.38	0.02	0.45
	2005	12.60	2.86	8.67	0.16	0.35	0.03	0.53
	2006	11.30	2.74	7.70	0.24	0.37	0.03	0.22
	2007	9.62	3.12	5.99	0.12	0.21	0.02	0.16
	2008	10.14	1.86	7.37	0.20	0.20	0.01	0.49
	2009	10.40	2.02	7.55	0.32	0.28	0.02	0.22
	2010	9.18	1.53	6.97	0.30	0.21	0.01	0.15

Appendix 10

Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	1001	7.62	13.7	40.7	53.4	18.0	33.6	12.6
	1002	7.83	13.8	41.5	53.0	17.6	33.3	12.2
	1003	8.03	13.6	41.2	51.4	17.0	33.1	13.0
	1004	7.77	13.4	41.4	53.3	17.3	32.5	12.5
	1005	7.96	13.4	41.6	52.3	16.9	32.3	12.1
	1006	7.57	13.7	41.3	54.5	18.1	33.2	13.0
	1007	7.38	13.7	40.5	54.8	18.5	33.7	12.7
	1008	7.32	13.4	40.4	55.1	18.2	33.1	13.1
	1009	7.90	14.6	44.8	56.6	18.5	32.6	11.7
	1010	7.44	13.6	40.4	54.3	18.3	33.6	14.1
2M	2001	8.24	13.8	43.0	52.2	16.8	32.1	12.6
	2102	7.72	13.2	40.2	52.0	17.1	32.9	13.5
	2003	7.85	13.5	41.4	52.7	17.2	32.7	13.4
	2004	8.23	13.6	41.6	50.5	16.5	32.7	13.3
	2005	7.97	13.8	42.8	53.6	17.3	32.3	13.0
	2006	7.52	14.0	42.2	56.1	18.6	33.2	12.5
	2007	7.43	12.8	39.6	53.3	17.3	32.4	13.8
	2008	8.01	13.7	41.2	51.4	17.1	33.2	12.8
	2009	7.56	13.9	41.8	55.3	18.4	33.2	12.8
	2010	7.64	13.6	41.6	54.5	17.8	32.6	12.8

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	ACAN	PLT MORPH	PLATELET CLUMPS
1M	1001	977	226.9	--	--	--	--	--
	1002	1291	187.4	--	--	--	--	--
	1003	1017	217.9	--	--	--	--	--
	1004	1064	215.5	--	--	--	--	--
	1005	1081	175.7	--	--	--	--	--
	1006	987	228.8	--	--	--	--	--
	1007	1107	233.5	--	--	--	--	--
	1008	997	200.8	--	--	--	--	--
	1009	1146	243.6	--	--	--	--	--
	1010	1119	270.7	--	--	--	--	--
2M	2001	1187	184.9	--	--	--	--	--
	2102	1081	222.3	--	--	--	--	--
	2003	1156	249.5	--	--	--	--	--
	2004	1064	204.3	--	--	--	--	--
	2005	800	216.2	--	--	--	--	--
	2006	990	190.5	--	--	--	--	--
	2007	887	220.4	--	--	--	--	--
	2008	1221	215.1	--	--	--	--	--
	2009	1070	292.0	--	--	--	--	--
	2010	982	239.0	--	--	--	--	--

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC MORPH
1M	1001	--
	1002	--
	1003	--
	1004	--
	1005	--
	1006	--
	1007	--
	1008	--
	1009	--
	1010	--
2M	2001	--
	2102	--
	2003	--
	2004	--
	2005	--
	2006	--
	2007	--
	2008	--
	2009	--
	2010	--

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
3M	3001	15.56	6.67	8.17	0.15	0.30	0.03	0.24
	3002	13.96	7.28	5.94	0.14	0.31	0.02	0.29
	3103	11.35	6.89	3.98	0.10	0.20	0.01	0.18
	3004	13.74	6.93	5.99	0.13	0.36	0.02	0.31
	3005	12.88	8.00	4.13	0.17	0.32	0.01	0.23
	3006	18.30	11.34	5.87	0.49	0.21	0.03	0.38
	3007	16.36	6.94	8.39	0.22	0.25	0.02	0.54
	3008	16.13	5.75	9.48	0.20	0.29	0.04	0.36
	3009	10.20	3.72	5.52	0.30	0.35	0.02	0.29
	3010	12.43	6.38	5.12	0.26	0.42	0.03	0.22
4M	4001	23.60	14.57	7.73	0.37	0.55	0.04	0.34
	4002	20.93	12.50	7.26	0.31	0.52	0.04	0.31
	4003	21.30	13.28	7.21	0.18	0.37	0.03	0.23
	4004	15.49	11.60	3.15	0.11	0.46	0.01	0.16
	4005	18.97	11.67	6.60	0.15	0.19	0.02	0.33
	4006	13.64	9.32	3.77	0.07	0.36	0.01	0.12
	4007	16.29	10.76	4.71	0.13	0.43	0.02	0.25
	4008	25.08	15.04	8.83	0.27	0.55	0.03	0.37
	4009	14.70	7.24	7.02	0.11	0.15	0.03	0.15
	4010	18.27	8.95	8.59	0.18	0.55	0.00	--MDIFF

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
3M	3001	7.30	13.0	38.9	53.3	17.8	33.3	13.6
	3002	7.50	13.0	40.3	53.7	17.4	32.4	13.4
	3103	7.33	12.9	38.9	53.0	17.5	33.1	14.2
	3004	7.70	13.4	41.1	53.4	17.4	32.7	13.7
	3005	7.81	13.9	42.2	54.1	17.7	32.8	14.0
	3006	7.90	13.8	42.0	53.1	17.5	32.9	13.8
	3007	7.91	13.5	40.9	51.7	17.0	32.9	13.2
	3008	7.41	12.8	39.2	52.9	17.2	32.5	13.2
	3009	7.57	13.7	42.0	55.5	18.1	32.7	13.1
	3010	7.47	13.0	39.5	52.9	17.5	33.0	12.4
4M	4001	7.78	13.7	41.7	53.6	17.6	32.8	14.5
	4002	8.15	14.5	44.7	54.8	17.8	32.5	13.3
	4003	8.05	14.2	43.5	54.0	17.7	32.7	13.9
	4004	7.90	13.4	42.2	53.4	17.0	31.8	14.4
	4005	8.32	14.7	45.1	54.2	17.7	32.6	13.6
	4006	7.52	13.3	39.8	52.9	17.7	33.5	13.9
	4007	7.67	13.7	42.0	54.7	17.9	32.6	13.4
	4008	7.98	14.1	42.6	53.4	17.7	33.1	14.2
	4009	7.74	14.0	42.8	55.3	18.1	32.7	13.6
	4010	7.89	13.7	41.4	52.5	17.4	33.1	13.4

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	ACAN	PLT MORPH	PLATELET CLUMPS
3M	3001	974	216.2	--	--	--	--	--
	3002	1050	207.3	--	--	--	--	--
	3103	1040	193.9	--	--	--	--	--
	3004	1163	244.5	--	--	--	--	--
	3005	952	192.1	--	--	--	--	--
	3006	1075	205.8	--	--	--	--	--
	3007	1034	177.1	--	--	--	--	--
	3008	1292	218.9	--	--	--	--	--
	3009	1134	211.5	--	--	--	--	--
	3010	878	265.7	--	--	--	--	--
4M	4001	1038	268.8	--	--	--	--	--
	4002	1040	224.3	--	--	--	--	--
	4003	1161	203.7	--	--	--	--	--
	4004	1132	253.6	--	--	--	--	--
	4005	1066	200.1	--	--	--	--	--
	4006	957	215.6	--	--	--	--	--
	4007	935	182.1	--	--	--	--	--
	4008	1078	230.8	1+	--	--	NAF	--
	4009	1125	206.9	--	--	--	--	--
	4010	1099	199.0	1+	--	--	NAF	--

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC MORPH
3M	3001	--
	3002	--
	3103	--
	3004	--
	3005	--
	3006	--
	3007	--
	3008	--
	3009	--
	3010	--
4M	4001	--
	4002	--
	4003	--
	4004	--
	4005	--
	4006	--
	4007	--
	4008	NAF
	4009	--
	4010	NAF

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	1501	7.48	0.70	6.31	0.25	0.08	0.01	0.12
	1502	5.85	0.54	4.98	0.13	0.09	0.01	0.10
	1503	6.39	0.69	5.46	0.14	0.04	0.01	0.06
	1504	5.98	1.19	4.49	0.16	0.05	0.01	0.09
	1505	5.18	0.75	4.08	0.21	0.07	0.01	0.05
	1506	7.34	1.41	5.51	0.22	0.08	0.01	0.10
	1507	5.15	0.37	4.55	0.12	0.05	0.01	0.06
	1508	4.32	0.47	3.69	0.07	0.04	0.00	0.04
	1509	6.53	0.73	5.50	0.11	0.10	0.01	0.08
	1510	11.19	0.39	10.41	0.10	0.09	0.02	0.17
2F	2501	6.89	2.98	3.57	0.07	0.21	0.01	0.06
	2502	8.15	3.22	4.43	0.10	0.28	0.01	0.11
	2503	7.90	3.64	3.54	0.21	0.25	0.02	0.25
	2504	7.14	4.14	2.60	0.07	0.26	0.00	0.06
	2505	9.22	3.48	5.20	0.21	0.19	0.01	0.15
	2506	10.31	4.22	5.59	0.10	0.29	0.01	0.10
	2507	8.74	3.84	4.22	0.09	0.38	0.01	0.20
	2508	6.86	2.63	3.64	0.09	0.27	0.00	0.23
	2509	6.49	2.53	3.46	0.10	0.27	0.00	0.12
	2510	7.49	2.52	4.01	0.22	0.35	0.01	0.38

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	1501	6.94	12.5	37.5	54.0	18.0	33.2	11.1
	1502	7.44	13.6	40.5	54.4	18.3	33.7	11.4
	1503	7.37	13.2	39.4	53.4	17.9	33.5	11.6
	1504	7.00	12.5	37.4	53.5	17.9	33.4	11.5
	1505	7.08	12.7	37.5	53.0	17.9	33.7	11.2
	1506	6.90	12.0	35.8	51.9	17.5	33.6	11.1
	1507	6.95	12.6	37.4	53.8	18.2	33.8	11.5
	1508	6.99	12.6	37.6	53.7	18.0	33.6	11.8
	1509	6.91	12.8	38.0	54.9	18.6	33.8	11.3
	1510	7.44	13.0	39.0	52.4	17.5	33.3	12.6
2F	2501	7.06	12.7	39.2	55.5	18.1	32.6	11.3
	2502	6.66	12.0	36.0	54.0	18.1	33.4	11.6
	2503	6.98	13.0	37.7	54.0	18.7	34.6	10.9
	2504	6.99	12.4	37.1	53.1	17.7	33.3	12.4
	2505	7.27	13.1	39.3	54.1	18.0	33.4	11.5
	2506	7.22	12.8	38.2	52.9	17.7	33.5	12.3
	2507	7.03	12.9	39.1	55.6	18.4	33.1	12.3
	2508	6.22	11.0	33.1	53.3	17.7	33.1	12.5
	2509	6.81	12.3	37.0	54.2	18.1	33.3	11.8
	2510	6.92	12.9	37.6	54.4	18.7	34.4	12.3

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	ACAN	PLT MORPH	PLATELET CLUMPS
1F	1501	848	150.3	--	--	--	--	--
	1502	1164	179.5	--	--	--	--	--
	1503	1049	211.8	--	--	--	--	--
	1504	1334	168.1	--	--	--	--	--
	1505	878	166.2	--	--	--	--	--
	1506	1067	188.9	--	--	--	--	--
	1507	964	180.1	--	--	--	--	--
	1508	1176	185.4	--	--	--	--	--
	1509	862	232.9	--	--	--	--	--
	1510	1262	193.6	--	--	--	--	--
2F	2501	1098	210.6	--	--	--	--	--
	2502	1119	154.3	--	--	--	--	--
	2503	987	153.0	--	--	--	--	--
	2504	952	185.9	--	--	--	--	--
	2505	929	219.9	--	--	--	--	--
	2506	990	183.3	--	--	--	--	--
	2507	950	262.8	--	--	--	--	--
	2508	1123	180.4	--	--	--	--	--
	2509	871	203.7	--	--	--	--	--
	2510	1172	208.1	--	--	--	--	--

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC MORPH
1F	1501	--
	1502	--
	1503	--
	1504	--
	1505	--
	1506	--
	1507	--
	1508	--
	1509	--
	1510	--
2F	2501	--
	2502	--
	2503	--
	2504	--
	2505	--
	2506	--
	2507	--
	2508	--
	2509	--
	2510	--

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
3F	3501	10.50	5.58	4.42	0.12	0.17	0.01	0.20
	3502	10.44	5.16	4.80	0.08	0.27	0.01	0.13
	3503	7.41	4.17	2.80	0.06	0.32	0.01	0.06
	3604	9.06	4.83	3.42	0.09	0.44	0.01	0.26
	3505	9.82	4.29	4.89	0.12	0.23	0.01	0.26
	3506	8.66	4.85	3.27	0.10	0.32	0.01	0.11
	3507	5.89	2.24	3.33	0.08	0.11	0.00	0.13
	3508	10.28	5.58	3.71	0.16	0.48	0.01	0.34
	3509	9.30	3.86	4.81	0.19	0.24	0.01	0.18
	3510	9.24	4.34	4.51	0.10	0.14	0.01	0.14
4F	4501	7.50	4.91	2.23	0.06	0.24	0.00	0.05
	4502	8.52	5.17	2.89	0.10	0.24	0.00	0.11
	4503	8.85	5.59	2.77	0.08	0.32	0.00	0.09
	4504	13.81	6.68	6.10	0.11	0.69	0.02	0.21
	4505	14.56	7.89	6.08	0.13	0.29	0.02	0.14
	4506	14.45	8.13	5.30	0.14	0.47	0.02	0.38
	4507	15.02	9.05	4.62	0.13	1.02	0.01	0.19
	4508	14.35	7.50	5.68	0.15	0.68	0.02	0.32
	4509	11.49	4.95	5.92	0.07	0.34	0.02	0.18
	4510	8.80	4.47	3.96	0.05	0.22	0.01	0.09

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
3F	3501	7.38	13.0	40.1	54.4	17.6	32.3	13.0
	3502	6.92	12.5	38.1	55.0	18.1	32.8	11.7
	3503	7.12	12.8	38.2	53.7	17.9	33.4	12.3
	3604	7.17	12.5	37.2	52.0	17.5	33.7	12.1
	3505	7.30	13.1	38.9	53.3	18.0	33.7	12.7
	3506	6.94	13.5	39.9	57.6	19.4	33.7	13.0
	3507	5.69	10.4	31.1	54.7	18.3	33.4	12.6
	3508	7.19	13.2	38.8	54.0	18.4	34.0	11.3
	3509	6.68	12.8	37.4	56.0	19.2	34.3	11.7
	3510	7.21	13.1	39.3	54.6	18.2	33.4	11.5
4F	4501	6.97	12.7	37.2	53.3	18.3	34.2	13.6
	4502	7.15	13.2	38.6	54.0	18.4	34.1	12.7
	4503	6.92	12.8	37.3	53.9	18.6	34.5	12.4
	4504	7.45	13.3	40.0	53.7	17.8	33.2	12.1
	4505	7.13	12.9	38.5	53.9	18.0	33.4	12.9
	4506	7.75	13.7	40.5	52.2	17.7	33.8	12.7
	4507	7.27	13.1	38.6	53.1	18.1	34.0	12.7
	4508	7.26	13.4	40.5	55.7	18.5	33.1	12.8
	4509	7.04	12.6	38.2	54.3	18.0	33.1	13.6
	4510	6.82	12.6	37.5	55.1	18.5	33.5	12.4

Appendix 10

Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	ACAN	PLT MORPH	PLATELET CLUMPS
3F	3501	862	249.5	--	--	--	--	--
	3502	1153	196.1	--	--	--	--	--
	3503	927	202.0	--	--	--	--	--
	3604	979	187.4	--	--	--	--	--
	3505	957	171.1	--	--	--	--	--
	3506	982	269.0	--	--	--	--	--
	3507	922	240.9	--	--	--	--	--
	3508	961	183.1	--	--	--	--	--
	3509	859	212.4	--	--	--	--	--
	3510	1109	269.6	--	--	--	--	--
4F	4501	775	170.7	--	--	--	--	--
	4502	870	236.8	--	--	--	--	--
	4503	835	208.0	--	--	--	--	--
	4504	934	153.7	--	--	--	--	--
	4505	922	260.4	--	--	--	--	--
	4506	936	212.5	--	--	--	--	--
	4507	1070	176.5	--	--	--	--	--
	4508	722	171.9	--	--	--	--	--
	4509	771	165.2	--	--	--	--	--
	4510	846	230.4	--	--	--	--	--

Appendix 10

Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC MORPH
3F	3501	--
	3502	--
	3503	--
	3604	--
	3505	--
	3506	--
	3507	--
	3508	--
	3509	--
	3510	--
4F	4501	--
	4502	--
	4503	--
	4504	--
	4505	--
	4506	--
	4507	--
	4508	--
	4509	--
	4510	--

Appendix 10

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1M	1011	8.16	1.21	6.56	0.14	0.16	0.01	0.07
	1012	11.56	1.43	9.32	0.40	0.14	0.02	0.25
	1013	7.02	1.05	5.58	0.17	0.16	0.01	0.05
	1015	13.25	4.79	7.80	0.44	0.07	0.02	0.13
4M	4011	9.60	1.33	7.72	0.29	0.07	0.01	0.18
	4012	11.22	1.25	9.56	0.21	0.09	0.02	0.08
	4013	12.15	1.32	9.73	0.70	0.20	0.02	0.18
	4014	10.40	1.77	7.85	0.50	0.18	0.02	0.08
	4015	10.14	1.04	8.60	0.22	0.11	0.01	0.17

Appendix 10

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	1011	7.89	13.8	41.6	52.7	17.5	33.2	12.1
	1012	7.84	13.4	41.1	52.4	17.1	32.7	12.4
	1013	8.07	13.7	41.3	51.2	17.0	33.2	13.3
	1015	7.57	13.6	39.6	52.4	17.9	34.2	13.1
4M	4011	7.41	13.1	39.6	53.4	17.7	33.1	14.5
	4012	7.63	13.1	40.5	53.1	17.2	32.4	15.4
	4013	7.42	13.3	40.6	54.7	18.0	32.9	14.7
	4014	7.86	13.4	41.7	53.0	17.0	32.1	13.7
	4015	7.96	13.9	42.6	53.5	17.5	32.7	14.7

Appendix 10

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	ACAN	PLT MORPH	PLATELET CLUMPS
1M	1011	995	199.1	--	--	--	--	--
	1012	1146	209.3	--	--	--	--	--
	1013	1036	241.0	1+	1+	2+	--	1+
	1015	819	209.1	1+	1+	--	--	1+
4M	4011	1228	247.7	--	--	--	--	--
	4012	944	281.1	--	--	--	--	--
	4013	1065	256.5	--	--	--	--	--
	4014	1221	228.3	--	--	--	--	--
	4015	1070	312.9	--	--	--	--	--

Appendix 10

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC MORPH
1M	1011	--
	1012	--
	1013	NAF
	1015	NAF
4M	4011	--
	4012	--
	4013	--
	4014	--
	4015	--

Appendix 10

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	1511	4.98	1.26	3.35	0.23	0.06	0.00	0.09
	1612	3.05	0.55	2.31	0.10	0.07	0.00	0.02
	1513	3.11	1.02	1.91	0.10	0.05	0.00	0.03
	1514	4.23	0.82	3.06	0.21	0.08	0.00	0.05
	1515	5.29	0.81	4.22	0.12	0.07	0.00	0.07
4F	4511	5.46	0.68	4.59	0.06	0.09	0.00	0.04
	4512	1.82	0.33	1.38	0.04	0.05	0.00	0.01
	4513	6.06	1.83	3.98	0.14	0.06	0.00	0.05
	4514	3.53	0.41	2.96	0.05	0.08	0.00	0.04
	4515	6.08	0.97	4.74	0.16	0.12	0.01	0.07

Appendix 10

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	1511	6.68	12.1	36.1	54.1	18.1	33.4	11.9
	1612	6.87	12.0	35.8	52.2	17.4	33.3	11.9
	1513	6.95	12.5	37.9	54.6	18.0	33.0	11.4
	1514	7.34	13.3	39.2	53.4	18.1	33.9	11.0
	1515	6.85	13.1	37.9	55.3	19.1	34.6	11.2
4F	4511	6.59	12.1	35.6	54.0	18.3	33.9	13.2
	4512	6.83	12.3	37.1	54.3	18.1	33.3	13.0
	4513	6.78	12.0	35.2	51.9	17.7	34.0	12.5
	4514	7.16	13.1	37.8	52.8	18.3	34.7	12.6
	4515	6.87	12.8	38.1	55.4	18.6	33.5	12.0

Appendix 10

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	ACAN	PLT MORPH	PLATELET CLUMPS
1F	1511	1118	154.9	--	--	--	--	--
	1612	1140	158.8	--	--	--	--	--
	1513	1150	183.3	--	--	--	--	--
	1514	823	178.0	--	--	--	--	--
	1515	989	143.9	--	--	--	--	--
4F	4511	1078	179.0	--	--	--	--	--
	4512	1105	197.9	--	--	--	--	--
	4513	1185	149.1	--	--	--	--	--
	4514	1173	148.4	--	--	--	--	--
	4515	985	173.3	--	--	--	--	--

Appendix 10

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	WBC MORPH
1F	1511	--
	1612	--
	1513	--
	1514	--
	1515	--
4F	4511	--
	4512	--
	4513	--
	4514	--
	4515	--

Appendix 11

Individual Coagulation Values Explanation Page

START 4 Compact Stago Analyzer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Activated Partial Thromboplastin Time	APTT	sec	Viscosity
Fibrinogen	FIB	mg/dL	Viscosity
Prothrombin Time	PT	sec	Viscosity

STA Compact Stago Analyser

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Prothrombin Time	PT	sec	Viscosity
Activated Partial Thromboplastin Time	APTT	sec	Viscosity
Fibrinogen	FIB	mg/dL	Viscosity

Plasma Appearance (Reported as SAMQ PLASMA)

Analyzed Parameter Descriptions

Parameter	Abbreviation	Degree is graded as	Methodology
Normal sample	N	Normal	Manual and visual
Hemolyzed sample	H	+ = slight (pale/light red) ++ = moderate (red) +++ = severe (dark red)	Manual and visual
Lipemic sample	L	+ = slight (cloudy) ++ = moderate (turbid) +++ = severe (lactescent)	Manual and visual
Icterus sample	I	+ = slight (dark yellow) ++ = moderate (very dark yellow) +++ = severe (dark yellow-green)	Manual and visual

Appendix 11

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
--	Not required for veterinary monitoring / Not scheduled to be performed / Dead	RSV	Refer to source data
AVS	Suspected aberrant value	SND	Stability not documented
CLOT	Sample clotted	SNR	Sample not received
COMM	Comment added	Unsc	Unscheduled bleed
NCD	No clot detected	UPTD	Unable to perform due to technical difficulty
NSCH	Not scheduled to be performed	UTD	Unable to determine
OA	Omitted activity	UTDR	Unable to determine, results not reproducible
OOS	Sample analysed outside of established stability, results for information only	Vet	Bleed for veterinary monitoring
QNS	Quantity not sufficient	VNC	Value not calculable
		X	Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 11

Individual Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1001	17.3	15.0	308	N
	1002	17.3	14.9	313	N
	1003	16.8	17.0	278	N
	1004	16.7	15.4	277	N
	1005	18.3	15.4	286	N
	1006	17.4	15.5	304	N
	1007	17.5	15.1	269	N
	1008	18.3	16.7	356	N
	1009	19.5	14.9	317	N
	1010	17.0	15.1	318	N
2M	2001	18.3	16.3	475	N
	2102	17.7	16.5	506	N
	2003	17.4	15.8	578	N
	2004	17.4	17.1	544	N
	2005	18.0	17.3	518	N
	2006	17.5	17.1	521	N
	2007	17.5	15.3	549	N
	2008	16.5	15.4	513	N
	2009	17.0	16.0	468	N
	2010	18.2	15.3	470	N

Appendix 11

Individual Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3M	3001	18.2	17.1	565	N
	3002	18.5	16.9	544	N
	3103	16.7	17.4	541	N
	3004	17.4	17.7	578	N
	3005	17.6	18.2	552	N
	3006	17.9	17.7	704	N
	3007	17.6	17.5	588	N
	3008	16.2	17.9	565	N
	3009	18.2	19.1	508	N
	3010	16.8	16.7	617	N
4M	4001	17.7	18.3	552	N
	4002	19.0	19.1	704	N
	4003	17.9	16.7	625	N
	4004	18.1	20.2	606	N
	4005	15.9	19.1	675	N
	4006	16.9	19.5	741	N
	4007	17.7	19.0	662	N
	4008	16.1	19.6	585	N
	4009	16.0	17.3	671	N
	4010	15.6	19.1	636	N

Appendix 11

Individual Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1501	17.2	16.2	311	L+
	1502	17.9	15.0	251	N
	1503	17.5	15.0	262	N
	1504	17.1	14.8	238	N
	1505	17.4	16.5	291	N
	1506	18.0	15.4	250	N
	1507	15.6	11.2	252	N
	1508	16.3	15.8	252	N
	1509	16.6	13.6	192	N
	1510	17.7	16.2	221	N
2F	2501	16.9	16.7	393	N
	2502	17.6	18.4	408	N
	2503	17.5	18.3	304	N
	2504	17.1	18.3	482	N
	2505	16.2	17.6	446	N
	2506	18.3	19.1	462	N
	2507	16.5	19.9	433	N
	2508	17.9	18.8	390	N
	2509	18.7	15.7	399	N
	2510	17.7	17.1	446	N

Appendix 11

Individual Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3F	3501	16.7	17.1	538	N
	3502	17.3	20.0	454	N
	3503	17.1	18.5	427	N
	3604	17.6	16.7	475	N
	3505	16.9	19.0	529	N
	3506	17.4	18.2	552	N
	3507	14.3	12.5	354	N
	3508	16.5	19.2	491	N
	3509	17.1	18.5	440	N
	3510	16.1	18.3	477	N
4F	4501	16.7	18.8	511	N
	4502	17.3	19.1	450	N
	4503	16.5	19.7	434	N
	4504	16.5	18.7	501	N
	4505	17.3	19.4	503	N
	4506	16.9	19.3	452	N
	4507	17.0	18.7	641	N
	4508	15.2	15.0	625	N
	4509	17.3	17.4	581	N
	4510	16.5	17.4	565	N

Appendix 11

Individual Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1011	19.1	16.0	310	N
	1012	17.6	15.8	262	N
	1013	18.3	16.3	278	N
	1015	17.4	16.2	304	N
4M	4011	18.5	16.7	280	N
	4012	19.2	15.6	264	N
	4013	17.2	16.5	268	N
	4014	18.0	16.0	292	N
	4015	19.0	15.0	268	N

Appendix 11

Individual Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1511	18.7	15.4	219	N
	1612	18.1	16.7	210	N
	1513	17.3	14.4	168	N
	1514	17.3	15.2	192	N
	1515	17.3	16.5	188	N
4F	4511	18.8	16.0	219	N
	4512	18.5	14.8	211	N
	4513	16.7	14.8	274	N
	4514	17.1	13.4	224	N
	4515	18.8	16.0	166	N

Appendix 12

Individual Clinical Chemistry Values Explanation Page

Modular Analytics

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Alanine Aminotransferase	ALT	U/L	ALT IFCC UV
Albumin	ALB	g/dL	Bromcresol green colorimetric
Alkaline Phosphatase	ALP	U/L	ALP IFCC liquid colorimetric
Aspartate Aminotransferase	AST	U/L	AST IFCC UV
Calcium	CA	mg/dL	O-cresolphthalein complexone colorimetric
Cholesterol	CHOL	mg/dL	CHOD-PAP enzymatic colorimetric
Creatinine	CREAT	mg/dL	Jaffe kinetic colorimetric. Rate-blanked and compensated
Creatine Kinase	CK	U/L	NAC activated UV
Direct Bilirubin	DBIL	mg/dL	Jendrassik colorimetric
GAMMA-Glutamyl Transferase	GGT	U/L	Nitro-Anilide, Glycylglycine; enzymatic colorimetric
Glucose	GLUC	mg/dL	Hexokinase UV
Iron	FE	µg/dL	Colorimetric
Lactate	LACT	mg/dL	Enzymatic colorimetric
Magnesium	MG	mg/dL	Colorimetric
Phosphorus	PHOS	mg/dL	Molybdate UV
Sodium, Potassium, Chloride (SI)	NA,K,CL	mmol/L	Indirect measurement (Ion selective electrode)
Total Bilirubin	TBIL	mg/dL	DPD colorimetric
Total Protein	TPROT	g/dL	Biuret colorimetric
Triglycerides	TRIG	mg/dL	GPO-PAP enzymatic colorimetric
Urea Nitrogen	UREAN	mg/dL	Urease kinetic UV

Calculations

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Calculation
Albumin/Globulin ratio	A/G	None	Albumin / Globulin
Globulin	GLOB	g/dL	Total Protein - Albumin
Indirect Bilirubin	IBIL	mg/dL	Total Bilirubin - Direct Bilirubin

Appendix 12

Serum Appearance
(Reported as SAMQ SERUM)

Analyzed Parameter Descriptions

Parameter	Abbreviation	Key to Results (Code)	Methodology
Normal sample	N	Normal	Manual and visual
Hemolyzed sample	H	+ = slight (pale/light red) ++ = moderate (red) +++ = severe (dark red)	Manual and visual
Lipemic sample	L	+ = slight (cloudy) ++ = moderate (turbid) +++ = severe (lactescent)	Manual and visual
Icterus sample	I	+ = slight (dark yellow) ++ = moderate (very dark yellow) +++ = severe (dark yellow-green)	Manual and visual

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
--	Not evaluated/Not required for veterinary monitoring	SNR	Sample not received
AVS	Suspected aberrant value	TNR	Test not reported
COMM	Comment added	Unsc	Unscheduled bleed
CLOT	Sample clotted	UPTD	Unable to perform due to technical difficulty
LLD	Less than lower limit of detection	UTD	Unable to determine
LLOQ/LLQ	Less than lower limit of quantitation	UTDH	Unable to determine due to marked hemolysis
NSCH	Not scheduled to be performed	UTDL	Unable to determine due to marked lipemia
OA	Omitted activity	UTDR	Unable to determine, results not reproducible
OOS	Sample analysed outside of established stability, results for information only	VARR	Assigned value above reportable range
QNS	Quantity not sufficient	VBRR	Assigned value below reportable range
RSV	Refer to source data	Vet	Bleed for veterinary monitoring
SND	Stability not documented	VNC	Value not calculable
		X	Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Appendix 12

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 12

Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1M	1001	104	37	115	2VBRR	636	0.05	16
	1002	84	50	147	2VBRR	222	0.08	18
	1003	110	45	136	2VBRR	676	0.05	14
	1004	107	34	98	2VBRR	275	0.05	11
	1005	147	46	138	2VBRR	1615	0.08	14
	1006	82	39	90	2VBRR	230	0.04	15
	1007	66	38	117	2VBRR	163	0.07	10
	1008	101	36	107	2VBRR	584	0.11	12
	1009	106	40	86	2VBRR	712	0.08	11
	1010	91	35	97	2VBRR	488	0.08	11
2M	2001	108	49	133	2VBRR	605	0.04	19
	2102	96	42	130	2VBRR	166	0.08	17
	2003	113	38	129	2VBRR	624	0.06	16
	2004	112	40	112	2VBRR	632	0.06	16
	2005	107	38	125	2VBRR	694	0.07	17
	2006	97	51	118	2VBRR	522	0.05	15
	2007	97	35	96	2VBRR	576	0.09	13
	2008	111	46	98	2VBRR	586	0.12	12
	2009	72	32	102	2VBRR	375	0.07	11
	2010	74	37	104	2VBRR	225	0.09	14

Appendix 12

Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	1001	0.4	167	65	78	5.8	3.4	2.4
	1002	0.4	157	81	40	6.0	3.6	2.4
	1003	0.4	195	46	153	5.9	3.8	2.1
	1004	0.3	205	52	131	6.0	3.8	2.2
	1005	0.3	238	74	122	5.6	3.5	2.1
	1006	0.3	192	64	65	5.4	3.6	1.8
	1007	0.3	185	71	46	5.5	3.6	1.9
	1008	0.3	137	51	52	5.9	3.7	2.2
	1009	0.4	214	77	98	5.7	3.6	2.1
	1010	0.3	192	100	103	5.9	3.8	2.1
2M	2001	0.4	281	108	172	6.1	3.6	2.5
	2102	0.4	137	54	42	5.5	3.2	2.3
	2003	0.4	154	55	56	6.0	3.4	2.6
	2004	0.3	154	70	74	6.1	3.4	2.7
	2005	0.4	222	67	61	5.9	3.4	2.5
	2006	0.4	212	81	83	6.0	3.5	2.5
	2007	0.3	185	86	51	5.9	3.4	2.5
	2008	0.4	226	87	73	5.9	3.6	2.3
	2009	0.3	164	82	44	5.9	3.3	2.6
	2010	0.4	211	59	50	5.5	3.0	2.5

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1M	1001	1.4	10.3	6.7	141	5.1	101	N
	1002	1.5	10.1	6.8	141	4.5	101	N
	1003	1.8	10.1	8.0	140	5.4	99	N
	1004	1.7	10.0	7.7	142	4.8	101	N
	1005	1.7	9.9	8.8	138	6.1	99	N
	1006	2.0	9.8	8.3	140	4.7	102	N
	1007	1.9	10.7	9.1	140	5.2	102	N
	1008	1.7	10.4	8.8	142	5.3	102	N
	1009	1.7	10.6	8.3	139	5.6	100	N
	1010	1.8	10.4	7.7	139	5.2	100	N
2M	2001	1.4	10.3	7.6	138	6.0	98	N
	2102	1.4	9.5	8.0	141	4.9	103	N
	2003	1.3	10.2	7.3	140	5.6	99	N
	2004	1.3	10.5	7.8	141	5.4	102	N
	2005	1.4	10.3	8.1	139	5.9	99	N
	2006	1.4	10.3	8.1	142	5.0	102	N
	2007	1.4	10.4	8.3	140	5.7	99	N
	2008	1.6	10.4	7.2	139	5.6	99	N
	2009	1.3	10.1	8.4	139	5.6	99	N
	2010	1.2	10.0	7.2	139	5.2	101	N

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
3M	3001	126	53	181	2VBRR	761	0.10	17
	3002	141	74	135	2VBRR	338	0.08	17
	3103	57	30	120	2VBRR	138	0.07	16
	3004	90	37	101	2VBRR	574	0.06	18
	3005	69	36	142	2VBRR	158	0.11	15
	3006	90	43	128	2VBRR	470	0.09	15
	3007	78	47	109	2VBRR	244	0.06	16
	3008	62	36	121	2VBRR	252	0.08	13
	3009	101	38	71	2VBRR	745	0.05	20
	3010	158	49	91	2VBRR	792	0.12	15
4M	4001	111	38	150	2VBRR	496	0.05	15
	4002	109	36	119	2VBRR	506	0.06	14
	4003	90	38	113	2VBRR	285	0.10	14
	4004	99	43	114	2VBRR	328	0.08	15
	4005	97	41	109	2VBRR	414	0.06	14
	4006	122	44	112	2VBRR	741	0.10	12
	4007	125	39	122	2VBRR	1087	0.07	17
	4008	123	40	153	2VBRR	617	0.10	13
	4009	74	31	114	2VBRR	227	0.09	11
	4010	77	37	106	2VBRR	255	0.11	13

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Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
3M	3001	0.5	212	77	88	5.9	3.3	2.6
	3002	0.4	199	80	44	5.7	3.4	2.3
	3103	0.4	201	85	47	5.7	3.2	2.5
	3004	0.3	188	72	76	5.7	3.2	2.5
	3005	0.3	177	79	74	5.6	3.3	2.3
	3006	0.4	173	67	78	6.4	3.4	3.0
	3007	0.4	258	61	67	5.6	3.2	2.4
	3008	0.4	189	74	62	5.8	3.3	2.5
	3009	0.4	230	91	48	6.2	3.4	2.8
	3010	0.4	149	69	47	5.9	3.2	2.7
4M	4001	0.4	147	53	57	5.4	3.0	2.4
	4002	0.4	136	67	66	6.1	3.2	2.9
	4003	0.4	139	76	61	5.9	3.4	2.5
	4004	0.4	185	74	75	5.8	3.3	2.5
	4005	0.4	236	95	131	6.1	3.5	2.6
	4006	0.4	198	78	76	6.3	3.3	3.0
	4007	0.4	181	83	71	6.2	3.4	2.8
	4008	0.4	176	67	53	5.8	3.3	2.5
	4009	0.3	206	82	46	6.0	3.2	2.8
	4010	0.4	184	43	51	5.8	3.1	2.7

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
3M	3001	1.3	10.2	7.1	138	5.7	98	N
	3002	1.5	10.5	7.5	139	5.5	101	N
	3103	1.3	10.4	7.9	140	5.5	101	N
	3004	1.3	10.3	8.6	140	5.8	101	N
	3005	1.4	10.6	9.5	139	5.6	100	N
	3006	1.1	10.9	7.6	142	5.5	102	N
	3007	1.3	10.3	7.6	138	6.5	98	N
	3008	1.3	10.5	7.9	140	5.1	102	N
	3009	1.2	10.5	8.2	139	6.1	98	N
	3010	1.2	10.0	7.7	139	5.4	100	N
4M	4001	1.3	9.6	8.1	141	5.7	100	N
	4002	1.1	10.1	9.1	142	5.4	101	N
	4003	1.4	10.3	8.8	141	5.9	101	N
	4004	1.3	10.4	8.2	140	6.0	103	N
	4005	1.3	10.7	7.7	138	6.1	98	N
	4006	1.1	10.9	9.4	141	5.9	100	H+
	4007	1.2	10.8	7.4	141	5.7	100	N
	4008	1.3	10.3	7.9	139	5.6	100	N
	4009	1.1	10.8	9.2	139	5.7	99	N
	4010	1.1	10.3	7.8	141	5.6	102	N

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1F	1501	124	47	44	2VBRR	647	0.06	14
	1502	111	39	93	2VBRR	545	0.09	11
	1503	72	32	60	2VBRR	206	0.04	17
	1504	73	33	60	2VBRR	148	0.06	16
	1505	69	32	58	2VBRR	385	0.06	17
	1506	125	51	73	2VBRR	601	0.07	14
	1507	69	33	78	2VBRR	114	0.09	15
	1508	100	37	51	2VBRR	537	0.07	12
	1509	75	25	38	2VBRR	350	0.07	13
	1510	79	38	73	2VBRR	122	0.03	13
2F	2501	124	36	67	2VBRR	650	0.06	17
	2502	119	56	84	2VBRR	438	0.08	22
	2503	79	39	70	2VBRR	145	0.07	14
	2504	111	34	50	2VBRR	721	0.11	15
	2505	92	31	60	2VBRR	457	0.09	12
	2506	95	46	86	2VBRR	335	0.09	15
	2507	152	29	61	2VBRR	844	0.07	14
	2508	77	30	58	2VBRR	277	0.09	19
	2509	76	39	77	2VBRR	286	0.05	13
	2510	76	46	68	2VBRR	123	0.06	14

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Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	1501	0.5	238	84	253	7.1	4.8	2.3
	1502	0.4	183	89	53	6.1	4.4	1.7
	1503	0.5	227	77	78	6.3	4.4	1.9
	1504	0.4	243	65	55	6.9	4.8	2.1
	1505	0.4	253	91	94	6.8	4.9	1.9
	1506	0.4	166	70	46	6.1	4.2	1.9
	1507	0.4	206	79	69	6.0	4.2	1.8
	1508	0.4	175	101	49	7.0	4.8	2.2
	1509	0.4	156	100	43	6.5	4.6	1.9
	1510	0.4	252	66	58	6.3	4.3	2.0
2F	2501	0.4	221	104	62	6.2	4.0	2.2
	2502	0.5	214	81	41	6.3	4.2	2.1
	2503	0.4	200	101	54	7.0	4.7	2.3
	2504	0.4	163	87	38	6.9	4.4	2.5
	2505	0.4	187	97	53	6.2	4.0	2.2
	2506	0.4	181	84	50	6.3	3.9	2.4
	2507	0.4	143	100	39	6.2	3.9	2.3
	2508	0.4	189	52	43	6.0	3.5	2.5
	2509	0.3	206	69	44	5.7	3.6	2.1
	2510	0.4	216	106	49	6.4	4.0	2.4

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1F	1501	2.1	11.1	5.3	139	5.2	99	L+
	1502	2.6	10.5	5.9	142	4.5	103	N
	1503	2.3	10.9	6.4	138	4.6	101	N
	1504	2.3	11.0	5.8	138	4.7	102	N
	1505	2.6	10.8	7.1	138	4.8	98	N
	1506	2.2	10.6	7.8	141	5.0	102	N
	1507	2.3	11.0	7.6	140	4.7	101	N
	1508	2.2	10.9	6.4	141	4.8	103	N
	1509	2.4	11.0	6.4	140	4.7	101	N
	1510	2.2	10.4	7.2	139	4.6	102	N
2F	2501	1.8	10.3	7.0	141	4.7	101	N
	2502	2.0	10.4	5.8	140	4.9	101	N
	2503	2.0	11.2	5.8	138	4.9	100	N
	2504	1.8	10.5	6.8	140	5.1	103	N
	2505	1.8	10.5	7.4	140	5.2	101	N
	2506	1.6	10.4	7.0	141	4.9	105	N
	2507	1.7	10.4	7.7	141	5.1	101	N
	2508	1.4	10.7	6.4	140	5.0	102	N
	2509	1.7	10.6	7.4	139	5.7	101	N
	2510	1.7	11.5	7.7	142	4.4	103	N

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
3F	3501	84	44	54	2VBRR	145	0.11	14
	3502	79	37	105	2VBRR	202	0.04	15
	3503	89	38	71	2VBRR	317	0.10	17
	3604	98	44	76	2VBRR	389	0.06	15
	3505	124	36	82	2VBRR	1047	0.11	18
	3506	88	31	60	2VBRR	482	0.10	14
	3507	72	25	47	2VBRR	153	0.10	15
	3508	208	82	50	2VBRR	859	0.10	19
	3509	126	28	49	2VBRR	799	0.07	16
	3510	82	36	52	2VBRR	381	0.06	14
4F	4501	127	61	98	2VBRR	749	0.08	21
	4502	115	35	78	2VBRR	643	0.10	19
	4503	160	45	71	2VBRR	911	0.08	15
	4504	92	35	92	2VBRR	450	0.06	19
	4505	111	42	63	2VBRR	572	0.12	18
	4506	90	41	74	2VBRR	142	0.11	16
	4507	92	22	68	2VBRR	500	0.04	15
	4508	80	25	63	2VBRR	186	0.11	22
	4509	80	39	74	2VBRR	95	0.08	16
	4510	119	38	63	2VBRR	757	0.09	14

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
3F	3501	0.4	204	59	60	6.2	3.8	2.4
	3502	0.3	193	87	84	6.3	4.0	2.3
	3503	0.4	167	88	34	6.3	4.1	2.2
	3604	0.4	191	74	67	6.4	3.9	2.5
	3505	0.4	186	97	58	6.4	3.9	2.5
	3506	0.5	172	73	44	6.3	4.1	2.2
	3507	0.5	200	87	53	6.7	4.4	2.3
	3508	0.5	124	96	65	6.6	4.4	2.2
	3509	0.4	183	108	70	6.5	4.2	2.3
	3510	0.4	193	86	42	6.3	3.9	2.4
4F	4501	0.4	200	109	76	6.5	4.1	2.4
	4502	0.4	167	70	43	6.3	4.1	2.2
	4503	0.5	181	96	60	6.7	4.4	2.3
	4504	0.5	180	77	42	5.9	3.7	2.2
	4505	0.5	145	70	39	6.3	3.9	2.4
	4506	0.5	192	65	51	6.5	3.9	2.6
	4507	0.4	165	57	48	6.2	3.6	2.6
	4508	0.5	200	77	80	6.4	3.9	2.5
	4509	0.4	214	72	83	6.2	3.7	2.5
	4510	0.4	179	72	42	6.5	4.0	2.5

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
3F	3501	1.6	10.5	6.7	140	4.8	99	N
	3502	1.7	10.5	7.2	143	4.5	105	N
	3503	1.9	10.6	7.3	139	4.7	98	N
	3604	1.6	10.5	7.4	141	4.9	104	N
	3505	1.6	10.8	7.4	139	5.5	99	N
	3506	1.9	10.8	6.8	142	4.9	103	N
	3507	1.9	11.4	8.3	140	5.0	99	N
	3508	2.0	11.0	7.0	141	4.9	102	N
	3509	1.8	11.1	6.5	140	5.5	101	N
	3510	1.6	10.6	5.9	140	4.9	105	N
4F	4501	1.7	10.8	7.6	139	5.0	97	N
	4502	1.9	10.3	6.5	140	5.0	104	N
	4503	1.9	10.9	7.9	140	5.3	100	N
	4504	1.7	10.3	6.6	139	5.2	102	N
	4505	1.6	10.6	7.7	141	5.0	102	N
	4506	1.5	10.4	7.0	139	4.7	102	N
	4507	1.4	10.4	7.5	140	5.2	101	H+
	4508	1.6	11.0	8.0	140	5.3	102	N
	4509	1.5	11.0	6.3	139	5.1	99	N
	4510	1.6	10.5	6.1	141	5.1	102	N

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Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1M	1011	113	57	136	2VBRR	800	0.10	21
	1012	86	31	117	2VBRR	411	0.05	15
	1013	93	39	111	2VBRR	833	0.07	14
	1015	99	35	116	2VBRR	602	0.07	18
4M	4011	71	45	108	2VBRR	329	0.05	15
	4012	87	46	129	2VBRR	401	0.07	16
	4013	78	38	84	2VBRR	318	0.07	14
	4014	94	38	90	2VBRR	439	0.06	19
	4015	56	37	112	2VBRR	130	0.07	11

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Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	1011	0.4	199	92	82	6.1	3.8	2.3
	1012	0.3	160	57	98	5.8	3.6	2.2
	1013	0.3	182	88	158	6.0	3.6	2.4
	1015	0.3	214	87	93	5.8	3.6	2.2
4M	4011	0.4	269	59	122	5.6	3.5	2.1
	4012	0.3	190	72	71	5.4	3.5	1.9
	4013	0.3	309	68	144	5.7	3.6	2.1
	4014	0.4	202	56	83	5.7	3.7	2.0
	4015	0.3	331	74	71	5.7	3.7	2.0

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Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1M	1011	1.7	10.5	6.6	140	5.4	99	N
	1012	1.6	10.3	7.4	142	5.0	103	N
	1013	1.5	10.8	7.4	139	5.2	98	N
	1015	1.6	10.2	6.8	140	5.2	99	N
4M	4011	1.7	10.0	7.3	137	5.6	99	N
	4012	1.8	9.8	8.2	139	5.3	101	N
	4013	1.7	10.9	7.7	136	5.2	96	N
	4014	1.9	10.8	7.7	139	5.3	101	N
	4015	1.9	11.0	7.1	136	4.8	97	N

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Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1F	1511	113	44	52	2VBRR	627	0.06	23
	1612	102	39	69	2VBRR	606	0.05	21
	1513	117	57	53	2VBRR	927	0.06	19
	1514	108	39	48	2VBRR	655	0.09	21
	1515	80	41	72	2VBRR	406	0.08	14
4F	4511	78	33	107	2VBRR	170	0.05	16
	4512	73	43	77	2VBRR	179	0.06	20
	4513	86	32	49	2VBRR	323	0.07	19
	4514	75	38	68	2VBRR	217	0.04	23
	4515	80	36	70	2VBRR	176	0.04	17

Appendix 12

Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	1511	0.5	174	71	203	6.5	4.8	1.7
	1612	0.5	216	60	91	6.5	4.6	1.9
	1513	0.4	209	81	132	6.6	4.6	2.0
	1514	0.4	158	118	153	6.7	4.8	1.9
	1515	0.4	219	82	97	6.3	4.6	1.7
4F	4511	0.5	218	75	58	5.7	3.9	1.8
	4512	0.4	180	57	62	5.8	4.2	1.6
	4513	0.4	162	56	56	6.5	4.6	1.9
	4514	0.4	130	72	58	6.6	4.6	2.0
	4515	0.4	221	68	63	6.0	4.2	1.8

Appendix 12

Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1F	1511	2.8	11.1	4.9	140	4.4	101	N
	1612	2.4	10.6	5.3	138	4.6	100	N
	1513	2.3	10.7	5.6	137	5.0	101	N
	1514	2.5	11.3	7.0	139	4.5	98	N
	1515	2.7	10.8	6.3	140	4.7	102	N
4F	4511	2.2	10.0	4.9	138	4.3	101	N
	4512	2.6	10.3	6.5	139	4.5	102	N
	4513	2.4	10.9	6.7	137	5.1	98	N
	4514	2.3	11.0	8.0	139	4.6	101	N
	4515	2.3	10.6	6.7	137	4.4	99	N

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values Explanation Page

Abbreviation	Description	Abbreviation	Description
--	No findings / Dead	QNS	Quantity not sufficient
CLOT	Sample clotted	SNR	Sample not received
NA	Not applicable	TNR	Test not reported
NC	Not calculable	X	Excluded from mean
NR	Not reported		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1647	8.9
3	mRNA-1647	27
4	mRNA-1647	89

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	1001	67.14	12.06
	1002	79.25	49.94
	1003	103.18	14.93
	1004	116.03	28.08
	1005	106.49	19.98
	1006	50.53	19.07
	1007	81.86	11.35
	1008	66.75	37.64
	1009	139.15	23.87
	1010	130.22	18.14

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
2	2001	255.77	229.52
	2003	213.14	42.86
	2004	269.82	180.70
	2005	225.01	82.70
	2006	309.87	140.02
	2007	304.45	136.49
	2008	207.41	33.87
	2009	247.31	54.78
	2010	216.65	64.57
	2102	324.89	186.43

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
3	3001	387.78	149.08
	3002	385.28	178.58
	3004	358.63	79.73
	3005	341.53	98.02
	3006	505.59	754.36
	3007	399.33	181.04
	3008	290.97	162.57
	3009	411.16	220.69
	3010	427.51	608.10
	3103	402.10	502.87

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
4	4001	432.06	137.66
	4002	538.44	608.02
	4003	568.43	223.81
	4004	497.30	358.99
	4005	487.32	229.42
	4006	527.83	853.89
	4007	960.12	452.23
	4008	424.57	281.64
	4009	506.74	333.96
	4010	572.88	345.69

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	1501	127.44	87.48
	1502	84.43	19.97
	1503	68.05	14.69
	1504	44.08	47.34
	1505	56.29	60.39
	1506	64.33	48.55
	1507	81.91	41.31
	1508	64.21	31.83
	1509	45.17	36.19
	1510	86.29	35.82

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
2	2501	221.48	48.20
	2502	156.28	31.07
	2503	151.10	87.54
	2504	275.79	66.42
	2505	252.48	52.85
	2506	225.72	48.97
	2507	254.49	47.72
	2508	235.65	58.16
	2509	328.11	66.21
	2510	255.24	52.80

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
3	3501	449.17	126.70
	3502	338.42	106.13
	3503	298.49	23.38
	3505	263.97	93.98
	3506	363.28	105.42
	3507	377.79	435.62
	3508	320.36	110.92
	3509	325.20	94.84
	3510	305.46	59.81
	3604	352.40	79.51

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
4	4501	426.98	122.57
	4502	444.92	57.20
	4503	415.63	75.65
	4504	513.84	65.16
	4505	396.96	84.66
	4506	431.49	100.80
	4507	529.63	871.51
	4508	870.18	271.58
	4509	509.63	50.64
	4510	514.95	163.80

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 57
Males

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	1011	91.61	20.05
	1012	98.43	17.09
	1013	81.77	27.61
	1015	81.95	18.34
4	4011	101.16	32.45
	4012	75.72	43.25
	4013	90.27	37.61
	4014	72.85	21.26
	4015	95.83	55.41

Appendix 13

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 57
Females

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	1511	62.01	57.96
	1513	65.89	21.81
	1514	71.22	32.44
	1515	71.87	28.25
	1612	73.67	35.30
4	4511	68.63	58.40
	4512	89.70	16.46
	4513	63.74	115.11
	4514	71.61	57.69
	4515	84.43	26.35

Appendix 14

Individual Cytokine Values Explanation Page

Abbreviation	Description	Abbreviation	Description
--	No findings / Dead	QNS	Quantity not sufficient
CLOT	Sample clotted	SNR	Sample not received
NA	Not applicable	TNR	Test not reported
NC	Not calculable	X	Excluded from mean
NR	Not reported	a	Less than 30 beads acquired in 2 different analysis. A mean of both analysis was reported
SNC	Sample not collected		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note:

For IL-1β and MIP-1-α

Lower Limit of Quantification (LLOQ) = 11.70 pg/mL, <11.70 was assigned as 11.70/2 (5.85 pg/mL) for statistical analysis purposes

For IL-6

Lower Limit of Quantification (LLOQ) = 352.00 pg/mL, <352.00 was assigned as 352.00/2 (176.00 pg/mL) for statistical analysis purposes

For MCP-1

Lower Limit of Quantification (LLOQ) = 141.00 pg/mL, <141.00 was assigned as 141.00/2 (70.50 pg/mL) for statistical analysis purposes

For TNF-α

Lower Limit of Quantification (LLOQ) = 2.93 pg/mL, <2.93 was assigned as 2.93/2 (1.47 pg/mL) for statistical analysis purposes

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1647	8.9
3	mRNA-1647	27
4	mRNA-1647	89

Appendix 14

Individual Cytokine Values

Males

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1-α pg/mL	MCP-1 pg/mL
1	1011	1 - 6 h Post Dose	<11.70	<352.00	<2.93	72.66	<11.70	462.41
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	89.55	<11.70	382.23
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	102.28	<11.70	514.04
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	100.39	<11.70	379.92
		57	<11.70	<352.00	<2.93	78.07	<11.70	330.83
	1012	1 - 6 h Post Dose	SNC	SNC	SNC	SNC	SNC	SNC
		15 - 6 h Post Dose	30.39	<352.00	<2.93	71.80	<11.70	412.69
		29 - 6 h Post Dose	70.01	<352.00	<2.93	72.00	<11.70	404.71
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	68.66	<11.70	370.88
		57	190.10	<352.00	<2.93	226.92	<11.70	<141.00
	1013	1 - 6 h Post Dose	<11.70	<352.00	<2.93	128.81	<11.70	317.70
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	54.41	<11.70	358.01
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	76.82	<11.70	321.13
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	59.28	<11.70	341.87
		57	<11.70	<352.00	<2.93	44.74	<11.70	<141.00

Appendix 14

Individual Cytokine Values

Males

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1-α pg/mL	MCP-1 pg/mL
1	1014	1 - 6 h Post Dose	309.52	<352.00	<2.93	193.97	<11.70	307.07
		15 - 6 h Post Dose	60.56	<352.00	<2.93	96.56	<11.70	367.80
		29 - 6 h Post Dose	209.31	<352.00	<2.93	178.68	<11.70	406.07
		43 - 6 h Post Dose	599.01	<352.00	<2.93	234.94	<11.70	306.78
	1015	1 - 6 h Post Dose	<11.70	<352.00	<2.93	81.29	<11.70	454.29
		15 - 6 h Post Dose	<11.70	<352.00	6.79	95.68	<11.70	516.54
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	111.20	<11.70	290.05
		43 - 6 h Post Dose	<11.70	<352.00	6.37	109.77	<11.70	361.06
		57	<11.70	<352.00	7.98	98.16	<11.70	366.18

Appendix 14

Individual Cytokine Values

Males

Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1-α pg/mL	MCP-1 pg/mL
4	4011	1 - 6 h Post Dose	96.39	<352.00	<2.93	1985.00	<11.70	533.42
		15 - 6 h Post Dose	29.17	<352.00	<2.93	730.19	<11.70	1191.17
		29 - 6 h Post Dose	188.19	<352.00	<2.93	677.34	<11.70	604.41
		43 - 6 h Post Dose	67.30	<352.00	<2.93	878.70	<11.70	743.76
		57	<11.70	<352.00	<2.93	77.81	<11.70	308.65
	4012	1 - 6 h Post Dose	63.37	<352.00	<2.93	917.74	<11.70	729.56
		15 - 6 h Post Dose	99.44	<352.00	<2.93	524.94	<11.70	495.48
		29 - 6 h Post Dose	87.89	<352.00	<2.93	558.39	<11.70	728.39
		43 - 6 h Post Dose	111.40	<352.00	<2.93	802.77	<11.70	752.96
		57	51.94	<352.00	<2.93	57.24	<11.70	<141.00
	4013	1 - 6 h Post Dose	<11.70	<352.00	<2.93	1229.44	<11.70	448.84
		15 - 6 h Post Dose	<11.70	<352.00	7.49	1228.65	26.53	759.05
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	1884.84	<11.70	672.48
		43 - 6 h Post Dose	<11.70	<352.00	6.34	611.94	<11.70	472.03
		57	<11.70	<352.00	<2.93	72.49	<11.70	<141.00

Appendix 14

Individual Cytokine Values

Males

Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1-α pg/mL	MCP-1 pg/mL
4	4014	1 - 6 h Post Dose	120.31	<352.00	<2.93	1227.45	<11.70	551.78
		15 - 6 h Post Dose	24.02	<352.00	6.34	735.06	<11.70	440.71
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	896.41	<11.70	380.23
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	431.04	<11.70	<141.00
		57	<11.70	<352.00	<2.93	98.66	<11.70	<141.00
	4015	1 - 6 h Post Dose	<11.70	<352.00	<2.93	718.93	<11.70	395.32
		15 - 6 h Post Dose	62.07	<352.00	<2.93	1192.94	<11.70	361.58
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	952.10	<11.70	430.95
		43 - 6 h Post Dose	<11.70	<352.00	7.98	612.87	<11.70	383.38
		57	<11.70	<352.00	<2.93	46.80	<11.70	310.59

Appendix 14

Individual Cytokine Values

Females

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1-α pg/mL	MCP-1 pg/mL
1	1511	1 - 6 h Post Dose	45.17	<352.00	<2.93	80.51	<11.70	<141.00
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	50.92	<11.70	<141.00
		29 - 6 h Post Dose	33.56	<352.00	<2.93	101.27	<11.70	<141.00
		43 - 6 h Post Dose	74.73	<352.00	<2.93	107.92	<11.70	<141.00
		57	30.04	<352.00	<2.93	83.16	<11.70	<141.00
	1513	1 - 6 h Post Dose	<11.70	<352.00	<2.93	47.84	<11.70	<141.00
		15 - 6 h Post Dose	<11.70	<352.00	8.07	44.17	<11.70	<141.00
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	49.14	<11.70	<141.00
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	131.80	<11.70	333.88
		57	<11.70	<352.00	7.16	51.91	<11.70	<141.00
	1514	1 - 6 h Post Dose	125.13	<352.00	<2.93	142.50	<11.70	303.22
		15 - 6 h Post Dose	157.51	<352.00	<2.93	112.15	<11.70	289.64
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	68.92	<11.70	348.15
		43 - 6 h Post Dose	130.10	<352.00	<2.93	140.64	<11.70	<141.00
		57	<11.70	<352.00	<2.93	48.97	<11.70	<141.00

Appendix 14

Individual Cytokine Values

Females

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1-α pg/mL	MCP-1 pg/mL
1	1515	1 - 6 h Post Dose	148.89	<352.00	<2.93	134.67	<11.70	<141.00
		15 - 6 h Post Dose	206.82	<352.00	<2.93	103.41	<11.70	289.64
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	46.87	<11.70	313.38
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	49.41	<11.70	303.48
		57	<11.70	<352.00	<2.93	34.79	<11.70	286.07
	1612	1 - 6 h Post Dose	SNC	SNC	SNC	SNC	SNC	SNC
		15 - 6 h Post Dose	32.82	<352.00	<2.93	82.78	<11.70	<141.00
		29 - 6 h Post Dose	72.22	<352.00	<2.93	112.95	<11.70	<141.00
		43 - 6 h Post Dose	42.19	<352.00	<2.93	98.99	<11.70	<141.00
		57	26.37	<352.00	6.84	45.43	<11.70	<141.00

Appendix 14

Individual Cytokine Values

Females

Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1-α pg/mL	MCP-1 pg/mL
4	4511	1 - 6 h Post Dose	<11.70	<352.00	<2.93	1739.42	<11.70	495.01
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	1382.43	<11.70	1277.44
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	1763.33	<11.70	1540.61
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	1224.05	<11.70	1047.52
		57	<11.70	<352.00	<2.93	47.34	<11.70	379.28
	4512	1 - 6 h Post Dose	106.22	<352.00	<2.93	1109.52	<11.70	<141.00
		15 - 6 h Post Dose	106.47	<352.00	<2.93	1253.11	<11.70	<141.00
		29 - 6 h Post Dose	54.57	<352.00	7.77	1147.36	<11.70	477.28
		43 - 6 h Post Dose	92.40	<352.00	6.84	433.35	<11.70	<141.00
		57	25.00	<352.00	<2.93	28.95	<11.70	<141.00
	4513	1 - 6 h Post Dose	<11.70	<352.00	<2.93	1777.15	32.53	621.91
		15 - 6 h Post Dose	<11.70	<352.00	11.78	1524.31	45.25	1918.09
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	1649.07	36.87	1227.21
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	1023.51	<11.70	<141.00
		57	<11.70	<352.00	<2.93	44.26	<11.70	<141.00

Appendix 14

Individual Cytokine Values

Females

Group 4 - mRNA-1647 89 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1-α pg/mL	MCP-1 pg/mL
4	4514	1 - 6 h Post Dose	<11.70	<352.00	<2.93	1204.21	31.51	766.19
		15 - 6 h Post Dose	<11.70	<352.00	7.77	874.88	29.37	989.23
		29 - 6 h Post Dose	<11.70	<352.00	7.80	760.21	32.24 a	1116.65
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	820.72	<11.70	<141.00
		57	<11.70	<352.00	<2.93	48.51	<11.70	<141.00
	4515	1 - 6 h Post Dose	<11.70	<352.00	<2.93	1593.30	26.63	672.23
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	1237.89	39.17	907.19
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	1554.02	42.35	798.45
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	1235.38	31.52	727.60
		57	<11.70	<352.00	<2.93	66.61	<11.70	<141.00

Appendix 15

charles river

FINAL REPORT

Study Phase: Ophthalmology Evaluation

Test Facility Study No. 5002034

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)

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Appendix 15

LIST OF APPENDICES

Appendix 15

1. INTRODUCTION

This report presents the ophthalmology evaluations for the study entitled *A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period* (Study No. 5002034).

For the work detailed in this report, the ophthalmology phase start date was 13 Mar 2017, and the ophthalmology phase completion date was 30 Apr 2017.

2. MATERIALS AND METHODS

Experimental procedures applicable to ophthalmology evaluations are summarized in Text Table 1.

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10/8.9	200	0.05/0.045	10	10	-	-
3	mRNA-1647	30/27	200	0.15/0.14	10	10	-	-
4	mRNA-1647	100/89	200	0.5/0.45	10	10	5	5

- : Not applicable
[a] Values based on Summary of Analysis (SoA) issued on 16 Mar 2017 / Values based on SoA issued on 31 May 2017 (Refer to memorandum in Appendix 2).

2.1. Ophthalmic Examinations

Frequency: Examinations were performed once prestudy and again toward the end of Week 6 of the dosing period.

Procedure: All animals were subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used was 0.126% Atropine.

2.2. Computerized Systems

The following critical computerized system was used by the Test Facility in the generation of this report (Text Table 2).

Text Table 2
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	8	Ophthalmic evaluations

Appendix 15

3. RESULTS AND DISCUSSION

(Appendix 1)

3.1. Pretreatment Evaluation

Background findings were recorded and recommendations for rejection from study groups were made when appropriate.

3.2. End of Week 6 Evaluation

There were no test item-related ocular changes observed during the course of the study. The findings noted were age-related or incidental in origin and to be expected in this population of animals.

4. CONCLUSIONS

Administration of mRNA-1647 by Intramuscular Injection to Sprague Dawley Rats for a 6 Weeks (4 doses) at doses of 8.9, 27, and 89 µg/dose did not result in any test item-related ophthalmic changes.

Appendix 15

5. REPORT APPROVAL

(b) (6)

(b) (6) Date: 09 Sep 2017

Appendix 15

Appendix 1
Individual Ophthalmic Findings

Appendix 15

Individual Ophthalmic Findings Explanation Page

Abbreviation	Description	Abbreviation	Description
Abs	Absence	Incomp Dil	Incomplete Dilation
Alt Ref	Altered Reflection	Inc	Increased
Ant	Anterior	Irreg	Irregular Reflectivity
Cap	Capsule	Mac	Macula
Ch	Chamber	Multi	Multifocal
Chor	Choroid	Myd	Mydriatic
C-L	Cell-like	Op	Opacity
C/NJ	Cortical/Nuclear Junction	Pers	Persistent
Conj	Conjunctiva	Pers Pup	Persistent Pupillary
Cont	Control	Pig	Pigmented/Pigmentation
Cort	Cortex	Post	Posterior
Depig	Depigmentation	Refl	Reflectivity
Detach	Detachment	Rej	Rejected
Diff	Diffuse	Ret	Retina
Disch	Discharge	Rupt	Rupture
Dru	Drusen	Subcap	Subcapsular
Endo	Endothelium	Subconj	Subconjunctiva
Foll	Follicular	Sut	Suture
Fov	Fovea	TA	Test Article
Hemo	Hemmorhage	Vac	Vacuole
Hyper	HyperPigmentation	Var Rx	Variation from dosing
Hyperpl	Hyperplasia	Vasc	Vascularization
Hypo	HypoPigmentation	V	Visualize
OD	Right Eye	Visu/Visuali	Visualized
OU	Both Eyes	OS	Left Eye

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Only animals with findings are presented in this appendix.

Appendix 15

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level[a] (µg/dose)
1	Reference Item	0
2	mRNA-1647	10/8.9
3	mRNA-1647	30/27
4	mRNA-1647	100/89

[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

Appendix 15
Appendix 1

Individual Ophthalmic Findings

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-10	-9	39	40
1	m	1001	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
			Lens,Op ,Nucleus	Left	.	.	.	1
		1002	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	1
			Lens,Op ,Nucleus	Left	.	1	.	1
		1003	Lens Op, Cortex, Ant, Focal	Right	.	.	.	1
		1004	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		1005	Vitreous, Hemorrhage	Left	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		1008	Iris, Pers Pup Membrane	Right	.	X	.	X
		1009	Lens Op, Cortex, Ant, Focal	Left Inferior	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		1010	Lens,Op ,Nucleus	Right	.	1	.	1
		1012	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		1014	Lens,Op ,Nucleus	Left	.	1	.	1
		1015	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 15
Appendix 1

Individual Ophthalmic Findings

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-10	-9	39	40
2	m	2102	Lens Op, Cortex, Ant, Focal	Left Inferior	.	.	.	1
		2003	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		2005	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	1
		2010	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 15
Appendix 1

Individual Ophthalmic Findings

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-10	-9	39	40
3	m	3001	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	1
			Lens,Op ,Nucleus	Right	.	1	.	1
		3004	Iris, Pers Pup Membrane	Right	.	X	.	X
		3005	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		3007	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
			Lens,Op ,Nucleus	Right	.	1	.	1
		3008	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		3009	Lens Op, Cortex, Ant, Focal	Left Temporal	.	.	.	2
			Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 15
Appendix 1

Individual Ophthalmic Findings

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-10	-9	39	40
4	m	4001	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4003	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
			Lens,Op ,Nucleus	Right	.	1	.	1
		4004	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
			Lens,Op ,Nucleus	Right	.	1	.	2
			Lens,Op ,Nucleus	Left	.	1	.	2
		4006	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4007	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		4008	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4009	Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4012	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4013	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		4014	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 15
Appendix 1

Individual Ophthalmic Findings

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-10	-9	39	40
1	f	1503	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1506	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1507	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		1508	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1612	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1513	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1514	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1515	Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 15
Appendix 1

Individual Ophthalmic Findings

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-10	-9	39	40
2	f	2501	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		2502	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		2503	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		2504	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		2508	Iris, Pers Pup Membrane	Left	X	.	X	.
			Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
			Lens,Op ,Nucleus	Left	.	.	1	.
		2509	Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
			Lens,Op ,Nucleus	Right	1	.	1	.
		2510	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 15
Appendix 1

Individual Ophthalmic Findings

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-10	-9	39	40
3	f	3501	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3502	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3503	Cornea, Op, Multi, Pinpoint	Right	1	.	.	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	.	.
		3604	Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
		3505	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	1	.
		3506	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3508	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	1	.
		3509	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
		3510	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 15
Appendix 1

Individual Ophthalmic Findings

5002034

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-10	-9	39	40
4	f	4501	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		4505	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4507	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
		4508	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Lens,Op ,Nucleus	Right	1	.	1	.
		4509	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4510	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	1	.
		4511	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	1	.
		4512	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4513	Lens Op, Cortex, Ant, Focal	Left Supero-Nasal	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4514	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4515	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 8.9 ug/dose Group 3 - 27 ug/dose Group 4 - 89 ug/dose

Appendix 16

Study Phase: Serology ELISA to detect Anti-Therapeutic Antibody (ATA)

Test Site Reference No. BS-3153
Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

TEST SITE:
Integrated BioTherapeutics, Inc.
4 Research Court, Suite 300
Rockville, MD 20850

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site
1580 Ida-Métivier
Sherbrooke, QC J1E 0B5
Canada

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Appendix 16

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Appendix 16

1. RESPONSIBLE PERSONNEL

Principal Investigator (b) (6)

2. INTRODUCTION

This report describes the detection of anti-CMV gH pentamer complex antibodies in vaccinated Sprague-Dawley rat sera from Charles River Study No. 5002034, entitled "A 6-Week Study (4 doses) of mRNA-1647 by Intramuscular Injection in Sprague-Dawley Rats with a 2-Week Recovery Period." The objectives of this study are to determine the potential toxicity of mRNA-1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

The study was sponsored by Moderna Therapeutics Inc., Cambridge, Massachusetts. (b) (6), ALM served as Sponsor Representative for Moderna Therapeutics Inc.

A total of 219 serum samples (98 samples from Day 1, 80 samples from Day 43, and 19 samples from Day 57; 22 pre-bleed samples noted as "SP") were received at Integrated BioTherapeutics, Inc. (IBT) from Charles River Laboratories on May 10, 2017 and May 31, 2017.

This study phase was not within the scope of regulations governing the conduct of nonclinical laboratory studies and was not intended to comply with such regulations. However, this non GLP study phase was conducted in accordance with the Standard Operating Procedures of Integrated Biotherapeutics, Inc.

Appendix 16

3. EXPERIMENTAL DESIGN

Table 1: Study Design

Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	8.9	200	0.045	10	10	-	-
3	mRNA-1647	27	200	0.140	10	10	-	-
4	mRNA-1647	89	200	0.450	10	10	5	5

Intramuscular injections for Groups 1-4 on days 1, 15, 29, and 43
* Values based on SoA issued on 31 May 2017.

4. MATERIALS AND METHODS

Table 2: Equipment

Equipment	Manufacturer	Model	IBT equipment#
(b) (4)			

Table 3: Materials

Material	Vendor	Cat#	Lot#	Expiry date
(b) (4)				N/A
				N/A

Table 4: Reagents

Reagent	Vendor	Cat#	Lot#	Expiry date
(b) (4)				(b) (4)
				N/A
				N/A
				b) (4)
				N/A

Appendix 16

4.1. CMV gH pentamer complex

Identification:	gH pentamer complex from hCMV strain VR1814
Supplier:	The Native Antigen Company
Batch/Lot No.:	422872/16082513
Concentration:	1 mg/mL
Used concentration:	3 µg/mL
Expiry:	Not available
Retest Date:	N/A
Storage conditions:	Kept in a freezer set to maintain -80°C

4.2. Standard

Identification:	Anti-CMV gH pentamer complex pooled rat serum Sprague Dawley rats vaccinated with mRNA-1647 Charles River Study 5002034, Group 4 (Day 43)
Supplier:	IBT Bioservices
Batch/Lot No.:	N/A
Concentration:	Not applicable
Expected Titer:	4,417 AU/mL
Expiry:	Not available
Retest Date:	N/A
Storage conditions:	Kept in a freezer set to maintain -80°C

4.3. Unknown test samples

Identification:	Sprague-Dawley rat sera (Charles River Study Number 5002034)
Supplier:	Charles River Laboratories
Storage conditions:	Kept in a freezer set to maintain -80°C
Duration:	Test samples will be discarded 30 days from completion of the project unless otherwise instructed

4.4. Detection Antibody

Appendix 16

Identification:	Goat anti-rat IgG (H+L)-HRP, mouse serum-adsorbed
Supplier:	KPL
Batch/Lot No.:	Catalog # 474-1612, lot 150317
Storage conditions:	Kept in a refrigerator set to maintain +4°C
Expiry:	Not available
Retest Date:	06Jul2018
Storage conditions:	Kept in a freezer set to maintain -80°C

4.5. Computerized Systems

Table 5: Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
SoftMax® Pro	5.4.5	• Collection of Absorbance Values at 650 nm • Calculations of Antibody Titers (X) based Absorbance Values (Y) by interpolating from a 4-parameter standard curve
Microsoft Excel	Office 365	Data summary
GraphPad Prism	Version 6	Graphs

4.6. Brief procedure

(b) (4)

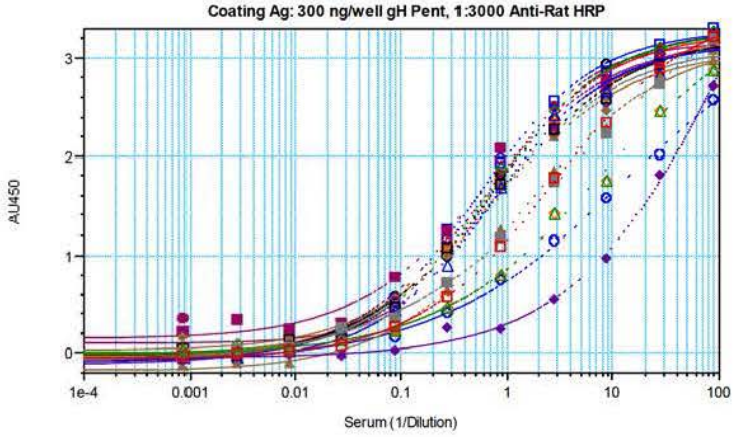
Appendix 16

5. RESULTS AND DISCUSSIONS

5.1. Standard

The standard is a well-characterized anti-CMV gH pentamer complex rat serum whose titer (Antibody Units/mL) has been assigned 4,417 AU/mL based on the average EC50 value of multiple runs during Assay Development. A cumulative graph of the standard curves tested is shown below in **Figure 1.** Variations in standard curves were not due to the pooled serum standards as study BS-3152 used the identical pool and resulted in consistent curves. Instead, these variations were likely due to the gH pentamer complex, which visibly precipitated when thawed at room temperature for 10 minutes

Figure 1: Cumulative Standard curves



4-P Fit: y = (A - D)/(1 + (x/C)^B) + D:	A	B	C	D	R^2
Plot#1 (gH Pent Standard #1: Concentration vs Mea...	-0.0976	0.479	12.9	3.59	0.998
Plot#5 (gH Pent Standard #8: Concentration vs Mea...	0.0985	0.951	0.731	3.16	0.993
Plot#9 (gH Pent Standard #9: Concentration vs Mea...	-0.0284	0.775	0.731	3.29	0.999
Plot#10 (gH Pent Standard #10: Concentration vs M...	-0.068	0.781	0.543	3.29	0.999
Plot#11 (gH Pent Standard #11: Concentration vs M...	-0.0651	0.731	0.626	3.27	0.999
Plot#12 (gH Pent Standard #12: Concentration vs M...	-0.00667	0.774	0.699	3.28	0.998
Plot#13 (gH Pent Standard #13: Concentration vs M...	-0.0533	0.671	0.811	3.27	0.998
Plot#14 (gH Pent Standard #14: Concentration vs M...	0.144	0.699	0.621	3.2	0.99
Plot#15 (gH Pent Standard #15: Concentration vs M...	-0.0606	0.709	0.741	3.12	0.999
Plot#16 (gH Pent Standard #16: Concentration vs M...	0.0238	0.703	0.8	3.08	0.995
Plot#17 (gH Pent Standard #17: Concentration vs M...	-0.118	0.669	0.586	3.21	0.993
Plot#18 (gH Pent Standard #18: Concentration vs M...	-0.0622	0.678	0.791	3.24	0.997
Plot#19 (gH Pent Standard #19: Concentration vs M...	-0.0754	0.796	0.726	3.14	0.996
Plot#7 (gH Pent Standard #6 (1xFT): Concentration ...	-0.189	0.663	1.51	3.17	0.999
Plot#8 (gH Pent Standard #7 (No F/T): Concentratio...	-0.0533	0.576	145	6.43	0.997
Plot#4 (gH Pent Standard #3: Concentration vs Mea...	-0.0227	0.559	7.6	3.61	0.997
Plot#6 (gH Pent Standard #5: Concentration vs Mea...	-0.087	0.507	4.05	3.84	0.999
Plot#3 (gH Pent Standard #3: Concentration vs Mea...	-0.0227	0.559	7.6	3.61	0.997
Plot#2 (gH Pent Standard #2: Concentration vs Mea...	-0.0611	0.664	2.79	3.53	1

Appendix 16

5.2. Study Samples

Antibody titers of Unknown Test Samples tested at 1:100 and 1:10,000 dilutions were calculated from the standard curve tested on each plate.

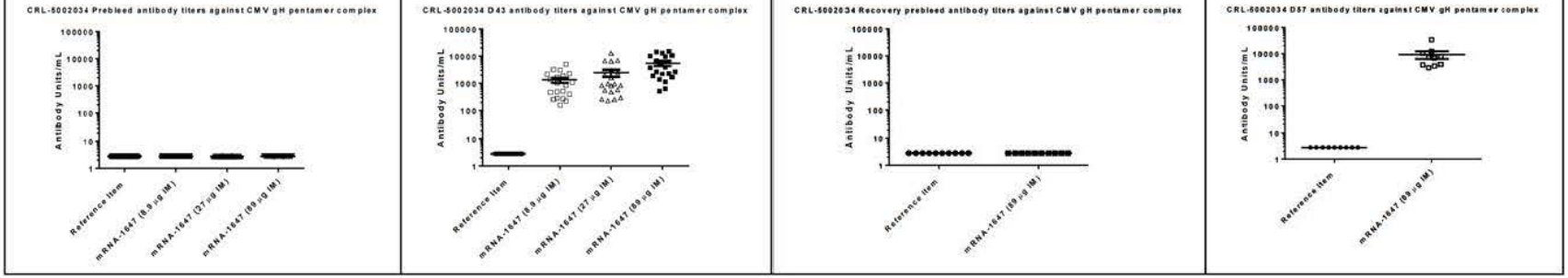
Main study: Day 43 rat sera from animals vaccinated with mRNA-1647 at 8.9 µg/dose, 27 µg/dose, 89 µg/dose on days 1, 15, 29, and 43 intramuscularly showed detectable antibody responses against CMV gH pentamer complex.

Recovery study: Day 57 rat sera from animals vaccinated with mRNA-1647 on days 1, 15, 29, and 43 showed similar antibody titers compared to Day 43 rats.

Individual Antibody Titers are shown in **Table 6 and Table 7**. Graphs are shown in **Figure 2**.

Figure 2: Graphs of Antibody Titers against CMV gH pentamer complex

Main Study		Recovery Study	
Day 1	Day 43	Day 1	Day 57



Appendix 16

Table 6: Antibody Titers (Antibody Units/mL) against CMV gH pentamer complex for Groups 1 & 2

Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 57	Mean Values Day 57	Animal ID	Day 1	Mean Values Day 1	Day 57	Mean Values Day 57
1	Reference Item	0	200	0	1001	2.8	2.8	2.8	2.8	1501	2.8	2.8	2.8	2.8	1011	2.8	2.8	2.8	2.8	1511	2.8	2.8	2.8	2.8
					1002	2.8		2.8		1502	2.8		2.8		1012	2.8		2.8		1612	2.8		2.8	
					1003	2.8		2.8		1503	2.8		2.8		1013	2.8		2.8		1513	2.8		2.8	
					1004	2.8		2.8		1504	2.8		2.8		1014	2.8		2.8		1514	2.8		2.8	
					1005	2.8		2.8		1505	2.8		2.8		1015	2.8		2.8		1515	2.8		2.8	
					1006	2.8		2.8		1506	2.8		2.8											
					1007	2.8		2.8		1507	2.8		2.8											
					1008	2.8		2.8		1508	2.8		2.8											
					1009	2.8		2.8		1509	2.8		2.8											
					1010	2.8		2.8		1510	2.8		2.8											
Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43										
2	mRNA-1647	8.9	200	0.045	2001	2.8	2.8	1101	953	2501	2.8	2.8	277	1721										
					2102	2.8		3191		2502	2.8		2305											
					2003	2.8		491		2503	2.8		1719											
					2004	2.8		832		2504	2.8		458											
					2005	2.8		273		2505	2.8		1389											
					2006	2.8		1017		2506	2.8		3114											
					2007	2.8		218		2507	2.8		5063											
					2008	2.8		400		2508	2.8		506											
					2009	2.8		1855		2509	2.8		2122											
					2010	2.8		153		2510	2.8		256											

Note: Values below the level of quantitation were assigned a value of 2.8 AU/mL for plotting purposes

* Values based on SoA issued on 31 May 2017.

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Table 7: Antibody Titers (Antibody Units/mL) against CMV gH pentamer complex for Groups 3 & 4

Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43
3	mRNA-1647	27	200	0.14	3001	2.8	2.8	552	685	3501	2.8	2.8	12794	4229
					3002	2.8		839		3502	2.8		6687	
					3103	2.8		295		3503	2.8		6538	
					3004	2.8		2043		3604	2.8		2979	
					3005	2.8		258		3505	2.8		820	
					3006	2.8		942		3506	2.8		1595	
					3007	2.8		230		3507	2.8		2552	
					3008	2.8		961		3508	2.8		576	
					3009	2.8		478		3509	2.8		835	
					3010	2.8		252.5		3510	2.8		6911	

Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 57	Mean Values Day 57	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43
4	mRNA-1647	89	200	0.45	4001	2.8	2.8	2277	2973	4501	2.8	2.8	10236	7987	4011	2.8	2.8	6707	5806	4511	2.8	2.8	7805	12594
					4002	2.8		3667		4502	2.8		12974		4012	2.8		2889		4512	2.8		10385	
					4003	2.8		2223		4503	2.8		15082		4013	2.8		3890		4513	2.8		3707	
					4004	2.8		521		4504	2.8		14314		4014	2.8		12186		4514	2.8		7070	
					4105	2.8		2602		4505	2.8		2638		4015	2.8		3358		4515	2.8		34001	
					4006	2.8		1905		4506	2.8		6798											
					4007	2.8		10818		4507	2.8		1360											
					4008	2.8		1140		4508	2.8		1671											
					4009	2.8		3930		4509	2.8		9704											
					4010	2.8		643		4510	2.8		5088											

Note: Values below the level of quantitation were assigned a value of 2.8 AU/mL for plotting purposes

* Values based on SoA issued on 31 May 2017.

6. CONCLUSION

A total of 219 rat serum samples were successfully tested to detect anti-CMV gH pentamer complex antibodies against CMV gH pentamer complex.

Appendix 16

7. REPORT APPROVAL

(b) (6) Date: August 23, 2017

Integrated BioTherapeutics, Inc.

8. REFERENCES:

N/A

Appendix 16

Study Phase: Serology ELISA to detect Anti-Therapeutic Antibody (ATA)

Test Site Reference No. BS-3152
Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

TEST SITE:
Integrated BioTherapeutics, Inc.
4 Research Court, Suite 300
Rockville, MD 20850

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site
1580 Ida-Métivier
Sherbrooke, QC J1E 0B5
Canada

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Appendix 16

1. RESPONSIBLE PERSONNEL

Principal Investigator (b) (6)

2. INTRODUCTION

This report describes the detection of anti-CMV gB protein antibodies in vaccinated Sprague-Dawley rat sera from Charles River Study No. 5002034, entitled "A 6-Week Study (4 doses) of mRNA-1647 by Intramuscular Injection in Sprague-Dawley Rats with a 2-Week Recovery Period." The objectives of this study are to determine the potential toxicity of mRNA-1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

The study was sponsored by Moderna Therapeutics Inc., Cambridge, Massachusetts. (b) (6), ALM served as Sponsor Representative for Moderna Therapeutics Inc.

A total of 219 serum samples (98 samples from Day 1, 80 samples from Day 43, and 19 samples from Day 57; 22 pre-bleed samples noted as "SP") were received at Integrated BioTherapeutics, Inc. (IBT) from Charles River Laboratories on May 10, 2017 and May 31, 2017.

This study phase was not within the scope of regulations governing the conduct of nonclinical laboratory studies and was not intended to comply with such regulations. However, this non GLP study phase was conducted in accordance with the Standard Operating Procedures of Integrated Biotherapeutics, Inc.

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3. EXPERIMENTAL DESIGN

Table 1: Study Design

Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	8.9	200	0.045	10	10	-	-
3	mRNA-1647	27	200	0.14	10	10	-	-
4	mRNA-1647	89	200	0.45	10	10	5	5
Intramuscular injections for Groups 1-4 on days 1, 15, 29 and 43 * Values based on SoA issued on 31 May 2017.								

4. MATERIALS AND METHODS

Table 2: Equipment

Equipment	Manufacturer	Model	IBT equipment#
(b) (4)			

Table 3: Materials

Material	Vendor	Cat#	Lot#	Expiry date
(b) (4)				N/A
				N/A

Table 4: Reagents

Reagent	Vendor	Cat#	Lot#	Expiry date
(b) (4)				(b) (4)
				N/A
				N/A
				(b) (4)
				N/A

Appendix 16

4.1. CMV gB Protein

Identification:	Human cytomegalovirus (HCMV) gB Protein (His Tag)
Supplier:	Sino Biological
Batch/Lot No.:	LC10AU1906
Concentration:	1 mg lyophilized
Used concentration:	2 µg/mL
Expiry:	Not available
Retest Date:	N/A
Storage conditions:	Kept in a freezer set to maintain -80°C

4.2. Standard

Identification:	Anti-CMV gB pooled rat serum Sprague Dawley rats vaccinated with mRNA-1647 Charles River Study 5002034, Group 4 (Day 43)
Supplier:	IBT Bioservices
Batch/Lot No.:	N/A
Concentration:	Not applicable
Expected Titer:	4,741 AU/mL
Expiry:	Not available
Retest Date:	N/A
Storage conditions:	Kept in a freezer set to maintain -80°C

4.3. Unknown test samples

Identification:	Sprague-Dawley rat sera (Charles River Study Number 5002034)
Supplier:	Charles River Laboratories
Storage conditions:	Kept in a freezer set to maintain -80°C
Duration:	Test samples will be discarded 30 days from completion of the project unless otherwise instructed

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4.4. Detection Antibody

Identification:	Goat anti-rat IgG (H+L)-HRP, mouse serum-adsorbed
Supplier:	KPL
Batch/Lot No.:	Catalog # 474-1612, lot 150317
Storage conditions:	Kept in a refrigerator set to maintain +4°C
Expiry:	Not available
Retest Date:	06Jul2018
Storage conditions:	Kept in a freezer set to maintain -80°C

4.5. Computerized Systems

Table 5: Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
SoftMax® Pro	5.4.5	• Collection of Absorbance Values at 650 nm • Calculations of Antibody Titers (X) based Absorbance Values (Y) by interpolating from a 4-parameter standard curve
Microsoft Excel	Office 365	Data summary
GraphPad Prism	Version 6	Graphs

4.6. Brief procedure

(b) (4)

[redacted]

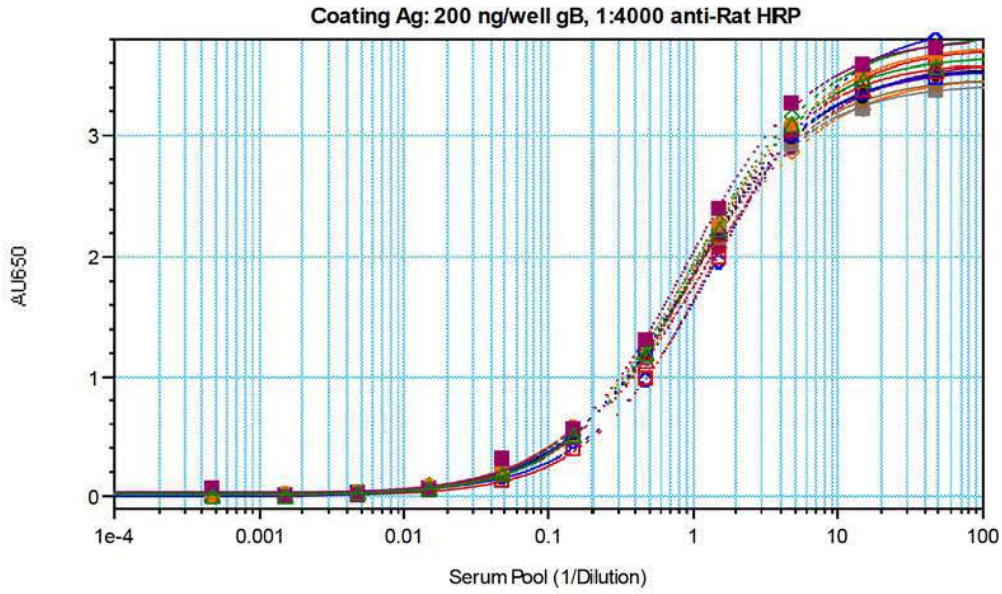
Appendix 16

5. RESULTS AND DISCUSSIONS

5.1. Standard

The standard is a well-characterized anti-CMV gB protein pooled rat serum whose titer (Antibody Units/mL) has been assigned 4,741 AU/mL based on the average EC50 value of multiple runs during Assay Development. A cumulative graph of the standard curves tested on is shown below in **Figure 1.**

Figure 1: Cumulative Standard curves



4-P Fit: y = (A - D)/(1 + (x/C)^B) + D:	A	B	C	D	R^2
Plot#1 (gB Standard #1: Concentration vs MeanVal...	0.0237	0.98	1.48	3.93	1
Plot#4 (gB Standard #4: Concentration vs MeanVal...	0.00456	0.945	1.01	3.5	1
Plot#5 (gB Standard #5: Concentration vs MeanVal...	-0.00311	0.932	1.09	3.63	1
Plot#2 (gB Standard #2: Concentration vs MeanVal...	0.00951	1.04	1.28	3.74	1
Plot#6 (gB Standard #6: Concentration vs MeanVal...	0.0113	1	0.88	3.43	1
Plot#7 (gB Standard #7: Concentration vs MeanVal...	0.0143	1	0.925	3.49	1
Plot#8 (gB Standard #8: Concentration vs MeanVal...	0.00643	0.984	0.933	3.56	1
Plot#9 (gB Standard #9: Concentration vs MeanVal...	0.00965	0.971	0.957	3.59	1
Plot#10 (gB Standard #10: Concentration vs Mean...	0.00405	0.982	0.914	3.57	1
Plot#11 (gB Standard #11: Concentration vs Mean...	0.0318	1.03	0.985	3.62	1
Plot#12 (gB Standard #12: Concentration vs Mean...	0.0125	0.958	0.999	3.84	1
Plot#13 (gB Standard #13: Concentration vs Mean...	0.0138	0.943	0.972	3.77	1
Plot#14 (gB Standard #14: Concentration vs Mean...	0.0266	1.01	0.894	3.81	0.999
Plot#3 (gB Standard #3: Concentration vs MeanVal...	0.014	1.02	0.965	3.66	1

Appendix 16

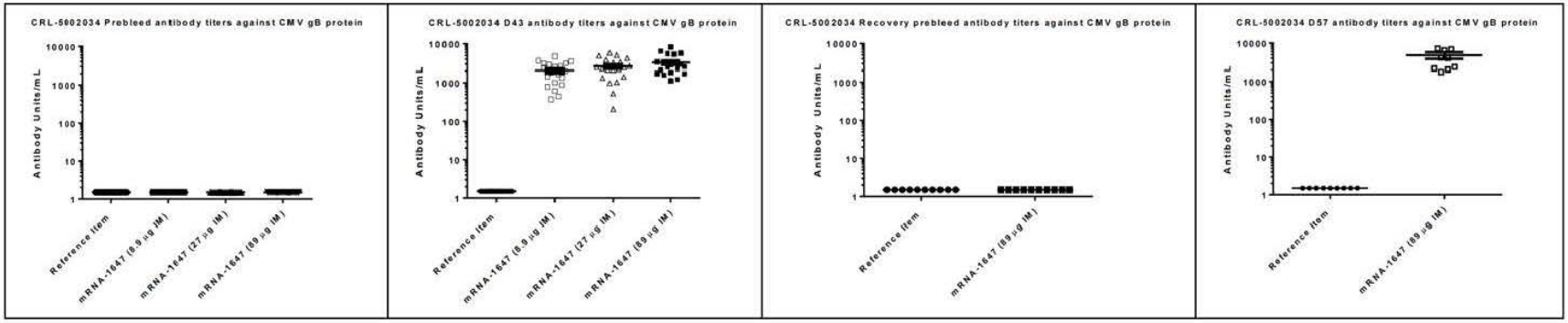
5.2. Study Samples

Antibody titers of Unknown Test Samples tested at 1:100 and 1:10,000 dilutions were calculated from the standard curve tested on each plate.
Main study: Day 43 rat sera from animals vaccinated with mRNA-1647 at 8.9 µg/dose, 27 µg/dose, 89 µg/dose on days 1, 15, 29, and 43 intramuscularly showed detectable antibody responses against CMV gB protein.
Recovery study: Day 57 rat sera from animals vaccinated with mRNA-1647 on days 1, 15, 29, showed similar antibody titers to day 43 titers.
Individual Antibody Titers are shown in

Table 6 **and Table 7**. Graphs are shown in **Figure 2**.

Figure 2: Graphs of Antibody Titers against CMV gB protein			
Main Study		Recovery Study	
Day 1	Day 43	Day 1	Day 57

Appendix 16


CRL-5002034 Prebleed antibody titers against CMV gB protein
Antibody Units/mL
10000
1000
100
10
1
Reference Item
mRNA-1647 (6.9 µg IM)
mRNA-1647 (27 µg IM)
mRNA-1647 (89 µg IM)
CRL-5002034 D43 antibody titers against CMV gB protein
Antibody Units/mL
10000
1000
100
10
1
Reference Item
mRNA-1647 (6.9 µg IM)
mRNA-1647 (27 µg IM)
mRNA-1647 (89 µg IM)
CRL-5002034 Recovery prebleed antibody titers against CMV gB protein
Antibody Units/mL
10000
1000
100
10
1
Reference Item
mRNA-1647 (89 µg IM)
CRL-5002034 D57 antibody titers against CMV gB protein
Antibody Units/mL
10000
1000
100
10
1
Reference Item
mRNA-1647 (89 µg IM)

Appendix 16

Table 6: Antibody Titers (Antibody Units/mL) against CMV gB protein for Groups 1 & 2

Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 57	Mean Values Day 57	Animal ID	Day 1	Mean Values Day 1	Day 57	Mean Values Day 57
1	Reference Item	0	200	0	1001	1.5	1.5	1.5	1.5	1501	1.5	1.5	1.5	1.5	1011	1.5	1.5	1.5	1.5	1511	1.5	1.5	1.5	1.5
					1002	1.5		1.5		1502	1.5		1.5		1012	1.5		1.5		1612	1.5		1.5	
					1003	1.5		1.5		1503	1.5		1.5		1013	1.5		1.5		1513	1.5		1.5	
					1004	1.5		1.5		1504	1.5		1.5		1014	1.5		1.5		1514	1.5		1.5	
					1005	1.5		1.5		1505	1.5		1.5		1015	1.5		1.5		1515	1.5		1.5	
					1006	1.5		1.5		1506	1.5		1.5											
					1007	1.5		1.5		1507	1.5		1.5											
					1008	1.5		1.5		1508	1.5		1.5											
					1009	1.5		1.5		1509	1.5		1.5											
					1010	1.5		1.5		1510	1.5		1.5											

Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43
2	mRNA-1647	8.9	200	0.045	2001	1.5	1.5	2688	1785	2501	1.5	1.5	2615	2347
					2102	1.5		3571		2502	1.5		3665	
					2003	1.5		785		2503	1.5		3143	
					2004	1.5		1848		2504	1.5		891	
					2005	1.5		3162		2505	1.5		4742	
					2006	1.5		2888		2506	1.5		1683	
					2007	1.5		372		2507	1.5		2348	
					2008	1.5		615		2508	1.5		2001	
					2009	1.5		1471		2509	1.5		1005	
					2010	1.5		446		2510	1.5		1374	

Note: Values below the level of quantitation were assigned a value of 1.5 AU/mL for plotting purposes

* Values based on SoA issued on 31 May 2017.

Appendix 16

Table 7: Antibody Titers (Antibody Units/mL) against CMV gB protein for Groups 3 & 4

Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43
3	mRNA-1647	27	200	0.14	3001	1.5	1.5	2453	1902	3501	1.5	1.5	5856	3377
					3002	1.5		4964		3502	1.5		3426	
					3103	1.5		980		3503	1.5		3277	
					3004	1.5		1432		3604	1.5		3874	
					3005	1.5		209.5		3505	1.5		1333	
					3006	1.5		1032		3506	1.5		2152	
					3007	1.5		532		3507	1.5		5127	
					3008	1.5		2233		3508	1.5		2121	
					3009	1.5		2524		3509	1.5		2325	
					3010	1.5		2664		3510	1.5		4278	

Group No.	Test Material	Dose Level (µg/dose)*	Dose Volume (µL/dose)	Dose Concentration (mg/mL)*	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 57	Mean Values Day 57	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43
4	mRNA-1647	89	200	0.45	4001	1.5	1.5	3439	2179	4501	1.5	1.5	3036	4460	4011	1.5	1.5	2043	2970	4511	1.5	1.5	10896	6652
					4002	1.5		1222		4502	1.5		6514		4012	1.5		1760		4512	1.5		4062	
					4003	1.5		1139		4503	1.5		5832		4013	1.5		2174		4513	1.5		4142	
					4004	1.5		2301		4504	1.5		5591		4014	1.5		6474		4514	1.5		6945	
					4105	1.5		2928		4505	1.5		8263		4015	1.5		2397		4515	1.5		7214	
					4006	1.5		1822		4506	1.5		3442											
					4007	1.5		2508		4507	1.5		1712											
					4008	1.5		2586		4508	1.5		3211											
					4009	1.5		1697		4509	1.5		5412											
					4010	1.5		2149		4510	1.5		1586											

Note: Values below the level of quantitation were assigned a value of 1.5 AU/mL for plotting purposes

* Values based on SoA issued on 31 May 2017.

6. CONCLUSION

A total of 219 rat serum samples were successfully tested to detect anti-CMV gB protein antibodies against CMV gB protein.

Appendix 16

7. REPORT APPROVAL

(b) (6) Date: August 23, 2017

Integrated BioTherapeutics, Inc.

8. REFERENCES:

N/A

Appendix 17

Final Report

To

Valera, A Moderna Venture

on

Immunogenic Response of Rat T Cells following mRNA-1647 Vaccination

August 14, 2017

Appendix 17

Final Report

Immunogenic Response of Rat T Cells following mRNA-1647 Vaccination

Submitted to:

Valera, A Moderna Venture
500 Technology Square, 7th Floor
Cambridge, MA 02139

by:

Southern Research
2000 Ninth Avenue South
P. O. Box 55305
Birmingham, AL 35255-5305

(b) (6)
(b) (6)
Cell Biology and Immunology Group

Project: 15118.01.01.38
Submitted: August 14, 2017

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Appendix 17

INTRODUCTION

The objective of the present study was to evaluate the T cell responses of rats vaccinated with mRNA-1647. Rat blood cells were stimulated with overlapping peptide library for Pentamer (Penta) and Glycoprotein B (gB). Interferon gamma (INFγ) producing T cells were then assessed by intracellular cytokine staining (ICS) and flow cytometric analysis.

MATERIALS AND METHODS

Blood Samples

Blood samples for evaluation were generated as part of a study conducted at Charles River Laboratories Montreal, CRLM (Test Facility Study No. 5002034). In total, 80 blood samples were received from CRLM over the course of two days, 05-May-2017 (male rat samples) and 06-May-2017 (female rat samples). Each shipment consisted of 40 whole blood samples in sodium heparin blood collection tubes with 10 samples from each of 4 study groups. Upon receipt, samples were verified against the shipping manifest and immediately processed and analyzed.

Appendix 17

Statistical Analysis

Means and standard deviations for each analyzed parameter were determined for each sex of each treatment group.

Study Design

The detailed Study Design is included in the Appendix (p. 5-6).

Appendix 17

RESULTS and **CONCLUSIONS**

A detailed table of individual animal responses is presented in the Appendix (p.8-15). Summary tables of INFγ production responses are presented in the tables below and the chart found in the Appendix (p. 7).

Results

Summary of Results - Pentamer Specific INFγ Response

	Group	Test material	N	Dose level (µg)	Pentamer specific CD4+ T cells Range (%)*;	Mean (%);	SD	Pentamer specific CD8+ T cells Range (%)*;	Mean (%);	SD
Males	1	Reference	9	0	0.00 - 0.46;	0.03;	0.30	0.00 - 0.32;	0.01;	0.23
	2	mRNA-1647	10	8.9	0.00 - 1.20;	0.04;	0.52	0.00 - 2.73;	0.43;	0.88
	3	mRNA-1647	10	27	0.00 - 0.46;	0.08;	0.25	0.00 - 0.74;	0.21;	0.33
	4	mRNA-1647	10	89	0.00 - 6.99;	0.90;	2.19	0.00 - 8.96;	1.29;	2.83
Females	1	Reference	10	0	0.00 - 1.13;	0.02;	0.70	0.00 - 0.33;	0.01;	0.24
	2	mRNA-1647	10	8.9	0.00 - 1.39;	0.09;	0.78	0.00 - 3.91;	1.10;	1.61
	3	mRNA-1647	10	27	0.00 - 2.16;	0.34;	1.01	0.00 - 2.70;	0.69;	1.30
	4	mRNA-1647	10	89	0.00 - 3.16;	0.31;	1.42	0.00 - 4.35;	0.95;	1.56

Summary of Results - Glycoprotein B Specific INFγ Response

	Group	Test material	N	Dose level (µg)	Glycoprotein B specific CD4+ T cells Range (%)*;	Mean (%);	SD	Glycoprotein B specific CD8+ T cells Range (%)*;	Mean (%);	SD
Males	1	Reference	9	0	0.00 - 0.57;	0.00;	0.31	0.00 - 0.12;	0.00;	0.17
	2	mRNA-1647	10	8.9	0.00 - 0.79;	0.00;	0.38	0.00 - 0.26;	0.00;	0.13
	3	mRNA-1647	10	27	0.00 - 0.91;	0.15;	0.35	0.00 - 0.64;	0.13;	0.28
	4	mRNA-1647	10	89	0.00 - 3.17;	0.53;	0.99	0.00 - 4.52;	0.46;	1.46
Females	1	Reference	10	0	0.00 - 0.79;	0.04;	0.41	0.00 - 0.69;	0.13;	0.36
	2	mRNA-1647	10	8.9	0.00 - 1.30;	0.03;	0.92	0.00 - 0.00;	0.00;	0.37
	3	mRNA-1647	10	27	0.00 - 2.15;	0.08;	1.28	0.00 - 4.17;	0.71;	1.62
	4	mRNA-1647	10	89	0.00 - 3.00;	0.00;	1.62	0.00 - 4.76;	0.79;	1.96

*For purpose of Range and Mean calculation, values < 0.00 following Unstimulated Control subtraction were set to 0.00 for reporting.

Conclusions

The mRNA-1647 elicited CD4 and CD8 T cell responses to both CMV Pentamer and gB. The animals that received 89 µg mRNA-1647 showed maximal but varying T cell responses for both Pentamer and gB. In male rats immunized with 89 µg of mRNA-1647, the range of Pentamer-specific CD4 and CD8 T cells secreting IFNγ were 0-6.99 % and 0-8.96%, respectively. In female rats that received 89 µg of mRNA-1647, the range of pentamer-specific CD4 and CD8 T cells were 0-3.16% and 0-4.35%, respectively.

The range of gB-specific T cell responses male rats dosed with 89 µg mRNA-1647 were 0-3.17% and 0-4.52% for CD4 and CD8 T cells, respectively. For female rats that received the same dose, the range of gB specific CD4 and CD8 T cell responses were 0-3.00% and 0-4.76%, respectively.

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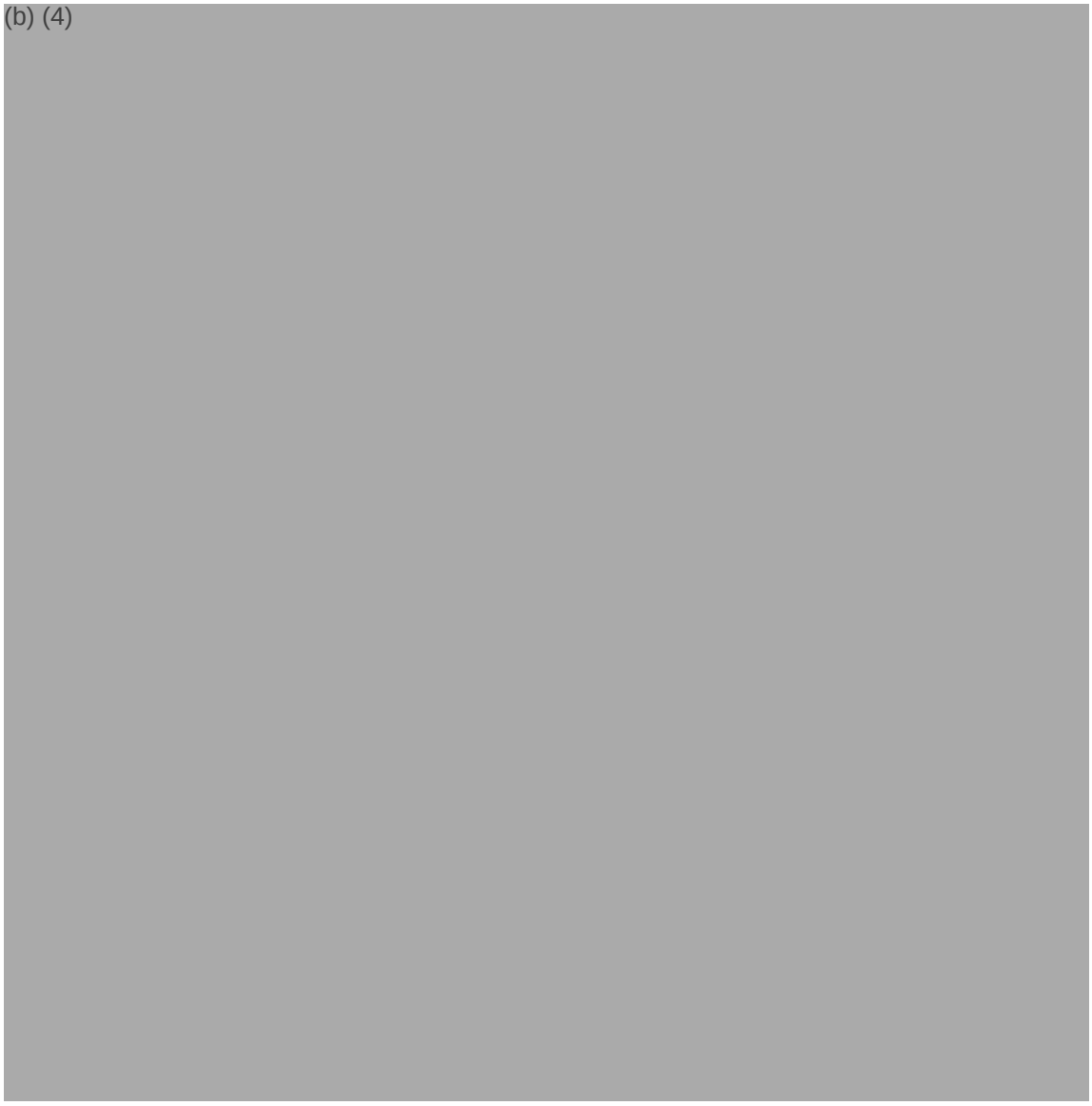

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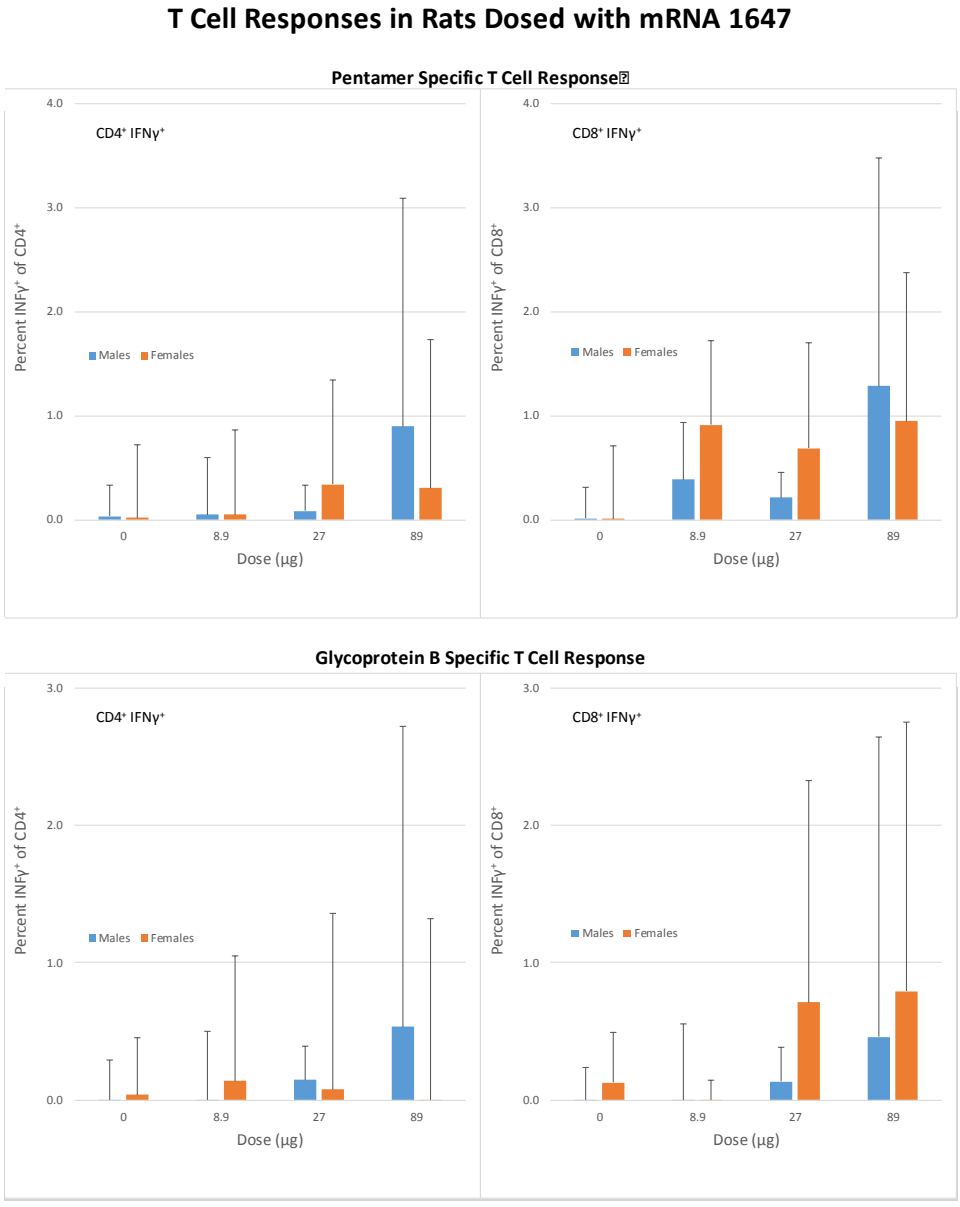
T Cell Responses in Rats Dosed with mRNA 1647
Pentamer Specific T Cell Response
CD4+ IFNγ+
CD8+ IFNγ+
Percent INFγ+ of CD4+
Percent INFγ+ of CD8+
Males
Females
Dose (µg)
0
8.9
27
89
Glycoprotein B Specific T Cell Response

Appendix 17

mRNA-1647 - Intracellular IFNγ Production following Antigen Stimulation
Group 1 - Males

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Background Subtracted: Percent of T_h	Unstimulated Background Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
1001	Unstimulated	0.44	0.22		
	Stimulated	13.48	18.80		
	Penta	0.12	0.00	-0.31	-0.22
	gB	0.36	0.00	-0.08	-0.22
1002	Unstimulated	0.24	0.00		
	Stimulated	4.28	13.92		
	Penta	0.62	0.15	0.38	0.15
	gB	0.50	0.00	0.26	0.00
1003	Unstimulated	0.00	0.00		
	Stimulated	13.00	51.74		
	Penta	0.46	0.17	0.46	0.17
	gB	0.57	0.00	0.57	0.00
1004	Unstimulated	*	*		
	Stimulated	*	*		
	Penta	0.30	0.00	**	**
	gB	0.38	0.00	**	**
1005	Unstimulated	0.24	0.44		
	Stimulated	8.03	36.42		
	Penta	0.37	0.00	0.12	-0.44
	gB	0.12	0.00	-0.12	-0.44
1006	Unstimulated	0.23	0.00		
	Stimulated	5.33	19.56		
	Penta	0.39	0.32	0.16	0.32
	gB	0.26	0.12	0.03	0.12
1007	Unstimulated	0.44	0.00		
	Stimulated	3.65	12.45		
	Penta	0.22	0.00	-0.22	0.00
	gB	0.29	0.00	-0.14	0.00
1008	Unstimulated	0.70	0.00		
	Stimulated	10.21	15.99		
	Penta	0.29	0.20	-0.40	0.20
	gB	0.15	0.00	-0.55	0.00
1009	Unstimulated	0.29	0.00		
	Stimulated	11.76	34.44		
	Penta	0.25	0.00	-0.04	0.00
	gB	0.43	0.00	0.14	0.00
1010	Unstimulated	0.30	0.27		
	Stimulated	12.01	26.83		
	Penta	0.46	0.20	0.16	-0.07
	gB	0.12	0.22	-0.18	-0.05

* Insufficient sample for analysis ** Unable to calculate

Appendix 17

mRNA-1647 - Intracellular IFNγ Production following Antigen Stimulation
Group 2 - Males

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Background Subtracted: Percent of T_h	Unstimulated Background Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
2001	Unstimulated	0.18	0.00		
	Stimulated	8.99	31.50		
	Penta	0.00	0.00	-0.18	0.00
	gB	0.00	0.00	-0.18	0.00
2102	Unstimulated	0.00	0.00		
	Stimulated	12.91	34.33		
	Penta	0.71	2.73	0.71	2.73
	gB	0.37	0.00	0.37	0.00
2003	Unstimulated	0.46	0.28		
	Stimulated	6.64	8.76		
	Penta	0.16	0.00	-0.30	-0.28
	gB	0.00	0.00	-0.46	-0.28
2004	Unstimulated	0.00	0.00		
	Stimulated	10.58	27.84		
	Penta	0.00	0.80	0.00	0.80
	gB	0.00	0.00	0.00	0.00
2005	Unstimulated	0.65	0.00		
	Stimulated	4.96	15.57		
	Penta	0.19	0.00	-0.46	0.00
	gB	0.40	0.00	-0.25	0.00
2006	Unstimulated	0.15	0.00		
	Stimulated	2.06	20.99		
	Penta	0.15	0.00	0.00	0.00
	gB	0.18	0.00	0.03	0.00
2007	Unstimulated	0.00	0.00		
	Stimulated	8.84	41.67		
	Penta	0.00	0.80	0.00	0.80
	gB	0.79	0.00	0.79	0.00
2008	Unstimulated	0.00	0.00		
	Stimulated	8.50	27.49		
	Penta	1.20	0.00	1.20	0.00
	gB	0.00	0.00	0.00	0.00
2009	Unstimulated	0.48	0.23		
	Stimulated	3.78	14.50		
	Penta	0.33	0.45	-0.15	0.22
	gB	0.12	0.48	-0.36	0.26
2010	Unstimulated	0.39	0.00		
	Stimulated	10.45	51.20		
	Penta	0.00	0.00	-0.39	0.00
	gB	0.00	0.00	-0.39	0.00

Appendix 17

mRNA-1647 - Intracellular IFNγ Production following Antigen Stimulation
Group 3 - Males

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Background Subtracted: Percent of T_h	Unstimulated Background Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
3001	Unstimulated	0.00	0.00		
	Stimulated	2.57	7.93		
	Penta	0.30	0.00	0.30	0.00
	gB	0.91	0.00	0.91	0.00
3002	Unstimulated	0.84	0.00		
	Stimulated	5.05	8.81		
	Penta	0.65	0.00	-0.20	0.00
	gB	0.57	0.26	-0.27	0.26
3103	Unstimulated	0.49	0.25		
	Stimulated	2.36	4.03		
	Penta	0.22	0.24	-0.27	-0.01
	gB	0.15	0.29	-0.34	0.04
3004	Unstimulated	0.00	0.00		
	Stimulated	3.55	8.18		
	Penta	0.00	0.00	0.00	0.00
	gB	0.13	0.25	0.13	0.25
3005	Unstimulated	0.22	0.35		
	Stimulated	5.35	6.35		
	Penta	0.68	0.00	0.46	-0.35
	gB	0.21	0.00	-0.01	-0.35
3006	Unstimulated	0.36	0.00		
	Stimulated	3.72	6.13		
	Penta	0.31	0.44	-0.05	0.44
	gB	0.36	0.48	0.00	0.48
3007	Unstimulated	0.00	0.00		
	Stimulated	7.95	25.83		
	Penta	0.21	0.74	0.21	0.74
	gB	0.22	0.00	0.22	0.00
3008	Unstimulated	0.00	0.00		
	Stimulated	4.34	11.86		
	Penta	0.35	0.46	0.35	0.46
	gB	0.23	0.64	0.23	0.64
3009	Unstimulated	0.13	0.22		
	Stimulated	9.28	22.34		
	Penta	0.00	0.58	-0.13	0.36
	gB	0.55	0.23	0.42	0.01
3010	Unstimulated	0.00	0.00		
	Stimulated	4.55	18.77		
	Penta	0.16	0.47	0.16	0.47
	gB	0.18	0.00	0.18	0.00

Appendix 17

mRNA-1647 - Intracellular IFNγ Production following Antigen Stimulation
Group 4 - Males

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Background Subtracted: Percent of T_h	Unstimulated Background Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
4001	Unstimulated	0.00	0.00		
	Stimulated	5.25	9.97		
	Penta	0.18	0.28	0.18	0.28
	gB	0.38	0.00	0.38	0.00
4002	Unstimulated	0.00	0.00		
	Stimulated	6.39	18.82		
	Penta	0.00	0.99	0.00	0.99
	gB	0.34	0.00	0.34	0.00
4003	Unstimulated	0.00	0.00		
	Stimulated	2.63	7.71		
	Penta	0.00	0.00	0.00	0.00
	gB	0.17	0.00	0.17	0.00
4004	Unstimulated	0.00	0.63		
	Stimulated	4.76	27.07		
	Penta	0.33	0.00	0.33	-0.63
	gB	0.32	0.00	0.32	-0.63
4005	Unstimulated	0.00	0.00		
	Stimulated	5.24	17.50		
	Penta	0.50	0.71	0.50	0.71
	gB	0.82	0.00	0.82	0.00
4006	Unstimulated	0.45	0.00		
	Stimulated	6.33	13.36		
	Penta	0.39	0.00	-0.05	0.00
	gB	0.30	0.00	-0.15	0.00
4007	Unstimulated	0.00	0.00		
	Stimulated	12.55	35.38		
	Penta	1.37	2.56	1.37	2.56
	gB	0.61	0.70	0.61	0.70
4008	Unstimulated	0.57	0.00		
	Stimulated	4.74	13.04		
	Penta	0.26	0.00	-0.32	0.00
	gB	0.26	0.00	-0.32	0.00
4009	Unstimulated	0.00	0.00		
	Stimulated	7.16	12.75		
	Penta	0.00	0.00	0.00	0.00
	gB	0.00	0.00	0.00	0.00
4010	Unstimulated	0.00	0.00		
	Stimulated	3.55	13.48		
	Penta	6.99	8.96	6.99	8.96
	gB	3.17	4.52	3.17	4.52

Appendix 17

mRNA-1647 - Intracellular IFNγ Production following Antigen Stimulation
Group 1 - Females

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Background Subtracted: Percent of T_h	Unstimulated Background Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
1501	Unstimulated	0.72	0.00		
	Stimulated	9.80	52.59		
	Penta	0.37	0.00	-0.34	0.00
	gB	1.51	0.41	0.79	0.41
1502	Unstimulated	1.26	0.00		
	Stimulated	6.59	17.33		
	Penta	1.20	0.33	-0.05	0.33
	gB	1.29	0.69	0.03	0.69
1503	Unstimulated	1.25	0.00		
	Stimulated	6.98	13.78		
	Penta	1.27	0.29	0.02	0.29
	gB	1.02	0.42	-0.23	0.42
1504	Unstimulated	0.64	0.00		
	Stimulated	4.36	15.65		
	Penta	0.43	0.00	-0.22	0.00
	gB	0.66	0.00	0.02	0.00
1505	Unstimulated	0.28	0.00		
	Stimulated	15.33	32.12		
	Penta	1.41	0.00	1.13	0.00
	gB	0.28	0.00	0.00	0.00
1506	Unstimulated	1.54	0.68		
	Stimulated	5.65	23.76		
	Penta	0.36	0.70	-1.18	0.03
	gB	1.65	0.54	0.11	-0.14
1507	Unstimulated	1.17	0.00		
	Stimulated	6.35	26.32		
	Penta	0.93	0.00	-0.24	0.00
	gB	1.72	0.44	0.54	0.44
1508	Unstimulated	1.07	0.00		
	Stimulated	8.89	18.12		
	Penta	1.46	0.00	0.40	0.00
	gB	0.51	0.00	-0.56	0.00
1509	Unstimulated	0.42	0.00		
	Stimulated	10.49	34.02		
	Penta	0.00	0.00	-0.42	0.00
	gB	0.56	0.00	0.14	0.00
1510	Unstimulated	0.76	0.56		
	Stimulated	4.82	10.53		
	Penta	1.85	0.00	1.09	-0.56
	gB	0.27	0.00	-0.48	-0.56

Appendix 17

mRNA-1647 - Intracellular IFNγ Production following Antigen Stimulation
Group 2 - Females

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Background Subtracted: Percent of T_h	Unstimulated Background Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
2501	Unstimulated	0.00	0.00		
	Stimulated	12.30	47.97		
	Penta	1.39	0.92	1.39	0.92
	gB	0.00	0.00	0.00	0.00
2502	Unstimulated	0.00	0.00		
	Stimulated	7.84	57.14		
	Penta	0.00	0.00	0.00	0.00
	gB	0.69	0.00	0.69	0.00
2503	Unstimulated	0.43	0.51		
	Stimulated	5.60	32.43		
	Penta	0.78	4.42	0.35	3.91
	gB	0.44	0.00	0.01	-0.51
2504	Unstimulated	1.35	0.00		
	Stimulated	4.03	27.88		
	Penta	1.79	2.78	0.43	2.78
	gB	0.47	0.00	-0.88	0.00
2505	Unstimulated	0.53	0.00		
	Stimulated	6.41	36.84		
	Penta	0.33	0.00	-0.20	0.00
	gB	1.82	0.00	1.30	0.00
2506	Unstimulated	0.69	0.57		
	Stimulated	5.61	22.54		
	Penta	0.30	1.24	-0.40	0.68
	gB	0.00	0.00	-0.69	-0.57
2507	Unstimulated	2.18	1.03		
	Stimulated	6.85	15.73		
	Penta	0.90	0.00	-1.28	-1.03
	gB	0.47	0.00	-1.71	-1.03
2508	Unstimulated	0.54	0.00		
	Stimulated	14.92	25.48		
	Penta	1.64	0.65	1.11	0.65
	gB	0.90	0.00	0.36	0.00
2509	Unstimulated	0.83	0.00		
	Stimulated	7.62	18.68		
	Penta	0.70	0.00	-0.13	0.00
	gB	1.87	0.00	1.04	0.00
2510	Unstimulated	0.74	0.00		
	Stimulated	15.81	30.82		
	Penta	0.34	3.10	-0.40	3.10
	gB	0.97	0.00	0.23	0.00

Appendix 17

mRNA-1647 - Intracellular IFNγ Production following Antigen Stimulation
Group 3 - Females

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Background Subtracted: Percent of T_h	Unstimulated Background Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
3501	Unstimulated	1.75	0.00		
	Stimulated	18.14	49.45		
	Penta	2.30	1.20	0.54	1.20
	gB	2.08	0.00	0.33	0.00
3502	Unstimulated	0.89	1.24		
	Stimulated	6.01	17.46		
	Penta	0.00	0.00	-0.89	-1.24
	gB	1.05	0.00	0.16	-1.24
3503	Unstimulated	1.34	0.00		
	Stimulated	9.13	22.22		
	Penta	1.39	0.00	0.05	0.00
	gB	3.50	4.17	2.15	4.17
3504	Unstimulated	0.91	0.00		
	Stimulated	12.66	51.11		
	Penta	3.07	0.00	2.16	0.00
	gB	0.61	0.00	-0.30	0.00
3505	Unstimulated	0.40	0.00		
	Stimulated	6.91	12.24		
	Penta	0.49	0.00	0.09	0.00
	gB	0.43	0.00	0.03	0.00
3506	Unstimulated	2.24	0.00		
	Stimulated	3.57	10.37		
	Penta	0.80	2.24	-1.45	2.24
	gB	0.69	0.00	-1.55	0.00
3507	Unstimulated	0.00	0.00		
	Stimulated	10.71	21.82		
	Penta	1.23	2.70	1.23	2.70
	gB	1.59	0.00	1.59	0.00
3508	Unstimulated	0.51	1.18		
	Stimulated	8.73	16.67		
	Penta	0.99	1.00	0.48	-0.18
	gB	1.05	3.95	0.54	2.77
3509	Unstimulated	2.17	0.00		
	Stimulated	16.67	50.79		
	Penta	2.78	2.17	0.60	2.17
	gB	0.00	1.41	-2.17	1.41
3510	Unstimulated	0.00	0.00		
	Stimulated	8.50	28.41		
	Penta	0.57	0.00	0.57	0.00
	gB	0.00	0.00	0.00	0.00

Appendix 17

mRNA-1647 - Intracellular IFNγ Production following Antigen Stimulation
Group 4 - Females

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Background Subtracted: Percent of T_h	Unstimulated Background Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
4501	Unstimulated	0.00	0.00		
	Stimulated	11.63	27.27		
	Penta	0.00	0.00	0.00	0.00
	gB	1.75	0.00	1.75	0.00
4502	Unstimulated	1.85	0.00		
	Stimulated	6.85	27.78		
	Penta	2.04	0.00	0.19	0.00
	gB	1.75	0.00	-0.10	0.00
4503	Unstimulated	0.00	0.00		
	Stimulated	10.37	27.27		
	Penta	3.16	0.00	3.16	0.00
	gB	3.00	3.23	3.00	3.23
4504	Unstimulated	0.73	1.96		
	Stimulated	13.58	36.11		
	Penta	0.00	2.94	-0.73	0.98
	gB	0.00	0.00	-0.73	-1.96
4505	Unstimulated	0.67	0.00		
	Stimulated	6.02	27.06		
	Penta	1.27	1.49	0.59	1.49
	gB	0.98	1.96	0.30	1.96
4506	Unstimulated	1.90	0.00		
	Stimulated	5.39	55.10		
	Penta	0.88	0.00	-1.03	0.00
	gB	0.00	0.00	-1.90	0.00
4507	Unstimulated	0.62	0.00		
	Stimulated	4.17	19.35		
	Penta	3.05	0.00	2.44	0.00
	gB	0.00	0.00	-0.62	0.00
4508	Unstimulated	1.77	1.33		
	Stimulated	12.35	53.57		
	Penta	0.74	1.06	-1.03	-0.27
	gB	0.75	1.28	-1.02	-0.05
4509	Unstimulated	1.68	0.00		
	Stimulated	8.48	28.77		
	Penta	1.61	2.94	-0.07	2.94
	gB	0.00	0.00	-1.68	0.00
4510	Unstimulated	1.98	0.00		
	Stimulated	17.07	54.05		
	Penta	1.52	4.35	-0.47	4.35
	gB	0.00	4.76	-1.98	4.76

Appendix 18

FINAL REPORT

Study Phase: Immunology - Alpha-1-acid Glycoprotein, Alpha-2-macroglobulin and Cytokines

Test Facility Study No. 5002034

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)

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Appendix 18

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Appendix 18

LIST OF APPENDICES

Appendix 18

1. INTRODUCTION

This report describes the evaluation of alpha-1-acid glycoprotein, alpha-2-macroglobulin and cytokines in rat plasma (EDTA) or serum samples from Study No. 5002034 titled "A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats followed by a 2-Week Recovery Period".

For the work detailed in this report, the phase experimental start date was 25 May 2017, and the phase experimental completion date was 08 Jun 2017.

1.1. Materials and Methods

The methodology and materials used for the analyses were detailed in their respective analytical procedures (only the latest version is appended) and listed in the table below:

Analyte	Analytical procedure(s) no.
Alpha-1-acid glycoprotein (AGP)	AP.5002034.AGP.01
Alpha-2-macroglobulin (A2M)	AP.5002034.A2M.01
IL-1β, IL-6, IP-10, MCP-1, MIP-1α and TNF-α	AP.5002034.Cyt.01

The methods were not validated.

1.2. Computerized Systems

Critical computerized systems used in this study phase are listed below (see Text Table 1)

Text Table 1
Computerized Systems

System name	Version no.	Description of data collected and/or analyzed
Softmax Pro GxP	5.4.6	Data collection
Bio Plex Manager (Bio-Rad)	Version 6.1	Data collection
Watson LIMS	7.4.2 SP1	Sample tracking/ analysis/regression
Microsoft Excel	2007	Descriptive statistics
Microsoft Word	2007	Data reporting
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 4.0.4	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

Appendix 18

2. RESULTS AND DISCUSSIONS

2.1. Standards and Quality Control samples for alpha-1-acid glycoprotein

Standards, Quality Control (QC) preparation and acceptance criteria are described in the latest version of the analytical procedure (Appendix 2). Standard curve and QC specifications are presented in (Text Table 2).

Text Table 2
Alpha-1-acid glycoprotein standard curve and Quality Controls specifications

Range of the Curve (ng/mL)	LLOQ (ng/mL)	ULOQ (ng/mL)	HQC (ng/mL)	MQC (ng/mL)	LQC (ng/mL)
3.13 to 800*	12.5	400	320	160	20.0

* Standard 3.13, 6.25 and 800 ng/mL are accessory standards used to define the lower and upper portion of the curve.

A total of 5 AGP assays were performed and all assays met the method's acceptance criteria.

2.2. Standards and Quality Control samples for alpha-2-macroglobulin

Standards, Quality Control (QC) preparation and acceptance criteria are described in the latest version of the analytical procedure (Appendix 3). Standard curve and QC specifications are presented in (Text Table 3).

Text Table 3
Alpha-2-Macroglobulin standard curve and Quality Controls specifications

Range of the Curve (ng/mL)	LLOQ (ng/mL)	ULOQ (ng/mL)	HQC (ng/mL)	MQC (ng/mL)	LQC (ng/mL)
3.13 to 400*	6.25	400	240	80.0	8.00

* Standard 3.13 ng/mL is an accessory standard used to define the lower portion of the curve.

A total of 7 A2M assays were performed and three assays were out of the method's acceptance criteria. A technical oversight during the preparation of the QCs is suspected since all assays performed the same day with the same preparation were out of acceptance criteria. All results were reported from the assays that met the acceptance criteria.

2.3. Standards and Quality Control samples for cytokine panel

Standard, Quality control (QC) preparation and acceptance criteria are described in the latest version of the analytical procedure (Appendix 4). Standard curve and quality control specifications are presented in (Text Table 4).

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Text Table 4
Cytokine standard curves and Quality Controls specifications

Cytokine panel	Range of the curve (pg/mL)	LLOQ (pg/mL)	ULOQ (pg/mL)	HQC (pg/mL)	MQC (pg/mL)	LQC (pg/mL)
IL-1β	11.7 to 1500	11.7	1500	1200	150	15.6
IL-6	352 to 45000	352	45000	36000	4500	469
IP-10	11.7 to 1500	11.7	1500	1200	150	15.6
MCP-1	141 to 18000	141	18000	14400	1800	188
MIP-1α	11.7 to 1500	11.7	1500	1200	150	15.6
TNF-α	2.93 to 375	2.93	375	300	37.5	7.81

A total of 9 cytokine assays were performed and 4 individual cytokines were out of the method's acceptance criteria (IL-1β and MCP-1 in the first assay, IL-1β in the second assay and TNF-α in the fourth assay). A technical oversight during the loading of QCs is suspected since the same cytokine analyses performed in other assays on the same day with the same preparations were within acceptance criteria. All results were reported from the assays that met the acceptance criteria.

2.4. Study Samples

For blood markers (AGP and A2M) analysis, approximately 0.7 mL of blood was collected from all animals (unscheduled and scheduled euthanasia) from the abdominal aorta on days 44 and 57. Blood samples were processed to serum and were stored in a freezer set to maintain -20°C until analysis.

Blood was collected from the jugular vein of all recovery animals on Days 1, 15, 29, 43 and 57 at 6 hours post dose for cytokine analysis (IL-1β, IL-6, TNF-α, IP-10, MIP-1α and MCP-1). Blood samples were processed to plasma, and to serum for IFN-α. Samples were stored in a freezer set to maintain -80°C until analysis. However due to method development issues, IFN-α analysis was withdrawn from the cytokine list and therefore IFN-α serum samples were not analyzed.

2.5. Cytokines

The study samples were analyzed in duplicate and results are presented in Table 10 and Appendice 14.

IL-1β

The quantifiable IL-1β concentration range in the reference item group was 26.37 pg/mL to 599.01 pg/mL. All IL-1β concentrations observed amongst the dosed group were lower or within the control group range. These changes were not statistically significant.

IL-6

For all animals, males and females, at all time points, the IL-6 concentrations observed were below the LLOQ. These changes were not statistically significant.

Appendix 18

TNF-α

Incidental TNF-α concentrations similar to the concentrations observed in the control group were detected in both genders. These changes were not statistically significant.

IP-10

Higher concentrations of IP-10, when compared to the reference item group, were observed in the high dosed group of mRNA-1647 with the highest concentrations being generally observed on Days 1, 15 and 29, 6 hours post dose in both genders. On Day 1, a 10.2-fold increase in males and 14.6-fold increase in females were observed when compared to the mean IP-10 concentration detected in the control group. On Day 15, a 10.8 and 15.9-fold increase were observed in males and females respectively. On Day 29, a 9.2 and 18.1-fold increase and on Day 43 a 5.8 to 9.0- fold increase were observed in both genders.

The changes were statistically significant on days 1, 15, 29 and 43 6 hours post dose in both genders.

On day 57, the concentration of IP-10 for the animal assigned to the dosed groups was very similar to the control group concentration for most animals, suggesting that animals had fully recovered.

MIP-1α

The MIP-1α concentrations observed across all males, at all time points were below the LLOQ, except for one dosed male where MIP-1α concentration close to the LLOQ was detected. In females, MIP-1α concentrations were detected in 3 out of 5 dosed animals on Days 1, 15 and 29 whereas all control group animals were < LLOQ. In one dosed animal, MIP-1α concentration was also detected on Day 43. These changes were not statistically significant.

MCP-1

In males, the quantifiable MCP-1 concentration range in the reference item group was 290.05 to 516.54 pg/mL. MCP-1 concentrations observed amongst the dosed group were higher than the control group range in 3 out of 5 animals. Concentrations of 533.42 to 1191.17 pg/mL were observed leading to a 1.4 to 1.6-fold increase on days 1, 15, 29 and 43.

In females, MCP-1 concentrations from the control group were lower than in control males. A 4.1-fold increase was observed on Day 1, a 6.5-fold increase on Day 15, a 5.9-fold increase on day 29 and a 2.3-fold increase on Day 43 6 hours post dose when compared to the mean MCP-1 concentration detected in the control group.

The changes were statistically significant on day 1, 15 and 29 6 hours post dose for females.

On day 57, the concentration of MCP-1 for the animal assigned to the dosed groups was similar to the control group concentration for most animals, suggesting that animals had fully recovered.

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3. CONCLUSION

Statistically significant increases of IP-10 concentrations were observed in both genders dosed with mRNA-1647 at 89 μg/dose at all timepoints, except Day 57 where the IP-10 concentration was back to control level. The highest IP-10 concentrations were generally observed on Day 1 6 hours post dose.

In dosed females, MCP-1 concentrations were increased on Days 1, 15 and 29 6 hours post dose when compared to the control group, and the increases were statistically significant. MCP-1 concentrations were back to control level on Day 57.

No changes were observed in the IL-1β, IL-6, MIP-1α and TNF-α levels following dosing.

All samples collected for the AGP, A2M and cytokines analyses were analyzed using qualified immunoassay methods. Based on the acceptable performance of the standards and QCs during sample analysis, it is concluded that the concentration values reported for the study samples are valid.

Appendix 18

4. REPORT APPROVAL

(b) (6) Date: 03 Oct 2017

(b) (6)

Appendix 18

Appendix 1
Deviations

Appendix 18

DEVIATIONS

All deviations that occurred during this study phase have been acknowledged by the Study Director, assessed for impact, and documented in the study records. None of the deviations were considered to have impacted the overall integrity of this study phase or the interpretation of the study phase results and conclusions.

Appendix 18

Appendix 2
AP.5002158.AGP.01

Appendix 18

ANALYTICAL PROCEDURE

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Title: ELISA METHOD FOR THE QUANTITATIVE DETECTION OF ALPHA 1 ACID GLYCOPROTEIN IN RAT SERUM	AP Number: AP.5002034.AGP.01	Effective Date: Signature of AP
	Page 1 of 6 pages	Supersedes: N/A
Prepared and approved by: (b) (6) (b) (6)	(b) (6)	Date: 25 May 2017
Authorized by: (b) (6) (b) (6)	(b) (6)	Date: 25/May/2017

1. **PURPOSE**

The purpose of this assay is to describe an ELISA method for the quantitation of alpha 1 acid glycoprotein in rat serum.

2. **SCOPE**

This analytical procedure applies to all personnel performing activities related to this method.

3. **RESPONSIBILITY**

All staff performing this assay are responsible for compliance with this analytical procedure.

4. **DEFINITIONS/ABBREVIATIONS**

ELISA:	enzyme-linked immunosorbent assay
% Diff:	% difference
LLOQ:	lower limit of quantitation
LQC:	low concentration quality control sample
MQC:	mid concentration quality control sample
HQC:	high concentration quality control sample
ULOQ:	upper limit of quantitation
N/A:	not applicable
QC:	quality control sample
RT:	ambient room temperature in a non-controlled environment in a normally acceptable room temperature
RF:	refrigerated in a refrigerator set at 4°C
F:	frozen in a freezer set at -20°C
STD:	standard
TBD:	to be determined
UPW:	Ultra Pure Water

5. **REQUIRED FORM**

Appendix #1: Assay Information Sheet.
Appendix #2: AGP standards and QC's Preparation Sheet.
Appendix #3: Study Samples Dilution Preparation Sheet.
Appendix #4: Working Solutions Preparation Sheet.
Appendix #5: Rat AGP Assay Sheets.

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No: AP.5002034.AGP.01	Date effective: Signature of AP	Supersedes: N/A	Page 2 of 6 pages

6. MATERIALS/EQUIPMENT/REAGENT

(b) (4)

7. PREPARATION OF SOLUTIONS, STANDARDS, QUALITY CONTROLS (QC) AND STUDY SAMPLES

(b) (4)

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(b) (4)

8. **ASSAY PROCEDURE**

(b) (4)

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(b) (4)

9. **EXPORTING DATA TO WATSON LIMS**

(b) (4)

10. **FORMULAS**

(b) (4)

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No: AP.5002034.AGP.01	Date effective: Signature of AP	Supersedes: N/A	Page 5 of 6 pages

(b) (4)

11. ACCEPTANCE CRITERIA

(b) (4)

Appendix 18

No: AP.5002034.AGP.01	Date effective: Signature of AP	Supersedes: N/A	Page 6 of 6 pages

(b) (4)

12. VERSION HISTORY

Version	Date	Reason for revision
01	Date of AP signature	N/A

Appendix 18

Assay Information Sheet

Study/reference number: 5002034 Assay ID:_____

Verified by/date: _____

1-Kits information

Kit	lot# to be used
Alpha 1 acid glycoprotein ELISA kit	

2-Standards and QC information

2.1 Calibrator lot to be used:

	lot# to be used	Volume for the reconstitution (mL)	Concentration obtained (ng/mL)
Calibrator			

2.2 Working range:

Working range	STD ID	Concentration (ng/mL)
ULOQ	STD 8	(b) (4)
LLOQ	STD 2	

2.3 Standard concentration:

Standards ID	Concentration (ng/mL)
STD 9	(b) (4)
STD 8	
STD 7	
STD 6	
STD 5	
STD 4	
STD 3	
STD 2	
STD 1	
STD 0	

2.4 Quality control concentration:

QC ID	Concentration (ng/mL)
LQC	(b) (4)
MQC	
HQC	

(b) (4)

Appendix #1 (AP.5002034.AGP.01) 1 of 1

Appendix 18

AGP standards and QC's Preparation Sheet

Study/reference number: 5002034

Assay ID:_____

Verified by/date: _____

Reagent ID:	Lot # or batch#:	Inventory ID:
Calibrator		
Sample diluent AGP		N/A

Standard ID	Stock ID	Reference quantity (ng)	# of vial used	Volume of UPW added to each vial (µL) and mix until dissolved	Performed (√)	Final calculated concentration (ng/mL)	Pool each vial together or N/A ( ) performed (√)
STD stock	Calibrator	(b) (4)			( )	(b) (4)	( )

Standard/QC ID	Target concentration (ng/mL)	Stock ID	Stock concentration (ng/mL)	Stock volume (µL)	Sample diluent AGP volume (µL)	Preparation performed (√)	Total volume (µL)	Final calculated concentration (ng/mL)
STD 9	(b) (4)	STD stock	(b) (4)		(b) (4)	( )	(b) (4)	
STD 8		STD 9				( )		
STD 7		STD 8				( )		
STD 6		STD 7				( )		
STD 5		STD 6				( )		
STD 4		STD 5				( )		
STD 3		STD 4				( )		
STD 2		STD 3				( )		
STD 1		STD 2				( )		
STD 0		N/A	N/A	N/A		( )		
HQC		STD stock	(b) (4)			( )		
MQC		HQC				( )		
LQC		MQC				( )		

Pipette ID(s): _____

Performed by/date: _____ Reviewed by/date: _____

Appendix #2 (AP.5002034.AGP.01) 1 of 1

Appendix 18

Study Samples Dilution Prepation Sheet

Study/reference number: 5002034 Assay ID:_____

Verified by/date: _____

Reagent ID:	Batch #:
Sample diluent AGP	

Sample ID	Dilution fold	Stock ID	Stock volume (µL)	Sample diluent AGP volume (µL)	Preparation performed (√)	Total volume (µL)
TS-1 stock 1	(b) (4)		(b) (4)		( )	(b) (4)
TS-1		TS-1 stock 1			( )	
TS-2 stock 1					( )	
TS-2		TS-2 stock 1			( )	
TS-3 stock 1					( )	
TS-3		TS-3 stock 1			( )	
TS-4 stock 1					( )	
TS-4		TS-4 stock 1			( )	
TS-5 stock 1					( )	
TS-5		TS-5 stock 1			( )	
TS-6 stock 1					( )	
TS-6		TS-6 stock 1			( )	
TS-7 stock 1					( )	
TS-7		TS-7 stock 1			( )	
TS-8 stock 1					( )	
TS-8		TS-8 stock 1			( )	
TS-9 stock 1					( )	
TS-9		TS-9 stock 1			( )	
TS-10 stock 1					( )	
TS-10		TS-10 stock 1			( )	
TS-11 stock 1					( )	
TS-11		TS-11 stock 1			( )	
TS-12 stock 1					( )	
TS-12		TS-12 stock 1			( )	
TS-13 stock 1					( )	
TS-13		TS-13 stock 1			( )	
TS-14 stock 1					( )	
TS-14		TS-14 stock 1			( )	
TS-15 stock 1					( )	
TS-15		TS-15 stock 1			( )	
TS-16 stock 1					( )	
TS-16		TS-16 stock 1			( )	

Pipette ID(s): _____

Performed by/date: _____ Reviewed by/date: _____

Appendix #3 (AP.5002034.AGP.01) 1 of 1

Appendix 18

Study/reference number: 5002034 Working Solutions Preparation Sheet Assay ID:_____

Verified by/date: _____

Preparation of: **Dectection working solution AGP (DWS AGP)**				
Reagent	Lot # or batch#:	Inventory ID:	Volume (µL)	Performed (√)
(b) (4)			(b) (4)	( )
		N/A		
Volume required (mL)				Performed (√)
The dectection working solution AGP was protected from light until use				( )
Preparation time:				

Pipette ID(s): _____

Timer ID: _____

Performed by/date: _____ Reviewed by/date: _____

Appendix #4 (AP.5002034.AGP.01) 1 of 1

Appendix 18

Rat AGP Assay Sheets

Study/reference number: 5002034 Assay ID:_____

Verified by/date:_____

Reagents/solutions/instruments/material used		
Name	**Lot#/batch#/ID:**	**Entered by/date:**
Alpha 1 Acid Glycoprotein ELISA kit: Inventory ID:_____		
Assay plate:		
Wash buffer AGP:		
Detection working solution AGP:	Refer to appendix #4	
TMB substrate solution:		
Stop solution:		
Pipette(s):		
Plate washer:		
Plate shaker:		
Multi-channel pipette(s):		
Timer:		

Comments:_____

Reviewed by/date:_____

Appendix #5 (AP.5002034.AGP.01) 1 of 4

Appendix 18

Rat AGP Assay Sheets

Study/reference number: 5002034

Pre-loading[a] and loading plate sequence assay ID: ____________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD 0	STD 0	STD 8	STD 8								
B	STD 1	STD 1	STD 9	STD 9								
C	STD 2	STD 2	LQC	LQC								
D	STD 3	STD 3	MQC	MQC								
E	STD 4	STD 4	HQC	HQC								
F	STD 5	STD 5									LQC	LQC
G	STD 6	STD 6									MQC	MQC
H	STD 7	STD 7									HQC	HQC

Pre-loading[a] and loading plate sequence assay ID: ____________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD 0	STD 0	STD 8	STD 8								
B	STD 1	STD 1	STD 9	STD 9								
C	STD 2	STD 2	LQC	LQC								
D	STD 3	STD 3	MQC	MQC								
E	STD 4	STD 4	HQC	HQC								
F	STD 5	STD 5									LQC	LQC
G	STD 6	STD 6									MQC	MQC
H	STD 7	STD 7									HQC	HQC

Pre-loading[a] and loading plate sequence assay ID: ____________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD 0	STD 0	STD 8	STD 8								
B	STD 1	STD 1	STD 9	STD 9								
C	STD 2	STD 2	LQC	LQC								
D	STD 3	STD 3	MQC	MQC								
E	STD 4	STD 4	HQC	HQC								
F	STD 5	STD 5									LQC	LQC
G	STD 6	STD 6									MQC	MQC
H	STD 7	STD 7									HQC	HQC

Pre-loading[a] and loading plate sequence assay ID: ____________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD 0	STD 0	STD 8	STD 8								
B	STD 1	STD 1	STD 9	STD 9								
C	STD 2	STD 2	LQC	LQC								
D	STD 3	STD 3	MQC	MQC								
E	STD 4	STD 4	HQC	HQC								
F	STD 5	STD 5									LQC	LQC
G	STD 6	STD 6									MQC	MQC
H	STD 7	STD 7									HQC	HQC

a = Only the shaded columns are used for the pre-loading plate sequence (in singlicate).

Reviewed by/date: ____________________

Appendix 18

Rat AGP Assay Sheets

Study/reference number: 5002034

Steps	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Performed by/date
(b) (4)	( )	( )	( )	( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	Time:	Time:	Time:	Time:	
	( )	( )	( )	( )	
	( )	( )	( )	( )	

*includes standards, QCs and diluted study samples.

Reviewed by/date:_____

Appendix #5 (AP.5002034.AGP.01)

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Appendix 18

Rat AGP Assay Sheets

Study/reference number: 5002034

Data review				
Assay acceptance criteria	Assay ID:	Assay ID:	Assay ID	Assay ID
(b) (4)	Yes or No	Yes or No	Yes or No	Yes or No
	/	/	/	/
	/	/	/	/
	/	/	/	/
	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/
Entered by/date:				

*with percent theoretical within 75% - 125% and within ±25% difference between replicate values.

SCIENTIFIC REVIEW				
	Assay ID:	Assay ID:	Assay ID	Assay ID
Assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No
Entered by/date:				

Reviewed by/date:_____

Appendix #5 (AP.5002034.AGP.01)

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Appendix 18

Appendix 3
AP.5002158.A2M.01

Appendix 18

ANALYTICAL PROCEDURE

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Title: ELISA METHOD FOR THE QUANTITATIVE DETECTION OF ALPHA 2-MACROGLOBULIN IN RAT SERUM	AP Number: AP.5002034.A2M.01	Effective Date: Signature of AP
	Page 1 of 5 pages	Supersedes: N/A
Approved by: (b) (6) (b) (6)	(b) (6)	Date: 19 May 2017
Authorized by: (b) (6) (b) (6)	(b) (6)	Date: 19/May 2017

1. **PURPOSE**
The purpose of this assay is to describe an ELISA method for the quantitation of alpha 2-macroglobulin in rat serum.

2. **SCOPE**
This analytical procedure applies to all personnel performing activities related to this method.

3. **RESPONSIBILITY**
All staff performing this assay are responsible for compliance with this analytical procedure.

4. **REQUIRED FORM**
Appendix #1: Assay information sheet
Appendix #2: Standards and QC's preparation sheet
Appendix #3: Study samples dilution sheet
Appendix #4: A2M detection working solution preparation sheet
Appendix #5: Rat A2M assay sheet

5. **MATERIALS/EQUIPMENT/REAGENT**
(b) (4)

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No: AP.5002034.A2M.01	Date effective: Signature of AP	Supersedes: N/A	Page 2 of 5 pages

(b) (4)

6. **PREPARATION ASSAY REAGENT**

(b) (4)

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No: AP.5002034.A2M.01	Date effective: Signature of AP	Supersedes: N/A	Page 3 of 5 pages

(b) (4)

7. **ASSAY PROCEDURE**

(b) (4)

8. **EXPORTING DATA TO WATSON LIMS**

(b) (4)

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No: AP.5002034.A2M.01	Date effective: Signature of AP	Supersedes: N/A	Page 4 of 5 pages

(b) (4)

9. FORMULAS

(b) (4)

10. ACCEPTANCE CRITERIA

(b) (4)

Appendix 18

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(b) (4)

[redacted]

Version	Date	Reason for revision
01	Date of AP signature	N/A

Appendix 18

Assay information sheet

Study/reference number: 5002034 Assay ID:_____

Verified by/date: _____

1-Kits information

Kit	lot# to be used
Alpha 2-macroglobulin ELISA kit	

2-Standards and QC information

2.1 Calibrator lot to be used:

	lot# to be used	Volume for the reconstitution (mL)	Concentration obtained (ng/mL)
Calibrator			

2.2 Working range:

Working range	STD ID:	Concentration (ng/mL)
ULOQ	STD 8	(b) (4)
LLOQ	STD 2	

2.3 Standard concentration:

Standards ID	Concentration (ng/mL)
STD 8	(b) (4)
STD 7	
STD 6	
STD 5	
STD 4	
STD 3	
STD 2	
STD 1	
STD 0	

2.4 Quality control concentration:

QC ID	Concentration (ng/mL)
LQC	(b) (4)
MQC	
HQC	

(b) (4)

_____

_____

Appendix #1 (AP.5002034.A2M.01) 1 of 1

Appendix 18

Standards and QC's preparation sheet

Study/reference number: 5002034

Assay ID:_____

Verified by/date: _____

Reagent ID:	Lot # or batch#:	Inventory ID:
Calibrator		
Sample diluent A2M		N/A

Standard ID	Stock ID	Reference quantity (ng)	# of vial used	Volume of UPW added to each vial (µL) and mix until dissolved	Performed (√)	Final calculated concentration (ng/mL)	Pool each vial together or N/A ( ) performed (√)
STD stock	Calibrator	(b) (4)			( )	(b) (4)	( )

Standard/QC ID	Target concentration (ng/mL)	Stock ID	Stock concentration (ng/mL)	Stock volume (µL)	Sample diluent A2M volume (µL)	Preparation performed (√)	Total volume (µL)	Final calculated concentration (ng/mL)
STD 8	(b) (4)	(b) (4)		(b) (4)		( )	(b) (4)	
STD 7						( )		
STD 6						( )		
STD 5						( )		
STD 4						( )		
STD 3						( )		
STD 2						( )		
STD 1						( )		
STD 0		N/A	N/A			( )		
HQC		(b) (4)				( )		
MQC						( )		
LQC						( )		

Pipette ID(s): _____

Performed by/date: _____ Reviewed by/date: _____

Appendix #2 (AP.5002034.A2M.01) 1 of 1

Appendix 18

Study samples dilution sheet

Study/reference number: 5002034

Assay ID:

Verified by/date:

Reagent ID:	Batch #:
Sample diluent A2M	

Sample ID	Dilution fold	Stock		Sample diluent A2M volume (µL)	Preparation performed (√)	Total volume (µL)
		ID	volume (µL)			
	(b) (4)				( )	(b) (4)
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
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					( )	
					( )	
					( )	

Pipette ID(s):

Performed by/date:

Reviewed by/date:

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Appendix 18

Study/reference number: 5002034 A2M detection working solution preparation sheet Assay ID:_____

Verified by/date: _____

Preparation of: **A2M dectection working solution (DWS)**				
Reagent	Lot # or batch#:	Inventory ID:	Volume (µL)	Performed (√)
(b) (4)			(b) (4)	( )
		N/A		
			Volume required (mL)	Performed (√)
The A2M dectection working solution was protected from light until use				( )
Preparation time:				

Pipette ID(s): _____

Timer ID: _____

Performed by/date: _____ Reviewed by/date: _____

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Appendix 18

Rat A2M Assay sheet

Study/reference number: 5002034 Assay ID:_____

Verified by/date:_____

Reagents/solutions/instruments/material used		
Name	**Lot#/batch#/ID:**	**Entered by/date:**
Alpha 2-Macroglobulin ELISA kit: Inventory ID:_____		
Assay plate:		
Wash buffer:		
Standards and QC's:	Refer to appendix #2	
Diluted samples:	Refer to appendix #3	
A2M detection working solution (DWS):	Refer to appendix #4	
TMB substrate solution:		
Stop solution:		
Pipette(s):		
Plate washer:		
Plate shaker:		
Multi-channel pipette(s):		
Timer:		

Comments:_____

Reviewed by/date:_____

Appendix #5 (AP.5002034.A2M.01) 1 of 4

Appendix 18

Rat A2M Assay sheet

Study/reference number: 5002034

Pre-loading[a] and loading plate sequence assay ID: ____________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD 0	STD 0	STD 8	STD 8								
B	STD 1	STD 1	LQC	LQC								
C	STD 2	STD 2	MQC	MQC								
D	STD 3	STD 3	HQC	HQC								
E	STD 4	STD 4										
F	STD 5	STD 5									LQC	LQC
G	STD 6	STD 6									MQC	MQC
H	STD 7	STD 7									HQC	HQC

Pre-loading[a] and loading plate sequence assay ID: ____________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD 0	STD 0	STD 8	STD 8								
B	STD 1	STD 1	LQC	LQC								
C	STD 2	STD 2	MQC	MQC								
D	STD 3	STD 3	HQC	HQC								
E	STD 4	STD 4										
F	STD 5	STD 5									LQC	LQC
G	STD 6	STD 6									MQC	MQC
H	STD 7	STD 7									HQC	HQC

Pre-loading[a] and loading plate sequence assay ID: ____________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD 0	STD 0	STD 8	STD 8								
B	STD 1	STD 1	LQC	LQC								
C	STD 2	STD 2	MQC	MQC								
D	STD 3	STD 3	HQC	HQC								
E	STD 4	STD 4										
F	STD 5	STD 5									LQC	LQC
G	STD 6	STD 6									MQC	MQC
H	STD 7	STD 7									HQC	HQC

Pre-loading[a] and loading plate sequence assay ID: ____________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD 0	STD 0	STD 8	STD 8								
B	STD 1	STD 1	LQC	LQC								
C	STD 2	STD 2	MQC	MQC								
D	STD 3	STD 3	HQC	HQC								
E	STD 4	STD 4										
F	STD 5	STD 5									LQC	LQC
G	STD 6	STD 6									MQC	MQC
H	STD 7	STD 7									HQC	HQC

a = Only the shaded columns are used for the pre-loading plate sequence (in singlicate).

Reviewed by/date:____________________

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Appendix 18

Rat A2M Assay sheet

Study/reference number: 5002034

Steps	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Performed by/date
(b) (4)	( )	( )	( )	( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	Time:	Time:	Time:	Time:	
	( )	( )	( )	( )	
	( )	( )	( )	( )	

*includes standards, QCs and diluted study samples.

Reviewed by/date:_____

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Appendix 18

Rat A2M Assay sheet

Study/reference number: 5002034

Data review				
Assay acceptance criteria	Assay ID:	Assay ID:	Assay ID	Assay ID
(b) (4)	Yes or No	Yes or No	Yes or No	Yes or No
	/	/	/	/
Number of LQC meet acceptance criteria*	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/
Number of HQC meet acceptance criteria*	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/
Entered by/date:				

*with percent theoretical within ±25% and within ±25% difference between replicate values.

SCIENTIFIC REVIEW				
	Assay ID:	Assay ID:	Assay ID	Assay ID
Assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No
Entered by/date:				

Reviewed by/date:_____

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Appendix 18

Appendix 4
AP.5002158.Cyt.01

Appendix 18

ANALYTICAL PROCEDURE

charles river | every step of the way.

Title: **MULTIPLEX METHOD FOR THE QUANTITATIVE DETECTION OF IL-1β, IL-6, IP-10, MCP-1, MIP-1 AND TNF-α IN RAT PLASMA**	AP Number: AP.5002034.Cyt.01	Effective Date: Date of AP signature
	Page 1 of 7 pages	Supersedes: N/A
Approved by: (b) (6) (b) (6) (b) (6)		Date: 23 May 2017
Authorized by: (b) (6) (b) (6) (b) (6)		Date: 23/May/2017

1. **PURPOSE**
   To describe a multiplex method for the quantitation of IL-1β, IL-6, IP-10, MCP-1, MIP-1 and TNF-α in rat plasma.
2. **SCOPE**
   This analytical procedure applies to all personnel performing activities related to this method.
3. **RESPONSIBILITY**
   All staff performing this assay is responsible for compliance with this analytical procedure.
4. **REQUIRED FORM**
   Appendix #1: Assay information sheet
   Appendix #2: Standards and QC's cytokine preparation sheet
   Appendix #3: Study samples dilution sheet
   Appendix #4: Beads working solution preparation sheet
   Appendix #5: Rat cytokines assay sheet
5. **MATERIALS/EQUIPMENT/REAGENT**

(b) (4)

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(b) (4)

6. **PREPARATION OF ASSAY REAGENTS**

(b) (4)

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(b) (4)

7. ASSAY PROCEDURE:

(b) (4)

8. THE BIO-PLEX SUSPENSION ARRAY PROTOCOL

(b) (4)

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(b) (4)

9. EXPORTING DATA TO WATSON LIMS

(b) (4)

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(b) (4)

11. ACCEPTANCE CRITERIA

(b) (4)

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11.3. Run Acceptance Criteria

(b) (4)

11.4. Sample acceptance criteria and reporting

(b) (4)

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(b) (4)

12. VERSION HISTORY

Version	Date	Updates
01	Date of AP signature	N/A

Appendix 18

Assay information sheet

Study/reference number: 5002034 Assay ID:_____

Verified by/date: _____

1-Kits information

Kit	lot# to be used
Rat cytokine/chemokine magnetic bead panel kit:	

2-Standards and QC information

2.1 Standard lot to be used:

Rat cytokine standard lot #: _____

2.2 Working range:

Working range	Concentration (pg/mL) IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
ULOQ	(b) (4)					
LLOQ						

2.3 Standard concentration:

Standards ID	Concentration (pg/mL) IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Standard stock	(b) (4)					
STD 11						
STD 10						
STD 9						
STD 8						
STD 7						
STD 6						
STD 5						
STD 4						
STD 3						
STD 2						
STD 1						
STD 0						

2.4 Quality control concentration:

QC ID	Concentration (pg/mL) IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
HQC B	(b) (4)					
HQC A						
MQC B						
MQC A						
LQC B						
LQC A						

3-Threshold value

The threshold value for a replicate to reach a limit of % CV acceptance criteria from LLOQ (pg/mL)*	Concentration (pg/mL) IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Threshold value:	(b) (4)					
% CV acceptance criteria:						

*Fold dilution not taken into account.

4-Additional information or N/A (____)

_____

_____

Reviewed by/date:_____

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Appendix 18

Standards and QCs cytokine preparation sheet

Study/reference number: 5002034 Assay ID:_____

Verified by/date: _____

Reagent ID:	Lot #	Inventory ID:
Rat cytokine/chemokine standard:		
Assay buffer		

Standard ID	Stock ID	# of vial(s) used	Volume of UPW added to each vial (µL)	Left at ambient RT for at least 5 minutes		Pool vials together (if applicable) Performed (√) ( )
STD stock	Rat cytokine /chemokine standard	(b) (4)		Start:	End:	

Standard/ QC ID	Stock ID	Stock concentration (pg/mL) IL-1β, IP-10, MIP-1α, TNF-α	IL-6	MCP-1	Stock volume	Assay buffer volume	Preparation performed (v)	Total volume (µL)	Final calculated concentration (pg/mL) IL-1β, IP-10, MIP-1α, TNF-α	IL-6	MCP-1
STD 11	STD stock	(b) (4)					( )	(b) (4)			
STD 10	STD 11						( )				
STD 9	STD 10						( )				
STD 8	STD 9						( )				
STD 7	STD 8						( )				
STD 6	STD 7						( )				
STD 5	STD 6						( )				
STD 4	STD 5						( )				
STD 3	STD 4						( )				
STD 2	STD 3						( )				
STD 1	STD 2						( )				
STD 0	N/A						( )				
HQC B	STD 10						( )				
HQC A	STD 8						( )				
MQC B	STD 10						( )				
MQC A	STD 8						( )				
LQC B	STD 5						( )				
LQC A	STD 5						( )				

Pipette(s) ID: _____

Timer ID: _____

Performed by/date: _____ Reviewed by/date: _____

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Appendix 18

Study samples dilution sheet

Study/reference number: 5002034 Assay ID:________________

Verified by/date: ____

Reagent:	Lot #:	Inventory ID:
Assay buffer		

Sample ID	Fold Dilution	Stock ID	Stock volume (µL)	Assay buffer volume (µL)	Dilution performed (√)	Total volume (µL)
	(b) (4) [redacted]		(b) (4) [redacted]		( )	(b) (4) [redacted]
					( )	
					( )	
					( )	
					( )	
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					( )	

Pipette ID(s): ____

Performed by/date: ________________________ Reviewed by/date: ________________

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Appendix 18

Study/reference number: 5002034 Beads working solution preparation sheet Assay ID:_____

Verified by/date: _____

Bead vials preparation:				Performed (√)
Sonicate antibody-bead bottles and then vortex thoroughly before the solution preparation				( )
Preparation of: **Antibody-immobilized beads working solution**				
Reagent	lot#:	Inventory ID:	Volume (µL)	Performed (√)
(b) (4)			(b) (4)	( )
				( )
				( )
				( )
				( )
				( )
				( )
Total volume (µL)				Performed (√)
The antibody-immobilized beads working solution was protected from light until use				( )

Pipette ID(s): _____

Sonic bath ID: _____

Performed by/date: _____ Reviewed by/date: _____

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Appendix 18

Rat cytokines assay sheet

Study/reference number: 5002034 Assay ID:_____

Verified by/date: _____

Reagents/solutions/instruments/material used on Day 1		
Name	**Lot / batch / ID**	**Entered by/date**
(b) (4)		
	Refer to appendix #4	

Reagents/solutions/instruments/material used on Day 2		
Name	**Lot / batch / ID**	**Entered by/date**
(b) (4)		

Comment(s): _____

Reviewed by/date:_____

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Appendix 18

Rat cytokines assay sheet

Study/reference number: 5002034

Pre-loading[a] and loading plate sequence assay ID: ______________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
B	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
C	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
D	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
E	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
F	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
G	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B
H	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B

Pre-loading[a] and loading plate sequence assay ID: ______________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
B	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
C	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
D	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
E	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
F	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
G	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B
H	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B

Pre-loading[a] and loading plate sequence assay ID: ______________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
B	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
C	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
D	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
E	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
F	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
G	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B
H	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B

Pre-loading[a] and loading plate sequence assay ID: ______________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
B	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
C	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
D	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
E	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
F	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
G	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B
H	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B

a = Only the shaded rows are used for the pre-loading plate sequence (in singlicate).

Reviewed by/date:______________________
Appendix #5 (AP.5002034.Cyt.01)

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Appendix 18

Rat cytokines assay sheet

Study/reference number: 5002034

Steps	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Performed by/date
(b) (4)	( )	( )	( )	( )	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	( ) or N/A ( )	( ) or N/A ( )	( ) or N/A ( )	( ) or N/A ( )	
	( )	( )	( )	( )	

*Includes standards, QCs and diluted study samples.

Reviewed by/date:_____

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Appendix 18

Rat cytokines assay sheet

Study/reference number: 5002034

Data Review						
Assay acceptance criteria Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of STDs in the curve with a % theoretical within ±25% except for LLOQ and ULOQ which should be within ±30%.	/	/	/	/	/	/
Number of LQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Number of HQC meet acceptance criteria*	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/
Assay acceptance criteria Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of STDs in the curve with a % theoretical within ±25% except for LLOQ and ULOQ which should be within ±30%.	/	/	/	/	/	/
Number of LQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Number of HQC meet acceptance criteria*	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/

*with percent theoretical within 25% and within 25% CV between duplicate. Also, at least one replicate has a acquired bead number≥ 30.

Performed by/date: _____

Scientific Review						
Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
Cytokine assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
At least one replicate has a acquired beads number ≥ 30 and the %CV is within 25% (or both replicates are LLOQ)	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
Cytokine assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
At least one replicate has a acquired beads number ≥ 30 and the %CV is within 25% (or both replicates are LLOQ)	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No

Performed by/date: _____

Reviewed by/date: _____

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Rat cytokines assay sheet

Study/reference number: 5002034

Data Review						
Assay acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**IP-10 N/A ( )**	**MCP-1 N/A ( )**	**MIP-1α N/A ( )**	**TNF-α N/A ( )**
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of STDs in the curve with a % theoretical within ±25% except for LLOQ and ULOQ which should be within ±30%.	/	/	/	/	/	/
Number of LQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Number of HQC meet acceptance criteria*	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/
Assay acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**IP-10 N/A ( )**	**MCP-1 N/A ( )**	**MIP-1α N/A ( )**	**TNF-α N/A ( )**
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of STDs in the curve with a % theoretical within ±25% except for LLOQ and ULOQ which should be within ±30%.	/	/	/	/	/	/
Number of LQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Number of HQC meet acceptance criteria*	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/

*with percent theoretical within 25% and within 25% CV between duplicate. Also, at least one replicate has a acquired bead number≥ 30.

Performed by/date: _____

Scientific Review						
Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**IP-10 N/A ( )**	**MCP-1 N/A ( )**	**MIP-1α N/A ( )**	**TNF-α N/A ( )**
Cytokine assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
At least one replicate has a acquired beads number ≥ 30 and the %CV is within 25% (or both replicates are LLOQ)	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**IP-10 N/A ( )**	**MCP-1 N/A ( )**	**MIP-1α N/A ( )**	**TNF-α N/A ( )**
Cytokine assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
At least one replicate has a acquired beads number ≥ 30 and the %CV is within 25% (or both replicates are LLOQ)	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No

Performed by/date: _____

Reviewed by/date: _____

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FINAL REPORT

Study Phase: Pathology

Testing Facility Study No. 5002034

TEST SITE:
Charles River Laboratories, Inc.
4025 Stirrup Creek Drive, Suite 150
Durham, NC 27703
United States

TESTING FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)
1580 Ida-Metiviere
Sherbrooke, QC J1E 0B5
Canada

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QUALITY ASSURANCE STATEMENT

Study No.: 5002034

This phase has been audited by Quality Assurance in accordance with the applicable Good Laboratory Practice regulations. Reports were submitted in accordance with standard operating procedures as follows:

QA INSPECTION DATES

		Dates Findings Submitted to:			
Date(s) of Audit	Phase(s) Audited	Principal Investigator	Principal Investigator Management	Study Director	Study Director Management
22-Aug-2017	Draft Phase Report – Pathology	22-Aug-2017	22-Aug-2017	22-Aug-2017	22-Aug-2017
14-Sep-2017	Final Phase Report – Pathology	14-Sep-2017	14-Sep-2017	14-Sep-2017	14-Sep-2017

Process-based inspections relevant to this study were conducted according to a predetermined schedule. The outcome of each inspection was reported to Management and, where relevant for processes seen as part of a study, the Study Director.

Facilities relevant to this study are included in Charles River's annual facility inspection programme. The outcome of each inspection is reported to Management.

The Final Report has been reviewed to assure that it accurately describes the materials and methods and the reported results accurately reflect the raw data.

(b) (6)

(b) (6)

20 Sep 2017

Date

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COMPLIANCE STATEMENT AND REPORT APPROVAL

The pathology phase of this study conducted in the USA was performed in accordance with the U.S. Department of Health and Human Services, Food and Drug Administration. United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (OECD Principles of Good Laboratory Practice), Japan (MHLW), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

This phase of the study was conducted in accordance with the procedures described herein. All deviations (if any) authorized/acknowledged by the Study Director are documented in the Study Records. The report represents an accurate and complete record of the results obtained for this study phase.

There were no deviations from the above regulations that affected the overall integrity of this study phase or the interpretation of the phase results and conclusions.

(b) (6) Date: 20Sep2017

(b) (6)

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1. SUMMARY

This report presents the pathology findings in rats assigned to Study No. 5002034. The objective of this study was to determine the potential toxicity of mRNA-1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

A complete gross pathological examination was performed on all animals, organ weights were recorded, and a detailed microscopic evaluation was performed on all protocol-specified tissues from all animals in Groups 1 and 4 and early death animals and all gross lesions from all animals. Additionally, bone marrow, sciatic nerve, liver, spleen, injection site, popliteal lymph node, and inguinal lymph node were evaluated in all Group 2 and 3 terminal euthanasia animals and all recovery euthanasia animals.

The administration of four doses of mRNA-1647 over 6 weeks at doses of 8.9, 27, or 89 µg/dose by intramuscular (IM) injection to rats was well tolerated with no mRNA-1647-related effects on survival. Both localized and systemic tissue reactions were noted; however, systemic effects were limited in severity.

mRNA-1647-related localized tissue reactions involved the intramuscular injection sites, the draining popliteal and/or inguinal lymph nodes, and the sciatic nerves in animals administered ≥ 18.9 µg/dose of mRNA-1647. At the intramuscular injection sites, gross observations of abnormal firm consistency, dark focus, and/or swelling generally correlated microscopically with minimal to moderate mixed cell inflammation involving the subcutaneous tissues, skeletal muscle, and to a lesser extent the dermis, as well as associated minimal to moderate subcutaneous edema and minimal to mild myofiber degeneration. In the draining inguinal and/or popliteal lymph nodes, gross enlargement generally correlated microscopically with minimal to marked mixed cell inflammation. In addition, minimal to marked mixed cell inflammation was noted in the perineurial tissue surrounding the sciatic nerve.

mRNA-1647-related systemic tissue reactions involved the bone marrow and spleen in animals administered ≥ 8.9 µg/dose of mRNA-1647. These systemic findings included minimal increased myeloid hematopoiesis in the bone marrow, increases in absolute and/or relative spleen weights without correlating histopathology, and minimal to mild decreased cellularity of the splenic periarteriolar lymphoid sheath.

Following a two-week recovery period, mRNA-1647-related macroscopic findings in any tissue and microscopic findings in the draining lymph nodes (popliteal and/or inguinal) or sciatic nerves were not present. A reduced incidence and severity of increased absolute and/or relative spleen weights (no histopathology correlate); the absence of mixed cell inflammation and edema, with a shift to minimal to mild mononuclear cell infiltration, at the intramuscular injections sites; and a reduced incidence and/or severity of perineurial mixed cell inflammation associated with the sciatic nerves, increased myeloid hematopoiesis in the bone marrow, and decreased cellularity of the periarteriolar lymphoid sheath in the spleen were consistent with partial recovery.

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2. RESPONSIBLE PERSONNEL

Principal Investigator, Pathology	(b) (6) Durham, North Carolina
Test Site Management	(b) (6) Charles River Laboratories, Inc. Horsham, Pennsylvania

3. INTRODUCTION

This report presents the pathology findings in rats assigned to Study No. 5002034. The objective of this study was to determine the potential toxicity of mRNA-1647, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

The study was sponsored by Moderna Therapeutics, Inc., Cambridge, MA. (b) (6), served as the Study Director.

4. MATERIALS AND METHODS

Experimental procedures applicable to pathology investigations are summarized in Text Table 1. Deviations to the pathology procedures performed by the Test Site are listed in Appendix 1.

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10/8.9	200	0.05/0.045	10	10	-	-
3	mRNA-1647	30/27	200	0.15/.014	10	10	-	-
4	mRNA-1647	100/89	200	0.5/0.45	10	10	5	5

- : Not applicable
a- Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 31 May 2017.

All surviving animals were submitted for necropsy on Day 44 (Terminal Euthanasia) or Day 57 (Recovery Euthanasia). Necropsies were performed and organ weights were collected by Testing Facility personnel. Statistical analysis of organ weight data was performed by the Testing Facility. Tissues required for microscopic evaluation were trimmed, processed routinely, embedded in paraffin, and stained with hematoxylin and eosin by Charles River Laboratories Inc, Montreal, Canada. Microscopic evaluation was conducted by the Principal Investigator, a board-certified veterinary pathologist, on all protocol-specified tissues from all animals in Groups 1 and 4 and early death animal and all gross lesions from all animals. Additionally, bone marrow, sciatic nerve, liver, spleen, injection site, popliteal lymph node, and inguinal lymph node were evaluated in all Group 2 and 3 terminal euthanasia animals and all recovery euthanasia animals. Tissues were evaluated by light microscopy.

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4.1. Computerized Systems

Critical computerized systems used in the study by the Test Site are listed in Text Table 2.

Text Table 2
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	8	Histopathology

4.2. Disposition of Study Materials

All study-specific raw data, pathology materials, documentation and Final Report generated from this study phase are to be transferred to CR MTL archive. Study materials will be retained for a period of 1 year following issue of the audited Draft Report. Electronic Provantis data generated by the Test Site will be archived, and the software and hardware required to produce it in a readable form will be maintained and available. The electronic data will be archived in Charles River Laboratories, Inc., Wilmington, MA.

5. RESULTS AND DISCUSSIONS

5.1. Mortality

One control group male (Animal No. 1014) was found dead on study day 43. Gross observations for this animal included small, dark discoloration, and soft abnormal consistency of the right adrenal gland (no histopathology correlates); dark discoloration of the corticomedullary junction of the kidneys (no histopathology correlate); dark focus and dark discoloration of the thymus (incidental thymic hemorrhage); and failure of the lungs to collapse (lung congestion). Histopathology findings were incidental and did not explain the cause of death for this animal.

5.2. Gross Pathology

5.2.1. Terminal Euthanasia Animals (Day 44)

(Table 1 and Appendix 8)

mRNA-1647-related gross pathology findings are summarized in Text Table 3.

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Text Table 3
Summary of Gross Pathology Findings – Terminal Euthanasia (Day 44)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**8.9**	**27**	**89**	**0**	**8.9**	**27**	**89**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injection (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency, firm	0	1	5	9	0	3	5	7
Swelling	0	5	6	9	0	5	5	7
Focus, dark	0	0	0	0	0	1	1	3
Lymph Node, Inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	1	1	0	5	0	0	0	1
Lymph Node, Popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	7	7	0	8	6	7

At the intramuscular injection sites, dose-dependent mRNA-1647-related gross observations of abnormal firm consistency, dark focus, and/or swelling were noted in animals administered ≥ 8.9 µg/dose of mRNA-1647. These gross observations correlated microscopically with mixed cell inflammation of the subcutaneous and/or muscular tissue and/or subcutaneous edema at the injection site.

In the draining inguinal and/or popliteal lymph nodes, mRNA-1647-related gross enlargement was noted in animals administered ≥ 8.9 µg/dose of mRNA-1647, and correlated microscopically to mixed cell inflammation. Gross enlargement and microscopic mixed cell inflammation most commonly involved the popliteal lymph nodes. Gross enlargement of the inguinal lymph node was noted in one control group male without any correlating microscopic finding.

Other gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in control and treated animals and, therefore, were considered unrelated to administration of mRNA-1647.

5.2.2. Recovery Euthanasia Animals (Day 57)

(Table 2 and Appendix 8)

mRNA-1647-related gross pathology findings noted at the terminal euthanasia were no longer observed at the end of the recovery period (Day 57) and are summarized in Text Table 4.

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Text Table 4
Summary of Gross Pathology Findings – Recovery Euthanasia (Day 57)

	Males		Females	
Group	**1**	**4**	**1**	**4**
Dose (µg/dose)	**0**	**89**	**0**	**89**
No. Animals Examined	**4**	**5**	**5**	**5**
Lymph Node, Inguinal (No. Examined)	4	5	5	5
Enlargement	0	1	0	0

Gross enlargement of the inguinal lymph node was noted in one 89 µg/dose mRNA-1647 group animal without any correlating microscopic finding. This finding could not be distinguished from the one affected control group animal at the terminal euthanasia and, thus, was not considered to be mRNA-1647-related.

All gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in control and treated animals and, therefore, were considered unrelated to administration of mRNA-1647.

5.3. Organ Weights

5.3.1. Terminal Euthanasia Animals (Day 44)

(Table 3, Table 4, Table 5, Appendix 2, Appendix 3, and Appendix 4)

mRNA-1647-related organ weight changes are summarized in Text Table 5.

Text Table 5
Summary of Organ Weight Data – Terminal Euthanasia (Day 44)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**8.9**	**27**	**89**	**8.9**	**27**	**89**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Spleen (No. Weighed)[a]	10	10	10	10	10	10
Absolute weight	1.0794	1.0824	**1.2070** [b]	0.7125	**0.7566** [a]	**0.7934** [b]
% of body weight	**0.21190** [a]	**0.21678** [a]	**0.23429** [c]	0.22732	**0.24041** [b]	**0.25394** [c]
% of brain weight	48.79592	49.81185	**55.10209** [b]	34.70430	**36.98272** [a]	**38.80259** [b]

[a] Significantly different from control group 1value p≤0.05 (Dunnett).
[b] Significantly different from control group 1 value p≤0.01 (Dunnett).
[c] Significantly different from control group 1 value p≤0.001 (Dunnett).
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – P ≤ 0.05; refer to data tables for actual significance levels and tests used.

In the spleen, slight dose-dependent increases in absolute and/or relative organ weights were noted in males and females administered ≥ 8.9 µg/dose of mRNA-1647. These changes were consistently statistically significant for increases in absolute and/or relative (to body and/or to brain) weights in males administered 89 µg/dose of mRNA-1647 and females administered ≥

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27 µg/dose of mRNA-1647. These splenic weight changes were not correlated with any specific histopathology finding.

No other mRNA-1647-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or related to difference of sexual maturity and unrelated to administration of mRNA-1647.

5.3.2. Recovery Euthanasia Animals (Day 57)

(Table 6, Table 7, Table 8, Appendix 5, Appendix 6, and Appendix 7)

mRNA-1647-related organ weight changes noted at the terminal euthanasia were still observed at the end of the recovery period (Day 57) and are summarized in Text Table 6.

Text Table 6
Summary of Organ Weight Data – Recovery Euthanasia (Day 57)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**8.9**	**27**	**89**	**8.9**	**27**	**89**
No. Animals per Group	**0**	**0**	**5**	**0**	**0**	**5**
Spleen (No. Weighed)[a]	0	0	5	0	0	5
Absolute value	-	-	1.1022	-	-	0.6522
% Difference	-	-	+18.90	-	-	+9.65
% of body weight	-	-	**0.18856** [a]	-	-	0.20057
% Difference	-	-	+21.50	-	-	+11.74
% of brain weight	-	-	48.35552	-	-	31.90101
% Difference	-	-	+19.86	-	-	+11.58

[a] Significantly different from control group 1 value p≤0.05 (T-Test).
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – P ≤ 0.05; refer to data tables for actual significance levels and tests used.

In the spleen, a slight increase in absolute and/or relative organ weights were noted in males and females administered 89 µg/dose of mRNA-1647. These changes were not statistically significant, with the exception of mean spleen weight relative to final body weight in the males; and thus, were considered to have limited toxicological importance. These splenic weight changes were not correlated with any specific histopathology finding.

No other mRNA-1647-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or related to difference of sexual maturity and unrelated to administration of mRNA-1647.

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5.4. Histopathology

5.4.1. Terminal Euthanasia (Day 44)

(Table 9 and Appendix 8)

mRNA-1647-related microscopic findings were noted at injection sites, draining lymph nodes (popliteal and/or inguinal), sciatic nerve, bone marrow, and spleen and these findings are summarized in Text Table 7.

Text Table 7
Summary of Microscopic Findings – Terminal Euthanasia (Day 44)

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (µg/dose)	0	8.9	27	89	0	8.9	27	89
No. Animals Examined	10	10	10	10	10	10	10	10
Site, Injection (No. Examined)	10	10	10	10	10	10	10	10
Inflammation: mixed cell; subcutaneous	0	10	9	10	0	10	10	10
Minimal	-	1	0	0	0	10	10	10
Mild	-	6	3	4	0	7	8	2
Moderate	-	3	6	6	0	2	1	7
Edema; subcutaneous	0	5	8	9	0	6	8	10
Minimal	-	2	0	2	-	2	2	0
Mild	-	3	2	3	-	3	4	3
Moderate	-	0	6	4	-	1	2	7
Degeneration; myofiber	4	7	9	6	4	5	8	6
Minimal	4	7	8	5	3	4	6	6
Mild	0	0	1	1	1	1	2	0
Lymph Node, Popliteal (No. Examined)	10	10	10	10	10	10	10	10
Inflammation; mixed cell	0	2	10	9	0	10	10	10
Minimal	-	0	2	1	-	4	2	0
Mild	-	2	4	3	-	6	7	5
Moderate	-	0	4	4	-	0	1	5
Marked	-	0	0	1	-	0	0	0
Lymph Node, Inguinal (No. Examined)	10	10	10	10	10	10	10	10
Inflammation; mixed cell	0	0	1	3	0	0	0	0
Minimal	-	-	1	1	-	-	-	-
Mild	-	-	0	2	-	-	-	-
Sciatic Nerve (No. Examined)	10	10	10	10	10	10	10	10
Inflammation; mixed; perineurial	0	10	10	10	0	10	10	9
Minimal	-	0	2	1		4	3	1
Mild	-	2	4	1	-	2	4	1
Moderate	-	3	4	8	-	4	3	6
Marked	-	5	0	0	-	0	0	1
Bone Marrow (No. Examined)	10	10	10	10	10	10	10	10
Increased hematopoiesis; myeloid	0	0	4	9	0	0	2	9
Minimal	-	-	4	9	-	-	2	9

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	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (µg/dose)	0	8.9	27	89	0	8.9	27	89
No. Animals Examined	10	10	10	10	10	10	10	10
Spleen (No. Examined)	10	10	10	10	10	10	10	10
Decreased cellarity; periarteriolar lymphoid sheath	0	4	9	10	0	7	10	10
Minimal	-	0	5	3	-	5	6	1
Mild	-	4	4	7	-	2	4	9

[a] Numbers in parentheses represent the number of animals with the finding.

Localized tissue reactions involved the intramuscular injection sites, the draining popliteal and/or inguinal lymph nodes, and the sciatic nerves. Systemic tissue reactions involved the bone marrow and spleen.

At the intramuscular injection sites, there was a dose-related inflammatory reaction characterized by minimal to moderate mixed cell inflammation involving the subcutaneous tissues, skeletal muscle, and to a lesser extent the dermis, as well as associated minimal to moderate subcutaneous edema and minimal to mild myofiber degeneration in animals administered ≥ 8.9 µg/dose of mRNA-1647. The inflammatory reaction, which increased in severity with increasing dose) often extended along and expanded endomysial and perimysial tissue layers, encircling individual muscle fibers and/or bundles. This reaction was characterized by varying numbers of intact and degenerating neutrophils, mononuclear cells, and macrophages (mixed cell inflammation); accumulations of protein-rich fluid (edema); and varying degrees of myofiber degeneration.

In the draining popliteal and/or inguinal lymph nodes, an increased incidence and/or severity of minimal to marked mixed cell inflammation were noted in male and female animals administered ≥ 8.9 µg/dose of mRNA-1647. The inflammation often involved the adventitia surrounding the lymph nodes, and most commonly involved the popliteal lymph nodes.

Minimal to marked mixed cell inflammation was frequently observed in the perineurial tissue surrounding the sciatic nerve of animals administered ≥ 8.9 µg/dose of mRNA-1647. This finding was considered to be an extension of the inflammatory reaction at the intramuscular injection sites to this region.

In the bone marrow, minimal increased myeloid hematopoiesis was noted in males and females administered ≥ 27 µg/dose of mRNA-1647. This finding was characterized by increased numbers of myeloid precursors in the marrow, and was secondary or compensatory inflammatory reaction noted at the intramuscular injection sites.

In the spleen, a dose-dependent minimal to mild decreased cellularity of the periarteriolar lymphoid sheath was noted in male and female animals administered ≥ 8.9 µg/dose of mRNA-1647.

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Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered unrelated to administration of mRNA-1647.

5.4.2. Recovery Euthanasia (Day 57)

(Table 10 and Appendix 8)

Following the recovery period, microscopic findings seen at the end of the terminal phase were no longer present in the draining lymph nodes (popliteal and/or inguinal), consistent with complete recovery.

Microscopic findings noted at the terminal euthanasia were observed at the end of the recovery period (Day 57) at injection sites (however, a shift to mononuclear cell infiltration rather than mixed cell inflammation was observed), sciatic nerve, bone marrow, and spleen and these findings are summarized in Text Table 8.

Text Table 8
Summary of Microscopic Findings – Recovery Euthanasia (Day 57)

	Males		Females	
Group	1	4	1	4
Dose (µg/dose)	0	89	0	89
No. Animals Examined	4	5	4	5
Site, Injection (No. Examined)	4	5	5	5
Infiltration, mononuclear cell; myofiber	0	2	0	5
Minimal	-	1	-	4
Mild	-	1	-	1
Nerve, Sciatic	4	5	5	5
Inflammation, mixed cell; perineurial	0	0	0	2
Minimal	-	-	-	2
Bone Marrow (No. Examined)	4	5	5	5
Increased hematopoiesis; myeloid	0	2	0	1
Minimal	-	2	-	1
Spleen (No. Examined)	4	5	5	5
Decreased cellularity; periarteriolar lymphoid sheath	0	2	0	0
Minimal	-	2	-	-

At the intramuscular injection sites, there was a residual inflammatory reaction characterized by minimal to mild mononuclear cell infiltration involving the subcutaneous tissues and skeletal muscle in the 89 µg/dose of mRNA-1647. Minimal to mild myofiber degeneration did not differ in incidence or severity from the reference group.

Mixed cell inflammation involving the draining lymph nodes (popliteal and/or inguinal) and sciatic nerves, as noted as the terminal euthanasia, was not noted at the recovery euthanasia, consistent with complete recovery.

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Minimal mixed cell inflammation was observed in the perineurial tissue surrounding the sciatic nerve of females administered 89 µg/dose of mRNA-1647. The incidence and severity of this finding was reduced compared to the terminal euthanasia.

In the bone marrow, minimal increased myeloid hematopoiesis was noted in males and females administered 89 µg/dose of mRNA-1647. The incidence of this finding was reduced compared to the terminal euthanasia.

In the spleen, a minimal decreased cellularity of the periarteriolar lymphoid sheath was noted in males administered 89 µg/dose of mRNA-1647. The incidence and severity of this finding was reduced compared to the terminal euthanasia.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered unrelated to administration of mRNA-1647.

6. CONCLUSIONS

The administration of four doses of mRNA-1647 over 6 weeks at doses of 8.9, 27 or 89 µg/dose by intramuscular (IM) injection to rats was well tolerated with no mRNA-1647-related effects on survival. Both localized and systemic tissue reactions were noted; however, systemic effects were limited in severity.

mRNA-1647-related localized tissue reactions involved the intramuscular injection sites, the draining popliteal and/or inguinal lymph nodes, and the sciatic nerves in animals administered ≥ 8.9 µg/dose of mRNA-1647. At the intramuscular injection sites, gross observations of abnormal firm consistency, dark focus, and/or swelling generally correlated microscopically with minimal to moderate mixed cell inflammation involving the subcutaneous tissues, skeletal muscle, and to a lesser extent the dermis, as well as associated minimal to moderate subcutaneous edema and minimal to mild myofiber degeneration. In the draining inguinal and/or popliteal lymph nodes, gross enlargement generally correlated microscopically with minimal to marked mixed cell inflammation. In addition, minimal to marked mixed cell inflammation was noted in the perineurial tissue surrounding the sciatic nerve.

mRNA-1647-related systemic tissue reactions involved the bone marrow and spleen in animals administered ≥ 8.9 µg/dose of mRNA-1647. These systemic findings included minimal increased myeloid hematopoiesis in the bone marrow, increases in absolute and/or relative spleen weights without correlating histopathology, and minimal to mild decreased cellularity of the splenic periarteriolar lymphoid sheath.

Following a two-week recovery period, mRNA-1647-related macroscopic findings in any tissue and microscopic findings in the draining lymph nodes (popliteal and/or inguinal) were not present. A reduced incidence and severity of increased absolute and/or relative spleen weights (no histopathology correlate); the absence of mixed cell inflammation and edema, with a shift to minimal to mild mononuclear cell infiltration, at the intramuscular injections sites; and a reduced

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incidence and/or severity of perineurial mixed cell inflammation associated with the sciatic nerves, increased myeloid hematopoiesis in the bone marrow, and decreased cellularity of the periarteriolar lymphoid sheath in the spleen were consistent with partial recovery.

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Table 1
Summary of Gross Pathology Findings (Day 44)

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BODY CAVITY, NASAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE MARROW								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE MARROW SMEAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
Not Examined: Not Required By Protocol/Study Plan	0	0	0	0	0	0	0	0
BONE, FEMUR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE, STERNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BRAIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
CERVIX								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
EPIDIDYMIS								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	9	10	10	.	.	.	.
Focus; pale	0	1	0	0	.	.	.	.
ESOPHAGUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

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5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
EYE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	9	10	10	10	10	10
Focus; dark	0	1	1	0	0	0	0	0
GALT								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, ADRENAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	9	8	8
Small	0	0	0	0	0	0	0	1
Abnormal consistency; soft	0	0	0	0	0	0	0	0
Discoloration; dark	0	0	0	0	0	0	0	0
Focus; dark	0	0	0	0	0	1	2	1
GLAND, HARDERIAN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, MAMMARY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PARATHYROID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PITUITARY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PROSTATE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	9	.	.	.	.
Small	0	0	0	1	.	.	.	.
Mass	0	0	0	1	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10

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5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, SALIVARY, MANDIBULAR (Continued...)								
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, SEMINAL VESICLE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, THYROID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	10	10	10	10	10	10	10
Small	1	0	0	0	0	0	0	0
HEART								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
KIDNEY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	8	10	10	10	9	10	9
Discoloration; dark	0	0	0	0	0	0	0	0
Focus; pale	0	2	0	0	0	0	0	0
Focus; raised	0	0	0	0	0	0	0	0
Adhesion	0	0	0	0	0	1	0	1
LARGE INTESTINE, CECUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, COLON								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, RECTUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	7	7	9	10	10	10	10
Parasite	0	3	3	1	0	0	0	0
LARYNX								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

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5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LIVER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	3	4	8	5	4	5	6	7
Focus; pale	7	6	2	5	6	5	4	3
LUNG								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	4	7	3	7	10	8	10	10
Failure to collapse	0	0	0	0	0	0	0	0
Focus; dark	6	3	7	3	0	2	0	0
LYMPH NODE								
Submitted	0	0	0	1	0	0	0	0
Focus; dark	.	.	.	1	.	.	.	.
LYMPH NODE, INGUINAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	8	10	5	9	10	10	9
Enlargement	1	1	0	5	0	0	0	1
Focus; dark	0	1	0	1	1	0	0	0
LYMPH NODE, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	5	6	6	10	6	8	7	4
Focus; dark	5	4	4	0	3	2	2	6
Enlargement	0	0	1	0	0	0	1	2
Discoloration; dark	0	0	0	0	1	0	0	0
LYMPH NODE, MESENTERIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LYMPH NODE, POPLITEAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	7	3	3	10	1	4	3
Enlargement	0	3	7	7	0	8	6	7
Focus; dark	0	0	0	1	0	2	0	0
MUSCLE, SKELETAL								
Submitted	10	10	10	10	10	10	10	10

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5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
MUSCLE, SKELETAL (Continued...)								
No Visible Lesions	10	10	10	10	10	10	9	10
Material accumulation; clot	0	0	0	0	0	0	1	0
NERVE, OPTIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, SCIATIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
OVARY								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
Cyst; pale	.	.	.	.	0	0	0	0
PANCREAS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SITE, INJECTION								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	4	0	0	10	2	0	0
Swelling	0	5	6	9	0	5	5	7
Abnormal consistency; firm	0	1	5	9	0	3	5	7
Focus; dark	0	0	0	0	0	1	1	3
SKIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	10	10	9	10	10	10
Scab; dark	0	1	0	0	1	0	0	0
SMALL INTESTINE, DUODENUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, ILEUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

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5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SMALL INTESTINE, JEJUNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, CERVICAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, LUMBAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, THORACIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPLEEN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	8	10	10	10	10	10
Focus; pale	0	1	2	0	0	0	0	0
STOMACH								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
TESTIS								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	9	10	10	.	.	.	.
Small	0	1	0	0	.	.	.	.
Abnormal consistency; soft	0	1	0	0	.	.	.	.
THYMUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	2	0	3	3	3	3	2	1
Discoloration; dark	1	0	1	0	0	2	1	1
Focus; dark	8	10	7	7	7	6	7	9
Focus; raised	0	0	1	0	0	0	0	0
Abnormal consistency; firm	1	0	0	1	0	0	1	0
Material accumulation; clot	0	0	0	0	0	0	1	0

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
TONGUE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
TRACHEA								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
URINARY BLADDER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
UTERUS								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
VAGINA								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10

Appendix 19

Table 2
Summary of Gross Pathology Findings (Found Dead & Day 57)

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
GALT		
Submitted	1	
No Visible Lesions	1	
GLAND, ADRENAL		
Submitted	1	
No Visible Lesions	0	
Small	1	
Abnormal consistency; soft	1	
Discoloration; dark	1	
Focus; dark	0	
GLAND, HARDERIAN		
Submitted	1	
No Visible Lesions	1	
GLAND, MAMMARY		
Submitted	1	
No Visible Lesions	1	
GLAND, PARATHYROID		
Submitted	1	
No Visible Lesions	1	
GLAND, PITUITARY		
Submitted	1	
No Visible Lesions	1	
GLAND, PROSTATE		
Submitted	1	
No Visible Lesions	1	
Small	0	
Mass	0	
GLAND, SALIVARY, MANDIBULAR		
Submitted	1	
No Visible Lesions	1	
GLAND, SEMINAL VESICLE		
Submitted	1	
No Visible Lesions	1	

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: FOUND DEAD	Male 0 ug/dose Group 1	
Number of Animals:	1	
GLAND, THYROID		
Submitted	1	
No Visible Lesions	1	
Small	0	
HEART		
Submitted	1	
No Visible Lesions	1	
KIDNEY		
Submitted	1	
No Visible Lesions	0	
Discoloration; dark	1	
Focus; pale	0	
Focus; raised	0	
Adhesion	0	
LARGE INTESTINE, CECUM		
Submitted	1	
No Visible Lesions	1	
LARGE INTESTINE, COLON		
Submitted	1	
No Visible Lesions	1	
LARGE INTESTINE, RECTUM		
Submitted	1	
No Visible Lesions	1	
Parasite	0	
LARYNX		
Submitted	1	
No Visible Lesions	1	
LIVER		
Submitted	1	
No Visible Lesions	1	
Focus; pale	0	
LUNG		
Submitted	1	
No Visible Lesions	0	

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: FOUND DEAD	Male 0 ug/dose Group 1	
Number of Animals:	1	
LUNG (Continued...)		
Failure to collapse	1	
Focus; dark	0	
LYMPH NODE		
Submitted	0	
LYMPH NODE, INGUINAL		
Submitted	1	
No Visible Lesions	1	
Enlargement	0	
Focus; dark	0	
LYMPH NODE, MANDIBULAR		
Submitted	1	
No Visible Lesions	1	
Focus; dark	0	
Enlargement	0	
Discoloration; dark	0	
LYMPH NODE, MESENTERIC		
Submitted	1	
No Visible Lesions	1	
LYMPH NODE, POPLITEAL		
Submitted	1	
No Visible Lesions	1	
Enlargement	0	
Focus; dark	0	
MUSCLE, SKELETAL		
Submitted	1	
No Visible Lesions	1	
Material accumulation; clot	0	
NERVE, OPTIC		
Submitted	1	
No Visible Lesions	1	
NERVE, SCIATIC		
Submitted	1	
No Visible Lesions	1	

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: FOUND DEAD	Male 0 ug/dose Group 1	
Number of Animals:	1	
PANCREAS		
Submitted	1	
No Visible Lesions	1	
SITE, INJECTION		
Submitted	1	
No Visible Lesions	1	
Swelling	0	
Abnormal consistency; firm	0	
Focus; dark	0	
SKIN		
Submitted	1	
No Visible Lesions	1	
Scab; dark	0	
SMALL INTESTINE, DUODENUM		
Submitted	1	
No Visible Lesions	1	
SMALL INTESTINE, ILEUM		
Submitted	1	
No Visible Lesions	1	
SMALL INTESTINE, JEJUNUM		
Submitted	1	
No Visible Lesions	1	
SPINAL CORD, CERVICAL		
Submitted	1	
No Visible Lesions	1	
SPINAL CORD, LUMBAR		
Submitted	1	
No Visible Lesions	1	
SPINAL CORD, THORACIC		
Submitted	1	
No Visible Lesions	1	
SPLEEN		
Submitted	1	
No Visible Lesions	1	

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: FOUND DEAD	Male 0 ug/dose Group 1	
Number of Animals:	1	
SPLEEN (Continued...)		
Focus; pale	0	
STOMACH		
Submitted	1	
No Visible Lesions	1	
TESTIS		
Submitted	1	
No Visible Lesions	1	
Small	0	
Abnormal consistency; soft	0	
THYMUS		
Submitted	1	
No Visible Lesions	0	
Discoloration; dark	1	
Focus; dark	1	
Focus; raised	0	
Abnormal consistency; firm	0	
Material accumulation; clot	0	
TONGUE		
Submitted	1	
No Visible Lesions	1	
TRACHEA		
Submitted	1	
No Visible Lesions	1	
URINARY BLADDER		
Submitted	1	
No Visible Lesions	1	

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
ARTERY, AORTA				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
BODY CAVITY, NASAL				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
BONE MARROW				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
BONE MARROW SMEAR				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
Not Examined: Not Required By Protocol/Study Plan	0	0	0	0
BONE, FEMUR				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
BONE, STERNUM				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
BRAIN				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
CERVIX				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
EPIDIDYMIS				
Submitted	4	5	.	.
No Visible Lesions	4	5	.	.
Focus; pale	0	0	.	.
ESOPHAGUS				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
EYE				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
Focus; dark	0	0	0	0
GALT				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
GLAND, ADRENAL				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
Small	0	0	0	0
Abnormal consistency; soft	0	0	0	0
Discoloration; dark	0	0	0	0
Focus; dark	0	0	0	0
GLAND, HARDERIAN				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
GLAND, MAMMARY				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
GLAND, PARATHYROID				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
GLAND, PITUITARY				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
GLAND, PROSTATE				
Submitted	4	5	.	.
No Visible Lesions	4	5	.	.
Small	0	0	.	.
Mass	0	0	.	.
GLAND, SALIVARY, MANDIBULAR				
Submitted	4	5	5	5

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
GLAND, SALIVARY, MANDIBULAR (Continued...)				
No Visible Lesions	4	5	5	5
GLAND, SEMINAL VESICLE				
Submitted	4	5	.	.
No Visible Lesions	4	5	.	.
GLAND, THYROID				
Submitted	4	5	5	5
No Visible Lesions	4	5	4	5
Small	0	0	1	0
HEART				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
KIDNEY				
Submitted	4	5	5	5
No Visible Lesions	3	5	5	5
Discoloration; dark	0	0	0	0
Focus; pale	0	0	0	0
Focus; raised	1	0	0	0
Adhesion	0	0	0	0
LARGE INTESTINE, CECUM				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
LARGE INTESTINE, COLON				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
LARGE INTESTINE, RECTUM				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
Parasite	0	0	0	0
LARYNX				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
LIVER				
Submitted	4	5	5	5
No Visible Lesions	2	4	3	3
Focus; pale	2	1	2	2
LUNG				
Submitted	4	5	5	5
No Visible Lesions	3	5	5	5
Failure to collapse	0	0	0	0
Focus; dark	1	0	0	0
LYMPH NODE				
Submitted	0	0	0	0
LYMPH NODE, INGUINAL				
Submitted	4	5	5	5
No Visible Lesions	4	4	5	5
Enlargement	0	1	0	0
Focus; dark	0	0	0	0
LYMPH NODE, MANDIBULAR				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	3
Focus; dark	0	0	0	2
Enlargement	0	0	0	1
Discoloration; dark	0	0	0	0
LYMPH NODE, MESENTERIC				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
LYMPH NODE, POPLITEAL				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
Enlargement	0	0	0	0
Focus; dark	0	0	0	0
MUSCLE, SKELETAL				
Submitted	4	5	5	5
No Visible Lesions	3	5	5	5

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
MUSCLE, SKELETAL (Continued...)				
Material accumulation; clot	1	0	0	0
NERVE, OPTIC				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
NERVE, SCIATIC				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
OVARY				
Submitted	.	.	5	5
No Visible Lesions	.	.	4	5
Cyst; pale	.	.	1	0
PANCREAS				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
SITE, INJECTION				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
Swelling	0	0	0	0
Abnormal consistency; firm	0	0	0	0
Focus; dark	0	0	0	0
SKIN				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
Scab; dark	0	0	0	0
SMALL INTESTINE, DUODENUM				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
SMALL INTESTINE, ILEUM				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
SMALL INTESTINE, JEJUNUM				
Submitted	4	5	5	5

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
SMALL INTESTINE, JEJUNUM (Continued...)				
No Visible Lesions	4	5	5	5
SPINAL CORD, CERVICAL				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
SPINAL CORD, LUMBAR				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
SPINAL CORD, THORACIC				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
SPLEEN				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
Focus; pale	0	0	0	0
STOMACH				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
TESTIS				
Submitted	4	5	.	.
No Visible Lesions	4	5	.	.
Small	0	0	.	.
Abnormal consistency; soft	0	0	.	.
THYMUS				
Submitted	4	5	5	5
No Visible Lesions	2	4	4	5
Discoloration; dark	0	0	0	0
Focus; dark	2	1	1	0
Focus; raised	0	0	0	0
Abnormal consistency; firm	0	0	0	0
Material accumulation; clot	0	0	0	0

Appendix 19

5002034 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
TONGUE				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
TRACHEA				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
URINARY BLADDER				
Submitted	4	5	5	5
No Visible Lesions	4	5	5	5
UTERUS				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
VAGINA				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5

Appendix 19

Table 3
Summary of Organ Weight Values - Absolute (Day 44)

Appendix 19

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	Mean	546.2	2.2096	1.2433	0.06399	0.01368	1.2443	0.02370
	SD	37.7	0.0569	0.0759	0.00939	0.00253	0.2282	0.00441
	N	10	10	10	10	10	10	10
2M	Mean	509.3	2.2108	1.2667	0.05993	0.01299	1.2647	0.02121
	SD	49.6	0.0997	0.1089	0.01065	0.00156	0.2526	0.00362
	N	10	10	10	10	10	10	10
	%Diff G1	-6.8	0.0543	1.8821	-6.34474	-5.04386	1.6395	-10.50633
3M	Mean	501.1	2.1685	1.2172	0.06257	0.01290	1.1256	0.01940
	SD	31.5	0.1063	0.0832	0.00744	0.00143	0.1686	0.00365
	N	10	10	10	10	10	10	10
	%Diff G1	-8.3	-1.8601	-2.0993	-2.21910	-5.70175	-9.5395	-18.14346
4M	Mean	514.0	2.1872	1.2340	0.07116	0.01421	1.1913	0.02252
	SD	28.9	0.0872	0.1128	0.00927	0.00431	0.1785	0.00461
	N	10	10	10	10	10	10	10
	%Diff G1	-5.9	-1.0138	-0.7480	11.20488	3.87427	-4.2594	-4.97890

Appendix 19

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	Mean	1.7548	3.1962	14.9816	1.7622	--	0.9560	3.9233
	SD	0.1280	0.2960	1.9001	0.1033	--	0.1546	0.4311
	N	10	10	10	10	--	10	10
2M	Mean	1.7253	3.1196	14.1684	1.8133	--	1.0794	3.8218
	SD	0.1492	0.3787	1.3269	0.2198	--	0.1780	0.3760
	N	10	10	10	10	--	10	10
	%Diff G1	-1.6811	-2.3966	-5.4280	2.8998	--	12.9079	-2.5871
3M	Mean	1.6585	2.8971	13.9754	1.7087	--	1.0824	3.7547
	SD	0.1148	0.2983	0.8041	0.1052	--	0.1579	0.3288
	N	10	10	10	10	--	10	10
	%Diff G1	-5.4878	-9.3580	-6.7162	-3.0360	--	13.2218	-4.2974
4M	Mean	1.6811	3.0812	14.9232	1.8089	--	1.2070b	3.8324
	SD	0.1173	0.2494	1.7834	0.1501	--	0.2087	0.4034
	N	10	10	10	10	--	10	10
	%Diff G1	-4.1999	-3.5980	-0.3898	2.6501	--	26.2552	-2.3169

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Appendix 19

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		THYMUS g	UTERUS g
1M	Mean	0.4927	--
	SD	0.1185	--
	N	10	--
2M	Mean	0.5105	--
	SD	0.1276	--
	N	10	--
	%Diff G1	3.6127	--
3M	Mean	0.4362	--
	SD	0.1176	--
	N	10	--
	%Diff G1	-11.4674	--
4M	Mean	0.5074	--
	SD	0.0948	--
	N	10	--
	%Diff G1	2.9836	--

Appendix 19

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1F	Mean	317.0	1.9901	--	0.06979	0.01643	--	0.01578
	SD	30.4	0.0547	--	0.00771	0.00159	--	0.00333
	N	10	10	--	10	10	--	10
2F	Mean	313.1	2.0484	--	0.07149	0.01645	--	0.01636
	SD	37.2	0.0876	--	0.01137	0.00250	--	0.00337
	N	10	10	--	10	10	--	10
	%Diff G1	-1.2	2.9295	--	2.43588	0.12173	--	3.67554
3F	Mean	315.3	2.0482	--	0.07227	0.01701	--	0.01596
	SD	32.9	0.0744	--	0.00603	0.00253	--	0.00287
	N	10	10	--	10	10	--	10
	%Diff G1	-0.5	2.9195	--	3.55352	3.53013	--	1.14068
4F	Mean	313.5	2.0397	--	0.07095	0.01671	--	0.01893
	SD	22.8	0.0707	--	0.00867	0.00254	--	0.00249
	N	10	10	--	10	10	--	10
	%Diff G1	-1.1	2.4923	--	1.66213	1.70420	--	19.96198

Appendix 19

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	Mean	1.1953	1.9343	8.2988	1.3272	0.0910	0.6045	--
	SD	0.1280	0.1945	0.9451	0.1173	0.0090	0.1114	--
	N	10	10	10	10	10	10	--
2F	Mean	1.2129	1.9519	9.1267	1.3837	0.1041	0.7125	--
	SD	0.1703	0.2380	2.0867	0.1340	0.0216	0.1266	--
	N	10	10	10	10	10	10	--
	%Diff G1	1.4724	0.9099	9.9761	4.2571	14.3956	17.8660	--
3F	Mean	1.2028	1.9876	8.8887	1.3904	0.1062	0.7566a	--
	SD	0.1103	0.1669	0.7953	0.1059	0.0127	0.1019	--
	N	10	10	10	10	10	10	--
	%Diff G1	0.6275	2.7555	7.1083	4.7619	16.7033	25.1613	--
4F	Mean	1.1862	2.0119	9.3739	1.4098	0.1002	0.7934b	--
	SD	0.1208	0.2191	0.9845	0.1245	0.0179	0.1490	--
	N	10	10	10	10	10	10	--
	%Diff G1	-0.7613	4.0118	12.9549	6.2236	10.1099	31.2490	--

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Appendix 19

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		THYMUS g	UTERUS g
1F	Mean	0.4097	0.6066
	SD	0.0688	0.2431
	N	10	10
2F	Mean	0.4310	0.7700
	SD	0.1013	0.2735
	N	10	10
	%Diff G1	5.1989	26.9370
3F	Mean	0.4500	0.7472
	SD	0.0883	0.2385
	N	10	10
	%Diff G1	9.8365	23.1784
4F	Mean	0.4699	0.8244
	SD	0.0931	0.2552
	N	10	10
	%Diff G1	14.6937	35.9050

Appendix 19

Table 4
Summary of Organ Weight Values - Relative to Body Weight (Day 44)

Appendix 19

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.40611	0.22898	0.01169	0.00250	0.22888	0.00437	0.32217
	SD	0.02725	0.02558	0.00135	0.00040	0.04470	0.00092	0.02701
	N	10	10	10	10	10	10	10
2M	Mean	0.43663	0.24936	0.01178	0.00256	0.24886	0.00417	0.33964
	SD	0.03378	0.01623	0.00191	0.00029	0.04986	0.00065	0.02259
	N	10	10	10	10	10	10	10
	%Diff G1	7.51644	8.90174	0.73613	2.29199	8.72808	-4.46209	5.42363
3M	Mean	0.43373	0.24328	0.01250	0.00258	0.22479	0.00386	0.33152
	SD	0.02550	0.01613	0.00136	0.00029	0.03323	0.00064	0.02269
	N	10	10	10	10	10	10	10
	%Diff G1	6.80056	6.24748	6.88770	3.11450	-1.78704	-11.47884	2.90328
4M	Mean	0.42619	0.24018	0.01387a	0.00274	0.23266	0.00439	0.32711
	SD	0.01871	0.01829	0.00188	0.00073	0.03841	0.00090	0.01499
	N	10	10	10	10	10	10	10
	%Diff G1	4.94436	4.89220	18.61484	9.71139	1.65298	0.49965	1.53531

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Appendix 19

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.58549	2.73804	0.32318	--	0.17474	0.72368	0.08988
	SD	0.04025	0.23490	0.01539	--	0.02349	0.11613	0.01951
	N	10	10	10	--	10	10	10
2M	Mean	0.61409	2.78684	0.35573b	--	0.21190a	0.75316	0.09973
	SD	0.06641	0.17402	0.02102	--	0.02860	0.06997	0.02076
	N	10	10	10	--	10	10	10
	%Diff G1	4.88461	1.78235	10.07199	--	21.26283	4.07245	10.95818
3M	Mean	0.57773	2.79261	0.34173	--	0.21678a	0.75075	0.08675
	SD	0.04136	0.13627	0.02368	--	0.03507	0.06754	0.02086
	N	10	10	10	--	10	10	10
	%Diff G1	-1.32594	1.99284	5.73940	--	24.05873	3.74025	-3.48609
4M	Mean	0.59994	2.89988	0.35196a	--	0.23429c	0.74572	0.09875
	SD	0.04452	0.26986	0.02229	--	0.03503	0.06863	0.01773
	N	10	10	10	--	10	10	10
	%Diff G1	2.46867	5.91070	8.90531	--	34.07596	3.04497	9.87112

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Appendix 19

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		UTERUS %
1M	Mean	--
	SD	--
	N	--
2M	Mean	--
	SD	--
	N	--
	%Diff G1	--
3M	Mean	--
	SD	--
	N	--
	%Diff G1	--
4M	Mean	--
	SD	--
	N	--
	%Diff G1	--

Appendix 19

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	Mean	0.63335	--	0.02212	0.00523	--	0.00502	0.37736
	SD	0.06645	--	0.00260	0.00071	--	0.00116	0.02358
	N	10	--	10	10	--	10	10
2F	Mean	0.66285	--	0.02315	0.00526	--	0.00523	0.38964
	SD	0.08571	--	0.00445	0.00062	--	0.00092	0.05071
	N	10	--	10	10	--	10	10
	%Diff G1	4.65767	--	4.65508	0.63683	--	4.03761	3.25255
3F	Mean	0.65539	--	0.02315	0.00542	--	0.00506	0.38354
	SD	0.06592	--	0.00310	0.00082	--	0.00082	0.03695
	N	10	--	10	10	--	10	10
	%Diff G1	3.48076	--	4.65370	3.76465	--	0.81428	1.63704
4F	Mean	0.65342	--	0.02272	0.00534	--	0.00606	0.37882
	SD	0.04819	--	0.00302	0.00084	--	0.00083	0.03251
	N	10	--	10	10	--	10	10
	%Diff G1	3.16888	--	2.71755	2.24886	--	20.60675	0.38695

Appendix 19

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	Mean	0.61225	2.62013	0.42016	0.02877	0.19011	--	0.12980
	SD	0.05365	0.19342	0.03250	0.00214	0.02550	--	0.02190
	N	10	10	10	10	10	--	10
2F	Mean	0.62446	2.91781	0.44477	0.03330	0.22732	--	0.13808
	SD	0.04332	0.59271	0.04305	0.00579	0.03008	--	0.03118
	N	10	10	10	10	10	--	10
	%Diff G1	1.99550	11.36112	5.85689	15.73599	19.57208	--	6.38654
3F	Mean	0.63350	2.82524	0.44300	0.03423	0.24041b	--	0.14289
	SD	0.05421	0.12623	0.03196	0.00661	0.02730	--	0.02473
	N	10	10	10	10	10	--	10
	%Diff G1	3.47204	7.82823	5.43527	18.96132	26.46140	--	10.09256
4F	Mean	0.64135	2.98745	0.45108	0.03206	0.25394c	--	0.15070
	SD	0.04822	0.17206	0.04495	0.00596	0.04914	--	0.03287
	N	10	10	10	10	10	--	10
	%Diff G1	4.75304	14.01889	7.36017	11.42040	33.57762	--	16.10831

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Appendix 19

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		UTERUS %
1F	Mean	0.19490
	SD	0.08839
	N	10
2F	Mean	0.25505
	SD	0.11342
	N	10
	%Diff G1	30.85784
3F	Mean	0.23860
	SD	0.07736
	N	10
	%Diff G1	22.41949
4F	Mean	0.26494
	SD	0.08409
	N	10
	%Diff G1	35.93458

Appendix 19

Table 5
Summary of Organ Weight Values - Relative to Brain Weight (Day 44)

Appendix 19

Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	56.27395	2.89627	0.61869	56.22519	1.07204	79.45764	144.65527
	SD	3.22939	0.41424	0.10845	9.74348	0.19409	6.01800	12.82378
	N	10	10	10	10	10	10	10
2M	Mean	57.25348	2.71036	0.58735	57.12497	0.95606	78.06082	140.88907
	SD	3.42603	0.45800	0.06338	10.72697	0.13021	6.00616	13.55601
	N	10	10	10	10	10	10	10
	%Diff G1	1.74066	-6.41882	-5.06478	1.60031	-10.81893	-1.75794	-2.60357
3M	Mean	56.12328	2.89319	0.59538	51.97757	0.89598	76.61145	133.67788
	SD	2.55393	0.38369	0.06331	7.99399	0.17204	6.01732	13.15500
	N	10	10	10	10	10	10	10
	%Diff G1	-0.26774	-0.10651	-3.76745	-7.55467	-16.42281	-3.58202	-7.58866
4M	Mean	56.41648	3.25770	0.64575	54.48840	1.02883	76.87532	140.74506
	SD	4.46788	0.44369	0.17579	8.10319	0.20093	4.63727	7.75110
	N	10	10	10	10	10	10	10
	%Diff G1	0.25328	12.47912	4.37495	-3.08899	-4.03081	-3.24994	-2.70312

Appendix 19

Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	Mean	678.01117	79.73647	--	43.31597	177.52321	22.31838	--
	SD	84.51070	3.78994	--	7.30011	18.86381	5.44936	--
	N	10	10	--	10	10	10	--
2M	Mean	641.64650	82.04727	--	48.79592	172.82700	23.09709	--
	SD	62.13732	9.48715	--	7.52558	14.29132	5.70316	--
	N	10	10	--	10	10	10	--
	%Diff G1	-5.36343	2.89805	--	12.65112	-2.64540	3.48911	--
3M	Mean	645.48618	78.87566	--	49.81185	173.43350	20.12564	--
	SD	43.23253	4.62917	--	5.85761	16.30726	5.19038	--
	N	10	10	--	10	10	10	--
	%Diff G1	-4.79712	-1.07956	--	14.99651	-2.30376	-9.82482	--
4M	Mean	682.56338	82.64475	--	55.10209b	175.12854	23.14829	--
	SD	78.90278	5.12745	--	8.56634	15.87039	3.90548	--
	N	10	10	--	10	10	10	--
	%Diff G1	0.67141	3.64736	--	27.20966	-1.34893	3.71851	--

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Appendix 19

Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	Mean	--	3.51030	0.82638	--	0.79317	60.09003	97.20470
	SD	--	0.40648	0.08606	--	0.16749	6.57034	9.44210
	N	--	10	10	--	10	10	10
2F	Mean	--	3.48427	0.80648	--	0.79988	59.17492	95.35525
	SD	--	0.48214	0.14263	--	0.16922	7.52063	11.54986
	N	--	10	10	--	10	10	10
	%Diff G1	--	-0.74174	-2.40825	--	0.84606	-1.52289	-1.90263
3F	Mean	--	3.52608	0.82865	--	0.77718	58.78604	97.08479
	SD	--	0.22496	0.10570	--	0.12717	5.69135	7.79909
	N	--	10	10	--	10	10	10
	%Diff G1	--	0.44927	0.27524	--	-2.01566	-2.17007	-0.12336
4F	Mean	--	3.48024	0.81945	--	0.92656	58.15124	98.51136
	SD	--	0.42298	0.12721	--	0.10181	5.48016	8.93063
	N	--	10	10	--	10	10	10
	%Diff G1	--	-0.85647	-0.83772	--	16.81791	-3.22647	1.34424

Appendix 19

Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	Mean	417.72118	66.69405	4.57675	30.40901	--	20.57235	30.56251
	SD	53.72562	5.66256	0.48841	5.78248	--	3.32484	12.57730
	N	10	10	10	10	--	10	10
2F	Mean	444.67022	67.62983	5.08212	34.70430	--	21.17107	37.86752
	SD	92.26555	6.95225	1.02217	5.43724	--	5.55976	14.14287
	N	10	10	10	10	--	10	10
	%Diff G1	6.45144	1.40309	11.04216	14.12509	--	2.91032	23.90186
3F	Mean	434.19588	67.94739	5.18712	36.98272a	--	21.97367	36.64568
	SD	38.31163	5.38255	0.61803	5.07752	--	4.24938	12.14505
	N	10	10	10	10	--	10	10
	%Diff G1	3.94395	1.87924	13.33629	21.61765	--	6.81165	19.90402
4F	Mean	459.57109	69.05532	4.93097	38.80259b	--	23.11359	40.33611
	SD	45.46286	4.79186	0.99469	6.62497	--	5.04152	12.01206
	N	10	10	10	10	--	10	10
	%Diff G1	10.01862	3.54046	7.73959	27.60228	--	12.35270	31.97905

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)

Appendix 19

Table 6
Summary of Organ Weight Values - Absolute (Day 57)

Appendix 19

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	Mean	598.0	2.2958	1.4053	0.06658	0.01685	1.2068	0.02945
	SD	37.4	0.0567	0.0843	0.00613	0.00252	0.3829	0.00566
	N	4	4	4	4	4	4	4
4M	Mean	584.4	2.2862	1.3588	0.07108	0.01518	1.2470	0.02746
	SD	26.5	0.0738	0.0542	0.00988	0.00100	0.0989	0.00318
	N	5	5	5	5	5	5	5
	%Diff G1	-2.3	-0.4160	-3.3055	6.76680	-9.91098	3.3354	-6.75722

Appendix 19

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	Mean	1.9788	3.2213	16.8685	1.7918	--	0.9270	3.9930
	SD	0.1845	0.3656	1.1767	0.0751	--	0.0736	0.5004
	N	4	4	4	4	--	4	4
4M	Mean	1.9118	3.4492	16.3504	1.9414	--	1.1022	3.9884
	SD	0.0559	0.2956	1.9043	0.1079	--	0.1378	0.2672
	N	5	5	5	5	--	5	5
	%Diff G1	-3.3834	7.0764	-3.0714	8.3522	--	18.8997	-0.1152

Appendix 19

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		THYMUS g	UTERUS g
1M	Mean	0.4568	--
	SD	0.1221	--
	N	4	--
4M	Mean	0.4136	--
	SD	0.0626	--
	N	5	--
	%Diff G1	-9.4472	--

Appendix 19

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1F	Mean	330.8	2.0708	--	0.06438	0.01702	--	0.01612
	SD	28.9	0.0708	--	0.00877	0.00135	--	0.00490
	N	5	5	--	5	5	--	5
4F	Mean	327.0	2.0442	--	0.06814	0.01498	--	0.01978
	SD	28.1	0.1227	--	0.00853	0.00279	--	0.00250
	N	5	5	--	5	5	--	5
	%Diff G1	-1.1	-1.2845	--	5.84032	-11.98590	--	22.70471

Appendix 19

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	Mean	1.2190	1.9594	9.1934	1.3648	0.1240	0.5948	--
	SD	0.1166	0.1796	0.8703	0.1262	0.0718	0.1418	--
	N	5	5	5	5	5	5	--
4F	Mean	1.1814	1.9612	8.5302	1.3356	0.0874	0.6522	--
	SD	0.0758	0.2252	0.7852	0.1186	0.0086	0.0891	--
	N	5	5	5	5	5	5	--
	%Diff G1	-3.0845	0.0919	-7.2139	-2.1395	-29.5161	9.6503	--

Appendix 19

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		THYMUS g	UTERUS g
1F	Mean	0.3574	0.6684
	SD	0.0992	0.2501
	N	5	5
4F	Mean	0.4030	0.6204
	SD	0.1260	0.2100
	N	5	5
	%Diff G1	12.7588	-7.1813

Appendix 19

Table 7
Summary of Organ Weight Values - Relative to Body Weight (Day 57)

Appendix 19

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.38465	0.23598	0.01115	0.00281	0.20211	0.00495	0.33053
	SD	0.01672	0.02416	0.00109	0.00031	0.06455	0.00104	0.01418
	N	4	4	4	4	4	4	4
4M	Mean	0.39227	0.23301	0.01220	0.00260	0.21390	0.00469	0.32788
	SD	0.02984	0.01629	0.00196	0.00025	0.02110	0.00041	0.02171
	N	5	5	5	5	5	5	5
	%Diff G1	1.97934	-1.25783	9.36747	-7.36885	5.83180	-5.15701	-0.80332

Appendix 19

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.53863	2.82283	0.30014	--	0.15520	0.66824	0.07612
	SD	0.05218	0.14881	0.01494	--	0.01172	0.08000	0.01817
	N	4	4	4	--	4	4	4
4M	Mean	0.59089	2.79171	0.33303	--	0.18856a	0.68518	0.07073
	SD	0.05424	0.21541	0.02816	--	0.02170	0.07593	0.00963
	N	5	5	5	--	5	5	5
	%Diff G1	9.70151	-1.10244	10.95802	--	21.49843	2.53452	-7.07519

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (T-test)

Appendix 19

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		UTERUS %
1M	Mean	--
	SD	--
	N	--
4M	Mean	--
	SD	--
	N	--
	%Diff G1	--

Appendix 19

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	Mean	0.62891	--	0.01948	0.00516	--	0.00484	0.36955
	SD	0.04326	--	0.00215	0.00031	--	0.00127	0.03242
	N	5	--	5	5	--	5	5
4F	Mean	0.62714	--	0.02092	0.00462	--	0.00607	0.36188
	SD	0.03935	--	0.00280	0.00098	--	0.00074	0.00932
	N	5	--	5	5	--	5	5
	%Diff G1	-0.28126	--	7.42090	-10.40678	--	25.33033	-2.07421

Appendix 19

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	Mean	0.59227	2.78003	0.41356	0.03711	0.17949	--	0.10728
	SD	0.01447	0.12604	0.03239	0.01985	0.03724	--	0.02520
	N	5	5	5	5	5	--	5
4F	Mean	0.60225	2.60925	0.40848	0.02674	0.20057	--	0.12235
	SD	0.07483	0.11349	0.01152	0.00171	0.03181	--	0.03043
	N	5	5	5	5	5	--	5
	%Diff G1	1.68493	-6.14299	-1.22840	-27.93178	11.74440	--	14.04122

Appendix 19

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		UTERUS %
1F	Mean	0.20753
	SD	0.09565
	N	5
4F	Mean	0.19110
	SD	0.06462
	N	5
	%Diff G1	-7.91764

Appendix 19

Table 8
Summary of Organ Weight Values - Relative to Brain Weight (Day 57)

Appendix 19

Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	61.23623	2.90274	0.73375	52.48772	1.28378	86.10689	140.11190
	SD	3.86646	0.29536	0.10492	16.37208	0.24977	6.37477	12.98111
	N	4	4	4	4	4	4	4
4M	Mean	59.45971	3.10585	0.66373	54.53689	1.20372	83.68267	151.08091
	SD	2.33771	0.38757	0.03258	3.91562	0.15963	3.35266	14.58956
	N	5	5	5	5	5	5	5
	%Diff G1	-2.90110	6.99743	-9.54351	3.90411	-6.23660	-2.81536	7.82875

Appendix 19

Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	Mean	734.97502	78.02476	--	40.34433	173.69610	19.86288	--
	SD	51.13297	1.62811	--	2.38512	18.61810	5.09154	--
	N	4	4	--	4	4	4	--
4M	Mean	717.26723	84.93114a	--	48.35552	174.36590	18.12334	--
	SD	100.22619	4.23401	--	7.17888	8.18093	2.93094	--
	N	5	5	--	5	5	5	--
	%Diff G1	-2.40931	8.85153	--	19.85703	0.38561	-8.75772	--

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (T-test)

Appendix 19

Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	Mean	--	3.10722	0.82144	--	0.77338	58.79355	94.49025
	SD	--	0.39932	0.05147	--	0.21035	4.06756	6.15035
	N	--	5	5	--	5	5	5
4F	Mean	--	3.33543	0.73839	--	0.96564	57.84649	96.36134
	SD	--	0.38101	0.16462	--	0.08212	3.14864	14.07290
	N	--	5	5	--	5	5	5
	%Diff G1	--	7.34452	-10.11020	--	24.85891	-1.61083	1.98019

Appendix 19

Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	Mean	443.26204	65.83577	5.97146	28.59109	--	17.15309	32.58785
	SD	28.86974	4.54946	3.40732	5.91747	--	4.21071	13.15518
	N	5	5	5	5	--	5	5
4F	Mean	417.60755	65.32745	4.27717	31.90101	--	19.51789	30.78885
	SD	36.16965	4.22012	0.37550	3.82345	--	4.97206	11.96388
	N	5	5	5	5	--	5	5
	%Diff G1	-5.78766	-0.77210	-28.37305	11.57676	--	13.78644	-5.52046

Appendix 19

Table 9
Summary of Histopathology Findings (Day 44)

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE MARROW								
Examined	10	0	0	0	0	0	0	0
No Visible Lesions	10	.	.	.	.	.	.	.
BONE MARROW, FEMUR								
Examined	0	10	10	10	10	10	10	10
No Visible Lesions	.	10	6	1	10	10	8	1
Increased hematopoiesis; myeloid	.	0	4	9	0	0	2	9
.... minimal	.	0	4	9	0	0	2	9
BONE MARROW, STERNUM								
Examined	0	10	10	10	10	10	10	10
No Visible Lesions	.	10	6	1	10	10	8	1
Increased hematopoiesis; myeloid	.	0	4	9	0	0	2	9
.... minimal	.	0	4	9	0	0	2	9
BONE, FEMUR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE, STERNUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BRAIN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
CERVIX								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
EPIDIDYMIS								
Examined	10	1	0	10	.	.	.	.
No Visible Lesions	10	0	.	10	.	.	.	.
Cellular debris	0	1	.	0	.	.	.	.
.... mild	0	1	.	0	.	.	.	.
Sperm granuloma	0	1	.	0	.	.	.	.
.... mild	0	0	.	0	.	.	.	.

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
EPIDIDYMIS (Continued...)								
.... moderate	0	1	.	0	.	.	.	.
ESOPHAGUS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
EYE								
Examined	10	1	1	10	10	0	0	10
No Visible Lesions	10	1	1	10	9	.	.	10
Dysplasia; retina	0	0	0	0	1	.	.	0
.... minimal	0	0	0	0	1	.	.	0
.... mild	0	0	0	0	0	.	.	0
GALT								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, ADRENAL								
Examined	10	0	0	10	10	1	2	10
No Visible Lesions	10	.	.	10	10	0	2	10
Hemorrhage; capsular	0	.	.	0	0	1	0	0
.... mild	0	.	.	0	0	1	0	0
GLAND, HARDERIAN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Infiltration, mononuclear cell	0	.	.	0	0	.	.	0
.... minimal	0	.	.	0	0	.	.	0
GLAND, MAMMARY								
Examined	6	0	0	9	10	0	0	10
No Visible Lesions	6	.	.	9	10	.	.	10
Not Examined: Not Present In Section.	4	0	0	1	0	0	0	0
GLAND, PARATHYROID								
Examined	10	0	0	7	10	0	0	8
No Visible Lesions	10	.	.	7	10	.	.	8
Not Examined: Not Present In Section.	0	0	0	3	0	0	0	2
GLAND, PITUITARY								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, PROSTATE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	6	.	.	5	.	.	.	.
Infiltration, mononuclear cell	4	.	.	5	.	.	.	.
.... minimal	3	.	.	4	.	.	.	.
.... mild	1	.	.	0	.	.	.	.
.... moderate	0	.	.	1	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Hemorrhage	0	.	.	0	0	.	.	0
.... moderate	0	.	.	0	0	.	.	0
GLAND, SEMINAL VESICLE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
GLAND, THYROID								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	5	.	.	2	5	.	.	4
Cyst	5	.	.	8	4	.	.	5
Ectopia	0	.	.	0	2	.	.	1
HEART								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	4	.	.	9	8	.	.	10
Infiltration, mononuclear cell	6	.	.	1	2	.	.	0
.... minimal	6	.	.	1	2	.	.	0
KIDNEY								
Examined	10	2	0	10	10	1	0	10
No Visible Lesions	0	0	.	4	7	0	.	6
Nephroblastoma, malignant	0	0	.	0	0	0	.	0
Hyperplasia; atypical, tubular	0	0	.	0	0	0	.	1
.... mild	0	0	.	0	0	0	.	1
Chronic progressive nephropathy	9	2	.	6	3	0	.	2
.... minimal	9	2	.	6	3	0	.	2
Dilatation; tubular	1	0	.	0	0	0	.	1
.... minimal	0	0	.	0	0	0	.	0

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
KIDNEY (Continued...)								
.... mild	1	0	.	0	0	0	.	1
Dilatation	1	0	.	0	0	0	.	0
.... mild	1	0	.	0	0	0	.	0
Dilatation; pelvis	1	0	.	0	0	0	.	0
.... minimal	1	0	.	0	0	0	.	0
Inflammation, mononuclear cell	2	0	.	1	1	1	.	1
.... minimal	2	0	.	1	1	1	.	1
Cyst	0	0	.	0	0	0	.	1
Pyelonephritis	0	0	.	0	0	0	.	0
.... mild	0	0	.	0	0	0	.	0
LARGE INTESTINE, CECUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	7	10	.	.	9
Parasitism; nematode	0	.	.	3	0	.	.	1
LARGE INTESTINE, COLON								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	9	10	.	.	9
Parasitism; nematode	0	.	.	1	0	.	.	1
LARGE INTESTINE, RECTUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
LIVER								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	0	0	0	1	0	0	0	0
Congestion	0	0	0	1	0	0	0	0
.... minimal	0	0	0	1	0	0	0	0
.... moderate	0	0	0	0	0	0	0	0
Vacuolation; centrilobular, microvesicular	1	0	0	1	0	0	0	0
.... minimal	0	0	0	0	0	0	0	0
.... mild	1	0	0	1	0	0	0	0
Vacuolation; centrilobular	0	0	0	0	0	1	0	0
.... moderate	0	0	0	0	0	1	0	0
Vacuolation; microvesicular	0	0	0	1	0	0	0	0

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LIVER (Continued...)								
.... minimal	0	0	0	1	0	0	0	0
Vacuolation	0	0	0	0	0	2	0	0
.... minimal	0	0	0	0	0	2	0	0
Necrosis	0	1	0	1	1	1	0	3
.... minimal	0	1	0	1	1	1	0	2
.... mild	0	0	0	0	0	0	0	1
Infiltration, mononuclear cell	10	10	10	9	10	10	10	10
.... minimal	9	10	10	8	10	10	10	10
.... mild	1	0	0	1	0	0	0	0
Tension lipidosis	5	0	1	3	3	1	1	2
.... minimal	4	0	1	3	2	1	1	2
.... mild	1	0	0	0	1	0	0	0
Fibrosis; capsular	0	0	0	0	0	1	0	0
.... minimal	0	0	0	0	0	1	0	0
LUNG								
Examined	10	3	7	10	10	2	0	10
No Visible Lesions	2	1	1	7	8	1	.	9
Congestion	2	0	0	0	0	0	.	0
.... minimal	1	0	0	0	0	0	.	0
.... mild	1	0	0	0	0	0	.	0
.... moderate	0	0	0	0	0	0	.	0
Hemorrhage	1	1	0	2	0	0	.	0
.... minimal	1	0	0	2	0	0	.	0
.... mild	0	1	0	0	0	0	.	0
Inflammation, mixed cell	5	1	6	1	1	1	.	1
.... minimal	5	1	5	1	1	0	.	1
.... mild	0	0	1	0	0	1	.	0
Metaplasia; osseous	0	0	0	0	0	0	.	0
.... minimal	0	0	0	0	0	0	.	0
Macrophage aggregation; alveolar	0	0	0	0	1	0	.	0
.... minimal	0	0	0	0	1	0	.	0
LYMPH NODE, INGUINAL								
Examined	10	0	0	0	0	0	0	0
No Visible Lesions	9	.	.	.	.	.	.	.

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, INGUINAL (Continued...)								
Erythrocytosis; sinus	1	.	.	.	.	.	.	.
.... minimal	1	.	.	.	.	.	.	.
LYMPH NODE, INGUINAL, RIGHT								
Examined	0	10	10	10	10	10	10	10
No Visible Lesions	.	9	9	6	9	10	10	10
Erythrocytosis; sinus	.	1	0	1	1	0	0	0
.... minimal	.	0	0	0	1	0	0	0
.... mild	.	1	0	1	0	0	0	0
Inflammation, mixed cell	.	0	1	3	0	0	0	0
.... minimal	.	0	1	1	0	0	0	0
.... mild	.	0	0	2	0	0	0	0
LYMPH NODE, MANDIBULAR								
Examined	10	4	3	10	10	2	3	10
No Visible Lesions	7	3	3	9	9	0	1	10
Erythrocytosis; sinus	3	1	0	1	1	2	2	0
.... minimal	1	0	0	0	1	0	1	0
.... mild	2	1	0	1	0	2	1	0
LYMPH NODE, MESENTERIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Erythrocytosis; sinus	0	.	.	0	0	.	.	0
.... minimal	0	.	.	0	0	.	.	0
LYMPH NODE, POPLITEAL								
Examined	10	0	0	0	0	0	0	0
No Visible Lesions	10	.	.	.	.	.	.	.
LYMPH NODE, POPLITEAL, RIGHT								
Examined	0	10	10	10	10	10	10	10
No Visible Lesions	.	8	0	1	10	0	0	0
Inflammation, mixed cell	.	2	10	9	0	10	10	10
.... minimal	.	0	2	1	0	4	2	0
.... mild	.	2	4	3	0	6	7	5
.... moderate	.	0	4	4	0	0	1	5
.... marked	.	0	0	1	0	0	0	0

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
MUSCLE, SKELETAL								
Examined	10	0	0	10	10	0	1	10
No Visible Lesions	9	.	.	8	8	.	0	8
Degeneration; myofiber	0	.	.	2	2	.	0	2
.... minimal	0	.	.	2	2	.	0	2
Infiltration, mononuclear cell	1	.	.	0	0	.	0	0
.... minimal	1	.	.	0	0	.	0	0
Hemorrhage	0	.	.	0	0	.	1	0
.... moderate	0	.	.	0	0	.	1	0
Inflammation, neutrophilic	0	.	.	0	0	.	0	0
.... mild	0	.	.	0	0	.	0	0
NERVE, OPTIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
NERVE, SCIATIC								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	0	0	0	10	0	0	0
Degeneration; neuroaxonal	0	0	0	1	0	0	0	0
.... mild	0	0	0	1	0	0	0	0
Inflammation, mixed cell; perineurial	0	10	10	10	0	10	10	10
.... minimal	0	0	2	1	0	4	3	1
.... mild	0	2	4	1	0	2	4	1
.... moderate	0	3	4	8	0	4	3	7
.... marked	0	5	0	0	0	0	0	1
OVARY								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
PANCREAS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Atrophy; acinar	1	.	.	0	0	.	.	0
.... minimal	1	.	.	0	0	.	.	0
Fibrosis; islet of langerhans	1	.	.	0	0	.	.	0
.... minimal	0	.	.	0	0	.	.	0
.... mild	1	.	.	0	0	.	.	0

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
PANCREAS (Continued...)								
Hemorrhage; islet of langerhans	1	.	.	0	0	.	.	0
.... minimal	1	.	.	0	0	.	.	0
Inflammation, mixed cell	1	.	.	0	0	.	.	0
.... minimal	1	.	.	0	0	.	.	0
Inflammation, mononuclear cell	0	.	.	0	0	.	.	0
.... minimal	0	.	.	0	0	.	.	0
SITE, INJECTION								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	4	0	0	0	5	0	0	0
Edema; subcutaneous tissue	0	5	8	9	0	6	8	10
.... minimal	0	2	0	2	0	2	2	0
.... mild	0	3	2	3	0	3	4	3
.... moderate	0	0	6	4	0	1	2	7
Hemorrhage; myofiber	1	0	0	0	0	0	0	0
.... mild	1	0	0	0	0	0	0	0
Hemorrhage; subcutaneous tissue	1	0	0	0	0	0	0	1
.... mild	1	0	0	0	0	0	0	1
Degeneration; myofiber	5	7	9	6	5	5	8	6
.... minimal	5	7	8	5	4	4	6	6
.... mild	0	0	1	1	1	1	2	0
Inflammation, mixed cell; dermal	0	0	0	5	0	0	0	9
.... minimal	0	0	0	2	0	0	0	9
.... mild	0	0	0	3	0	0	0	0
Inflammation, mixed cell; myofiber	0	10	10	10	0	10	10	10
.... mild	0	6	4	2	0	6	5	4
.... moderate	0	4	6	8	0	4	5	6
Inflammation, mixed cell; subcutaneous tissue	0	10	9	10	0	10	10	10
.... minimal	0	1	0	0	0	1	1	1
.... mild	0	6	3	4	0	7	8	2
.... moderate	0	3	6	6	0	2	1	7
Exudate; epidermal	0	0	0	1	0	0	0	0
.... minimal	0	0	0	1	0	0	0	0
Infiltration, mononuclear cell; myofiber	1	0	0	0	0	0	0	0

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SITE, INJECTION (Continued...)								
.... minimal	1	0	0	0	0	0	0	0
.... mild	0	0	0	0	0	0	0	0
Infiltration, mononuclear cell; subcutaneous tissue	0	0	0	0	0	0	0	0
.... minimal	0	0	0	0	0	0	0	0
.... mild	0	0	0	0	0	0	0	0
SKIN								
Examined	10	1	0	10	10	0	0	10
No Visible Lesions	10	0	.	10	9	.	.	10
Hyperkeratosis	0	1	.	0	1	.	.	0
.... mild	0	1	.	0	1	.	.	0
Exudate; epidermal	0	1	.	0	1	.	.	0
.... mild	0	1	.	0	1	.	.	0
Inflammation, mixed cell; dermal	0	1	.	0	0	.	.	0
.... mild	0	1	.	0	0	.	.	0
Inflammation, mixed cell	0	0	.	0	1	.	.	0
.... mild	0	0	.	0	1	.	.	0
Degeneration; muscularis carnosus	0	0	.	0	0	.	.	0
.... minimal	0	0	.	0	0	.	.	0
SMALL INTESTINE, DUODENUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, ILEUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, JEJUNUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPINAL CORD								
Examined	0	0	0	10	10	0	0	10
No Visible Lesions	.	.	.	10	10	.	.	10
SPINAL CORD, CERVICAL								
Examined	10	0	0	0	0	0	0	0
No Visible Lesions	10	.	.	.	.	.	.	.

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SPINAL CORD, LUMBAR								
Examined	10	0	0	0	0	0	0	0
No Visible Lesions	10	.	.	.	.	.	.	.
SPINAL CORD, THORACIC								
Examined	10	0	0	0	0	0	0	0
No Visible Lesions	10	.	.	.	.	.	.	.
SPLEEN								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	6	1	0	10	3	0	0
Decreased cellularity; periarteriolar lymphoid sheath	0	4	9	10	0	7	10	10
.... minimal	0	0	5	3	0	5	6	1
.... mild	0	4	4	7	0	2	4	9
STOMACH								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
TESTIS								
Examined	10	1	0	10	.	.	.	.
No Visible Lesions	9	0	.	10	.	.	.	.
Degeneration	1	1	.	0	.	.	.	.
.... severe	0	1	.	0	.	.	.	.
.... minimal	1	0	.	0	.	.	.	.
THYMUS								
Examined	10	10	7	10	10	7	8	10
No Visible Lesions	3	1	1	5	3	0	0	1
Hemorrhage	7	9	6	5	7	7	8	9
.... minimal	2	3	1	2	1	2	1	3
.... mild	2	6	4	1	4	2	4	3
.... moderate	3	0	1	2	2	3	3	3
TONGUE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
TRACHEA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
TRACHEA (Continued...)								
Inflammation, mixed cell	0	.	.	0	0	.	.	0
.... mild	0	.	.	0	0	.	.	0
URINARY BLADDER								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
UTERUS								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
VAGINA								
Examined	.	.	.	.	10	0	0	10
Diestrus	.	.	.	.	4	.	.	3
Estrus	.	.	.	.	4	.	.	2
Proestrus	.	.	.	.	2	.	.	5

Appendix 19

Table 10
Summary of Histopathology Findings (Found Dead & Day 57)

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
ARTERY, AORTA		
Examined	1	
No Visible Lesions	1	
BONE MARROW		
Examined	1	
No Visible Lesions	1	
Increased hematopoiesis; myeloid	0	
.... minimal	0	
BONE, FEMUR		
Examined	1	
No Visible Lesions	1	
BONE, STERNUM		
Examined	1	
No Visible Lesions	1	
BRAIN		
Examined	1	
No Visible Lesions	1	
EPIDIDYMIS		
Examined	1	
No Visible Lesions	1	
Cellular debris	0	
.... mild	0	
Sperm granuloma	0	
.... mild	0	
.... moderate	0	
ESOPHAGUS		
Examined	1	
No Visible Lesions	1	
EYE		
Examined	1	
No Visible Lesions	1	
Dysplasia; retina	0	
.... minimal	0	
.... mild	0	
GALT		
Examined	1	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
GALT (Continued...)		
No Visible Lesions	1	
GLAND, ADRENAL		
Examined	1	
No Visible Lesions	1	
Hemorrhage; capsular	0	
.... mild	0	
GLAND, HARDERIAN		
Examined	1	
No Visible Lesions	1	
Infiltration, mononuclear cell	0	
.... minimal	0	
GLAND, MAMMARY		
Examined	1	
No Visible Lesions	1	
Not Examined: Not Present In Section.	0	
GLAND, PARATHYROID		
Examined	1	
No Visible Lesions	1	
Not Examined: Not Present In Section.	0	
GLAND, PITUITARY		
Examined	1	
No Visible Lesions	1	
GLAND, PROSTATE		
Examined	1	
No Visible Lesions	0	
Infiltration, mononuclear cell	1	
.... minimal	1	
.... mild	0	
.... moderate	0	
GLAND, SALIVARY, MANDIBULAR		
Examined	1	
No Visible Lesions	1	
Hemorrhage	0	
.... moderate	0	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
GLAND, SEMINAL VESICLE		
Examined	1	
No Visible Lesions	1	
GLAND, THYROID		
Examined	1	
No Visible Lesions	0	
Cyst	1	
Ectopia	0	
HEART		
Examined	1	
No Visible Lesions	1	
Infiltration, mononuclear cell	0	
.... minimal	0	
KIDNEY		
Examined	1	
No Visible Lesions	1	
Nephroblastoma, malignant	0	
Hyperplasia; atypical, tubular	0	
.... mild	0	
Chronic progressive nephropathy	0	
.... minimal	0	
Dilatation; tubular	0	
.... minimal	0	
.... mild	0	
Dilatation	0	
.... mild	0	
Dilatation; pelvis	0	
.... minimal	0	
Inflammation, mononuclear cell	0	
.... minimal	0	
Cyst	0	
Pyelonephritis	0	
.... mild	0	
LARGE INTESTINE, CECUM		
Examined	1	
No Visible Lesions	1	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
LARGE INTESTINE, CECUM (Continued...)		
Parasitism; nematode	0	
LARGE INTESTINE, COLON		
Examined	1	
No Visible Lesions	1	
Parasitism; nematode	0	
LARGE INTESTINE, RECTUM		
Examined	1	
No Visible Lesions	1	
LIVER		
Examined	1	
No Visible Lesions	0	
Congestion	1	
.... minimal	0	
.... moderate	1	
Vacuolation; centrilobular, microvesicular	0	
.... minimal	0	
.... mild	0	
Vacuolation; centrilobular	0	
.... moderate	0	
Vacuolation; microvesicular	0	
.... minimal	0	
Vacuolation	0	
.... minimal	0	
Necrosis	0	
.... minimal	0	
.... mild	0	
Infiltration, mononuclear cell	1	
.... minimal	1	
.... mild	0	
Tension lipidosis	0	
.... minimal	0	
.... mild	0	
Fibrosis; capsular	0	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
LIVER (Continued...)		
.... minimal	0	
LUNG		
Examined	1	
No Visible Lesions	0	
Congestion	1	
.... minimal	0	
.... mild	0	
.... moderate	1	
Hemorrhage	0	
.... minimal	0	
.... mild	0	
Inflammation, mixed cell	0	
.... minimal	0	
.... mild	0	
Metaplasia; osseous	0	
.... minimal	0	
Macrophage aggregation; alveolar	0	
.... minimal	0	
LYMPH NODE, INGUINAL		
Examined	1	
No Visible Lesions	1	
Erythrocytosis; sinus	0	
.... minimal	0	
.... mild	0	
Inflammation, mixed cell	0	
.... minimal	0	
.... mild	0	
LYMPH NODE, INGUINAL, RIGHT		
Examined	0	
LYMPH NODE, MANDIBULAR		
Examined	1	
No Visible Lesions	1	
Erythrocytosis; sinus	0	
.... minimal	0	
.... mild	0	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
LYMPH NODE, MESENTERIC		
Examined	1	
No Visible Lesions	1	
Erythrocytosis; sinus	0	
.... minimal	0	
LYMPH NODE, POPLITEAL		
Examined	1	
No Visible Lesions	1	
Inflammation, mixed cell	0	
.... minimal	0	
.... mild	0	
.... moderate	0	
.... marked	0	
MUSCLE, SKELETAL		
Examined	1	
No Visible Lesions	1	
Degeneration; myofiber	0	
.... minimal	0	
Infiltration, mononuclear cell	0	
.... minimal	0	
Hemorrhage	0	
.... moderate	0	
Inflammation, neutrophilic	0	
.... mild	0	
NERVE, OPTIC		
Examined	1	
No Visible Lesions	1	
NERVE, SCIATIC		
Examined	1	
No Visible Lesions	1	
Degeneration; neuroaxonal	0	
.... mild	0	
Inflammation, mixed cell; perineurial	0	
.... minimal	0	
.... mild	0	
.... moderate	0	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
NERVE, SCIATIC (Continued...)		
.... marked	0	
PANCREAS		
Examined	1	
No Visible Lesions	1	
Atrophy; acinar	0	
.... minimal	0	
Fibrosis; islet of langerhans	0	
.... minimal	0	
.... mild	0	
Hemorrhage; islet of langerhans	0	
.... minimal	0	
Inflammation, mixed cell	0	
.... minimal	0	
Inflammation, mononuclear cell	0	
.... minimal	0	
SITE, INJECTION		
Examined	1	
No Visible Lesions	1	
Edema; subcutaneous tissue	0	
.... minimal	0	
.... mild	0	
.... moderate	0	
Hemorrhage; myofiber	0	
.... mild	0	
Hemorrhage; subcutaneous tissue	0	
.... mild	0	
Degeneration; myofiber	0	
.... minimal	0	
.... mild	0	
Inflammation, mixed cell; dermal	0	
.... minimal	0	
.... mild	0	
Inflammation, mixed cell; myofiber	0	
.... mild	0	
.... moderate	0	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
SITE, INJECTION (Continued...)		
Inflammation, mixed cell; subcutaneous tissue	0	
.... minimal	0	
.... mild	0	
.... moderate	0	
Exudate; epidermal	0	
.... minimal	0	
Infiltration, mononuclear cell; myofiber	0	
.... minimal	0	
.... mild	0	
Infiltration, mononuclear cell; subcutaneous tissue	0	
.... minimal	0	
.... mild	0	
SKIN		
Examined	1	
No Visible Lesions	1	
Hyperkeratosis	0	
.... mild	0	
Exudate; epidermal	0	
.... mild	0	
Inflammation, mixed cell; dermal	0	
.... mild	0	
Inflammation, mixed cell	0	
.... mild	0	
Degeneration; muscularis carnosus	0	
.... minimal	0	
SMALL INTESTINE, DUODENUM		
Examined	1	
No Visible Lesions	1	
SMALL INTESTINE, ILEUM		
Examined	1	
No Visible Lesions	1	
SMALL INTESTINE, JEJUNUM		
Examined	1	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male	
	0 ug/dose Group 1	
Number of Animals:	1	
SMALL INTESTINE, JEJUNUM (Continued...)		
No Visible Lesions	1	
SPINAL CORD		
Examined	0	
SPINAL CORD, CERVICAL		
Examined	1	
No Visible Lesions	1	
SPINAL CORD, LUMBAR		
Examined	1	
No Visible Lesions	1	
SPINAL CORD, THORACIC		
Examined	1	
No Visible Lesions	1	
SPLEEN		
Examined	1	
No Visible Lesions	1	
Decreased cellularity; periarteriolar lymphoid sheath	0	
.... minimal	0	
.... mild	0	
STOMACH		
Examined	1	
No Visible Lesions	1	
TESTIS		
Examined	1	
No Visible Lesions	1	
Degeneration	0	
.... severe	0	
.... minimal	0	
THYMUS		
Examined	1	
No Visible Lesions	0	
Hemorrhage	1	
.... minimal	0	
.... mild	1	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: FOUND DEAD	Male 0 ug/dose Group 1	
Number of Animals:	1	
THYMUS (Continued...)		
.... moderate	0	
TONGUE		
Examined	1	
No Visible Lesions	1	
TRACHEA		
Examined	1	
No Visible Lesions	1	
Inflammation, mixed cell	0	
.... mild	0	
URINARY BLADDER		
Examined	1	
No Visible Lesions	1	

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
ARTERY, AORTA				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
BONE MARROW				
Examined	4	5	5	5
No Visible Lesions	4	3	5	4
Increased hematopoiesis; myeloid	0	2	0	1
.... minimal	0	2	0	1
BONE, FEMUR				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
BONE, STERNUM				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
BRAIN				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
CERVIX				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
EPIDIDYMIS				
Examined	4	5	.	.
No Visible Lesions	3	5	.	.
Cellular debris	0	0	.	.
.... mild	0	0	.	.
Sperm granuloma	1	0	.	.
.... mild	1	0	.	.
.... moderate	0	0	.	.
ESOPHAGUS				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
EYE				
Examined	4	5	5	5
No Visible Lesions	3	5	5	4
Dysplasia; retina	1	0	0	1

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
EYE (Continued...)				
.... minimal	1	0	0	0
.... mild	0	0	0	1
GALT				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
GLAND, ADRENAL				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
Hemorrhage; capsular	0	0	0	0
.... mild	0	0	0	0
GLAND, HARDERIAN				
Examined	4	5	5	5
No Visible Lesions	4	5	5	4
Infiltration, mononuclear cell	0	0	0	1
.... minimal	0	0	0	1
GLAND, MAMMARY				
Examined	4	4	5	5
No Visible Lesions	4	4	5	5
Not Examined: Not Present In Section.	0	1	0	0
GLAND, PARATHYROID				
Examined	4	5	5	4
No Visible Lesions	4	5	5	4
Not Examined: Not Present In Section.	0	0	0	1
GLAND, PITUITARY				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
GLAND, PROSTATE				
Examined	4	5	.	.
No Visible Lesions	2	0	.	.
Infiltration, mononuclear cell	2	5	.	.
.... minimal	1	1	.	.
.... mild	1	3	.	.
.... moderate	0	1	.	.

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
GLAND, SALIVARY, MANDIBULAR				
Examined	4	5	5	5
No Visible Lesions	4	5	4	5
Hemorrhage	0	0	1	0
.... moderate	0	0	1	0
GLAND, SEMINAL VESICLE				
Examined	4	5	.	.
No Visible Lesions	4	5	.	.
GLAND, THYROID				
Examined	4	5	5	5
No Visible Lesions	1	4	3	2
Cyst	3	0	2	3
Ectopia	0	1	0	0
HEART				
Examined	4	5	5	5
No Visible Lesions	2	3	5	5
Infiltration, mononuclear cell	2	2	0	0
.... minimal	2	2	0	0
KIDNEY				
Examined	4	5	5	5
No Visible Lesions	1	2	3	1
Nephroblastoma, malignant	1	0	0	0
Hyperplasia; atypical, tubular	0	0	0	0
.... mild	0	0	0	0
Chronic progressive nephropathy	2	3	1	3
.... minimal	2	3	1	3
Dilatation; tubular	0	0	1	0
.... minimal	0	0	1	0
.... mild	0	0	0	0
Dilatation	0	0	0	0
.... mild	0	0	0	0
Dilatation; pelvis	0	0	0	0
.... minimal	0	0	0	0
Inflammation, mononuclear cell	0	0	1	2
.... minimal	0	0	1	2

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
KIDNEY (Continued...)				
Cyst	1	0	0	1
Pyelonephritis	0	0	0	1
.... mild	0	0	0	1
LARGE INTESTINE, CECUM				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
Parasitism; nematode	0	0	0	0
LARGE INTESTINE, COLON				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
Parasitism; nematode	0	0	0	0
LARGE INTESTINE, RECTUM				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
LIVER				
Examined	4	5	5	5
No Visible Lesions	0	1	1	0
Congestion	0	0	0	0
.... minimal	0	0	0	0
.... moderate	0	0	0	0
Vacuolation; centrilobular, microvesicular	1	0	0	0
.... minimal	1	0	0	0
.... mild	0	0	0	0
Vacuolation; centrilobular	0	0	0	0
.... moderate	0	0	0	0
Vacuolation; microvesicular	0	0	0	0
.... minimal	0	0	0	0
Vacuolation	0	0	0	0
.... minimal	0	0	0	0
Necrosis	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Infiltration, mononuclear cell	4	4	4	5

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
LIVER (Continued...)				
.... minimal	4	4	4	5
.... mild	0	0	0	0
Tension lipidosis	1	0	2	0
.... minimal	1	0	0	0
.... mild	0	0	2	0
Fibrosis; capsular	0	0	0	0
.... minimal	0	0	0	0
LUNG				
Examined	4	5	5	5
No Visible Lesions	1	3	4	5
Congestion	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
.... moderate	0	0	0	0
Hemorrhage	2	0	0	0
.... minimal	2	0	0	0
.... mild	0	0	0	0
Inflammation, mixed cell	0	1	0	0
.... minimal	0	1	0	0
.... mild	0	0	0	0
Metaplasia; osseous	1	1	0	0
.... minimal	1	1	0	0
Macrophage aggregation; alveolar	0	0	1	0
.... minimal	0	0	1	0
LYMPH NODE, INGUINAL				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
Erythrocytosis; sinus	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Inflammation, mixed cell	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
LYMPH NODE, INGUINAL, RIGHT				
Examined	0	0	0	0
LYMPH NODE, MANDIBULAR				
Examined	4	5	5	5
No Visible Lesions	4	5	5	3
Erythrocytosis; sinus	0	0	0	2
.... minimal	0	0	0	2
.... mild	0	0	0	0
LYMPH NODE, MESENTERIC				
Examined	4	5	5	5
No Visible Lesions	3	5	5	5
Erythrocytosis; sinus	1	0	0	0
.... minimal	1	0	0	0
LYMPH NODE, POPLITEAL				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
Inflammation, mixed cell	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
.... moderate	0	0	0	0
.... marked	0	0	0	0
MUSCLE, SKELETAL				
Examined	4	5	5	5
No Visible Lesions	3	5	5	4
Degeneration; myofiber	0	0	0	1
.... minimal	0	0	0	1
Infiltration, mononuclear cell	0	0	0	0
.... minimal	0	0	0	0
Hemorrhage	1	0	0	0
.... moderate	1	0	0	0
Inflammation, neutrophilic	1	0	0	0
.... mild	1	0	0	0
NERVE, OPTIC				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
NERVE, SCIATIC				
Examined	4	5	5	5
No Visible Lesions	4	5	5	3
Degeneration; neuroaxonal	0	0	0	0
.... mild	0	0	0	0
Inflammation, mixed cell; perineurial	0	0	0	2
.... minimal	0	0	0	2
.... mild	0	0	0	0
.... moderate	0	0	0	0
.... marked	0	0	0	0
OVARY				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
PANCREAS				
Examined	4	5	5	5
No Visible Lesions	3	5	5	4
Atrophy; acinar	0	0	0	0
.... minimal	0	0	0	0
Fibrosis; islet of langerhans	1	0	0	0
.... minimal	1	0	0	0
.... mild	0	0	0	0
Hemorrhage; islet of langerhans	0	0	0	0
.... minimal	0	0	0	0
Inflammation, mixed cell	0	0	0	0
.... minimal	0	0	0	0
Inflammation, mononuclear cell	0	0	0	1
.... minimal	0	0	0	1
SITE, INJECTION				
Examined	4	5	5	5
No Visible Lesions	2	1	4	0
Edema; subcutaneous tissue	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
.... moderate	0	0	0	0
Hemorrhage; myofiber	0	0	0	0

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
SITE, INJECTION (Continued...)				
.... mild	0	0	0	0
Hemorrhage; subcutaneous tissue	0	0	0	0
.... mild	0	0	0	0
Degeneration; myofiber	2	1	1	2
.... minimal	2	1	1	1
.... mild	0	0	0	1
Inflammation, mixed cell; dermal	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Inflammation, mixed cell; myofiber	0	0	0	0
.... mild	0	0	0	0
.... moderate	0	0	0	0
Inflammation, mixed cell; subcutaneous tissue	0	0	0	1
.... minimal	0	0	0	1
.... mild	0	0	0	0
.... moderate	0	0	0	0
Exudate; epidermal	0	0	0	0
.... minimal	0	0	0	0
Infiltration, mononuclear cell; myofiber	0	2	0	5
.... minimal	0	1	0	4
.... mild	0	1	0	1
Infiltration, mononuclear cell; subcutaneous tissue	0	4	0	4
.... minimal	0	2	0	4
.... mild	0	2	0	0
SKIN				
Examined	4	5	5	5
No Visible Lesions	4	5	4	5
Hyperkeratosis	0	0	0	0
.... mild	0	0	0	0
Exudate; epidermal	0	0	0	0
.... mild	0	0	0	0
Inflammation, mixed cell; dermal	0	0	0	0

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
SKIN (Continued...)				
.... mild	0	0	0	0
Inflammation, mixed cell	0	0	0	0
.... mild	0	0	0	0
Degeneration; muscularis carnosus	0	0	1	0
.... minimal	0	0	1	0
SMALL INTESTINE, DUODENUM				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
SMALL INTESTINE, ILEUM				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
SMALL INTESTINE, JEJUNUM				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
SPINAL CORD				
Examined	1	0	0	0
No Visible Lesions	1	.	.	.
SPINAL CORD, CERVICAL				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
SPINAL CORD, LUMBAR				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
SPINAL CORD, THORACIC				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
SPLEEN				
Examined	4	5	5	5
No Visible Lesions	4	3	5	5
Decreased cellularity; periarteriolar lymphoid sheath	0	2	0	0
.... minimal	0	2	0	0
.... mild	0	0	0	0

Appendix 19

5002034 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	4	5	5	5
STOMACH				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
TESTIS				
Examined	4	5	.	.
No Visible Lesions	4	5	.	.
Degeneration	0	0	.	.
.... severe	0	0	.	.
.... minimal	0	0	.	.
THYMUS				
Examined	4	5	5	5
No Visible Lesions	3	4	4	5
Hemorrhage	1	1	1	0
.... minimal	1	1	1	0
.... mild	0	0	0	0
.... moderate	0	0	0	0
TONGUE				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
TRACHEA				
Examined	4	5	5	5
No Visible Lesions	3	5	5	5
Inflammation, mixed cell	1	0	0	0
.... mild	1	0	0	0
URINARY BLADDER				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
UTERUS				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
VAGINA				
Examined	.	.	5	5
Diestrus	.	.	2	3
Estrus	.	.	0	1
Proestrus	.	.	3	1

Appendix 19

Appendix 1
Deviations

Appendix 19

DEVIATIONS

All deviations (if any) that occurred during this study phase have been acknowledged by the Study Director, assessed for impact, and documented in the study records. All protocol deviations and those SOP deviations regarded as significant are listed below. None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

- None

Appendix 19

Appendix 2
Individual Organ Weight Values -Absolute (Day 44)

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	1001	552	2.201	1.230	0.0670	0.0119	1.358	0.0230
	1002	510	2.237	1.220	0.0573	0.0113	1.260	0.0289
	1003	514	2.243	1.341	0.0451	0.0106	1.382	0.0295
	1004	559	2.174	1.118	0.0625	0.0127	0.666	0.0216
	1005	575	2.286	1.351	0.0751	0.0158	1.499	0.0243
	1006	554	2.204	1.185	0.0592	0.0121	1.208	0.0292
	1007	480	2.168	1.337	0.0595	0.0144	1.320	0.0201
	1008	535	2.163	1.221	0.0722	0.0158	1.142	0.0165MPI
	1009	611	2.300	1.219	0.0759	0.0188	1.383	0.0200
	1010	572	2.120	1.211	0.0661	0.0134	1.225	0.0239
2M	2001	489	2.184	1.179	0.0461	0.0124	1.066	0.0189
	2102	503	2.247	1.222	0.0778	0.0142	1.455	0.0195
	2003	517	2.213	1.282	0.0527	0.0157	1.328	0.0189
	2004	446	2.152	1.199	0.0602	0.0102	0.733	0.0181
	2005	537	2.140	1.274	0.0645	0.0124	1.197	0.0220
	2006	479	2.007	1.111	0.0563	0.0119	1.193	0.0168
	2007	510	2.269	1.435	0.0688	0.0146	1.674	0.0212
	2008	510	2.350	1.287	0.0560	0.0130	1.279	0.0289
	2009	472	2.214	1.219	0.0457	0.0122	1.450	0.0233
	2010	630	2.332	1.459	0.0712	0.0133	1.272	0.0245

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	1001	1.641	2.881	15.022	1.755	--	1.049	4.156
	1002	1.560	3.132	14.287	1.677	--	0.793	4.163
	1003	1.638	2.890	13.756	1.687	--	0.843	3.888
	1004	1.665	3.451	16.169	1.731	--	0.927	3.289
	1005	1.784	3.800	18.259	1.865	--	1.029	4.278
	1006	1.964	3.155	13.539	1.751	--	1.253	3.514
	1007	1.827	2.891	12.125	1.653	--	0.759	4.733
	1008	1.797	3.062	13.524	1.848	--	0.884	3.553
	1009	1.907	3.322	15.875	1.975	--	0.905	3.993
	1010	1.765	3.378	17.260	1.680	--	1.118	3.666
2M	2001	1.580	2.480	14.566	1.734	--	0.774	4.055
	2102	1.902	3.196	12.530	1.828	--	1.234	3.713
	2003	1.738	3.621	15.196	1.940	--	1.351	4.210
	2004	1.664	3.066	12.175	1.521	--	0.956	3.604
	2005	1.864	2.967	14.661	2.145	--	1.147	3.464
	2006	1.557	2.685	14.676	1.663	--	0.941	3.416
	2007	1.798	3.048	13.848	1.633	--	1.027	3.392MPI
	2008	1.647	3.517	14.622	1.810	--	0.996	3.833
	2009	1.547	3.012	12.890	1.670	--	1.075	4.004
	2010	1.956	3.604	16.520	2.189	--	1.293	4.527

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1M	1001	0.538	--
	1002	0.551	--
	1003	0.313	--
	1004	0.564	--
	1005	0.626	--
	1006	0.560	--
	1007	0.351	--
	1008	0.357	--
	1009	0.435MPI	--
	1010	0.632	--
2M	2001	0.348	--
	2102	0.381	--
	2003	0.482	--
	2004	0.364	--
	2005	0.595	--
	2006	0.619	--
	2007	0.482	--
	2008	0.668	--
	2009	0.469	--
	2010	0.697	--

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
3M	3001	495	2.074	1.146	0.0616	0.0118	1.167	0.0188
	3002	463	2.147	1.208	0.0524	0.0131	0.735	0.0203
	3103	466	1.964	1.055	0.0598	0.0116	1.252	0.0154
	3004	490	2.268	1.236	0.0705	0.0107	1.229	0.0167
	3005	497	2.208	1.282	0.0613	0.0127	1.079	0.0193
	3006	489	2.189	1.242	0.0577	0.0124	1.018	0.0220
	3007	512	2.204	1.132	0.0619	0.0143	1.287	0.0236
	3008	555	2.345	1.324	0.0550	0.0136	1.276	0.0194
	3009	554	2.094	1.256	0.0768	0.0131	1.030	0.0252
	3010	490	2.192	1.291	0.0687	0.0157	1.183	0.0133
4M	4001	492	2.239	1.289	0.0768	0.0119	1.389	0.0198
	4002	568	2.318	1.470	0.0781	0.0225	1.155	0.0265
	4003	502	2.131	1.238	0.0809	0.0103	1.391	0.0225
	4004	535	2.135	1.128	0.0732	0.0128	0.918	0.0159
	4005	533	2.172	1.307	0.0748	0.0142	1.442	0.0247
	4006	469	2.035	1.117	0.0582	0.0102	1.142	0.0238
	4007	505	2.238	1.246	0.0662	0.0205	1.135	0.0317
	4008	492	2.099	1.257	0.0815	0.0115	1.008	0.0180
	4009	537	2.236	1.210	0.0549	0.0166	1.047MPI	0.0233
	4010	507	2.269	1.078	0.0670	0.0116	1.286	0.0190

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
3M	3001	1.575	2.724	14.440	1.634	--	1.003	3.458
	3002	1.499	2.766	13.178	1.744	--	1.145	3.630
	3103	1.607	2.473	12.914	1.605	--	0.870	3.641
	3004	1.700	2.605	14.461	1.580	--	1.464	3.789
	3005	1.585	3.107	13.304	1.703	--	0.974	4.479
	3006	1.873	2.683	14.751	1.633	--	1.109	3.374
	3007	1.708	3.339	13.904	1.711	--	1.053	3.536
	3008	1.663	3.062	14.387	1.859	--	1.125	3.754
	3009	1.802	3.317	15.273	1.717	--	0.992	4.126
	3010	1.573	2.895	13.142	1.901	--	1.089	3.760
4M	4001	1.636	3.390	12.419	1.786	--	1.021	3.914
	4002	1.826	3.265	15.954	1.915	--	1.489	4.286
	4003	1.605	3.078	13.171	1.868	--	1.239	4.076
	4004	1.753	3.109	16.216	1.720	--	1.141	3.565
	4005	1.820	2.891	16.811	1.795	--	1.273	3.719
	4006	1.579	2.690	14.315	1.526	--	0.949	3.227
	4007	1.518	2.991	16.453	1.795	--	1.577	4.244
	4008	1.547	2.749	13.127	1.718	--	1.136	3.750
	4009	1.732	3.367	17.203	2.106	--	1.273	4.300
	4010	1.795	3.282	13.563	1.860	--	0.972	3.243

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
3M	3001	0.381MPI	--
	3002	0.488	--
	3103	0.492	--
	3004	0.340	--
	3005	0.420	--
	3006	0.298	--
	3007	0.484	--
	3008	0.689	--
	3009	0.473	--
	3010	0.297	--
4M	4001	0.472	--
	4002	0.520	--
	4003	0.533	--
	4004	0.482	--
	4005	0.386	--
	4006	0.432	--
	4007	0.656MPI	--
	4008	0.401	--
	4009	0.662	--
	4010	0.530	--

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1F	1501	350	1.921	--	0.0644	0.0179	--	0.0168
	1502	318	2.050	--	0.0773	0.0170	--	0.0173
	1503	312	1.984	--	0.0614	0.0128	--	0.0212
	1504	335	2.036	--	0.0709	0.0153	--	0.0106
	1505	287	2.044	--	0.0573	0.0165	--	0.0182
	1506	350	1.962	--	0.0756	0.0154	--	0.0188
	1507	357	1.984	--	0.0822	0.0179	--	0.0134
	1508	301	1.908	--	0.0699	0.0175	--	0.0115
	1509	268	1.954	--	0.0736	0.0164	--	0.0153
	1510	292	2.058	--	0.0653	0.0176	--	0.0147
2F	2501	279	2.050	--	0.0719	0.0162	--	0.0151
	2502	308	1.937	--	0.0687	0.0190	--	0.0133
	2503	371	2.091	--	0.0658	0.0192	--	0.0222
	2504	242	2.045	--	0.0644	0.0109	--	0.0112
	2505	355	1.926	--	0.0544	0.0189	--	0.0169
	2506	326	2.170	--	0.0641	0.0152	--	0.0175
	2507	287	1.952	--	0.0686	0.0179	--	0.0213
	2508	314	2.169	--	0.0944	0.0159	--	0.0156
	2509	326	2.076	--	0.0805	0.0160	--	0.0161
	2510	323	2.068	--	0.0821	0.0153	--	0.0144

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	1501	1.308	1.987	10.204	1.426	0.103	0.732	--
	1502	1.294	2.163	7.914	1.456	0.094	0.705	--
	1503	1.116	1.750	7.692	1.308	0.089	0.635	--
	1504	1.304	2.257	9.017	1.507	0.087	0.514	--
	1505	1.110	1.823	7.851	1.232	0.080	0.604	--
	1506	1.401	2.151	8.344	1.424	0.104	0.769	--
	1507	1.173	1.803	8.711	1.248	0.098	0.647	--
	1508	1.116	1.869	8.786	1.186	0.077	0.491	--
	1509	0.974	1.691	6.734	1.189	0.086	0.460	--
	1510	1.157	1.849	7.735	1.296	0.092	0.488	--
2F	2501	1.150	1.788	8.127	1.387	0.076	0.677	--
	2502	1.091	1.971	8.399	1.546	0.093	0.668	--
	2503	1.143	2.143	9.795	1.455	0.130	0.786	--
	2504	0.985	1.509	6.809	1.161	0.090	0.479	--
	2505	1.313	2.093	9.951	1.417	0.099	0.680	--
	2506	1.415	1.857	8.190	1.323	0.101	0.755	--
	2507	1.116	1.677	7.345	1.154	0.104	0.563	--
	2508	1.430	2.146MPI	14.333	1.507	0.101	0.875	--
	2509	1.048	2.254	9.132	1.461	0.152	0.875	--
	2510	1.438	2.081	9.186	1.426	0.095	0.767	--

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1F	1501	0.502	0.393
	1502	0.514	0.433
	1503	0.395	0.462
	1504	0.392	0.516
	1505	0.380	0.577
	1506	0.408	1.030
	1507	0.348	0.548
	1508	0.349	0.495
	1509	0.320	1.081
	1510	0.489	0.531
2F	2501	0.322	1.226
	2502	0.399	0.516
	2503	0.458	0.489
	2504	0.343	1.003
	2505	0.572	0.986
	2506	0.472	0.492
	2507	0.603	1.037
	2508	0.311	0.617
	2509	0.465	0.785
	2510	0.365	0.549

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
3F	3501	293	1.991	--	0.0675	0.0181	--	0.0150
	3502	302	2.013	--	0.0788	0.0149	--	0.0134
	3503	311	2.112	--	0.0746	0.0186	--	0.0192
	3604	371	2.030	--	0.0715	0.0159	--	0.0167
	3505	350	2.062	--	0.0639	0.0171	--	0.0153
	3506	305	2.005	--	0.0713	0.0139	--	0.0178
	3507	288	2.200	--	0.0831	0.0198	--	0.0175
	3508	316	2.079	--	0.0733	0.0170	--	0.0149
	3509	352	2.063	--	0.0743	0.0213	--	0.0197
	3510	265	1.927	--	0.0644	0.0135	--	0.0101
4F	4501	328	1.952	--	0.0592	0.0138	--	0.0169
	4502	286	1.946	--	0.0650	0.0123	--	0.0160
	4503	319	2.130	--	0.0585MPI	0.0172	--	0.0244
	4504	282	2.066	--	0.0709	0.0184	--	0.0202
	4505	332	2.037	--	0.0680	0.0189	--	0.0211
	4506	287	2.063	--	0.0756	0.0150	--	0.0180
	4507	304	1.940	--	0.0791	0.0207	--	0.0171
	4508	350	2.061	--	0.0834	0.0184	--	0.0182
	4509	320	2.076	--	0.0692	0.0165	--	0.0197
	4510	327	2.126	--	0.0806	0.0159	--	0.0177

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
3F	3501	1.119	1.862	8.039	1.346	0.107	0.840	--
	3502	1.357	2.079	9.059	1.318	0.097	0.697	--
	3503	1.142	2.289	9.096	1.520	0.116	0.796	--
	3604	1.339	2.061	9.928	1.499	0.083	0.806	--
	3505	1.317	2.023	10.100	1.566	0.093	0.736	--
	3506	1.131	1.823	8.201	1.300	0.100	0.754	--
	3507	1.131	1.796	8.280	1.262	0.119	0.590	--
	3508	1.302	1.993	8.603	1.333	0.108	0.871	--
	3509	1.096	2.155	9.629	1.435	0.119	0.874	--
	3510	1.094	1.795	7.952	1.325	0.120	0.602	--
4F	4501	1.199	1.929	9.391	1.232	0.112	0.594	--
	4502	1.115	1.561	7.959	1.197	0.080	0.662	--
	4503	1.131	2.113	9.047	1.429	0.086	0.839	--
	4504	1.248	2.005	8.728	1.564	0.107	0.896	--
	4505	1.108	2.250	9.286	1.492	0.104	0.924	--
	4506	1.055	1.863MPI	8.597	1.362	0.088	0.914	--
	4507	1.054	1.846	9.156	1.347	0.139	0.665	--
	4508	1.447	2.266	11.515	1.551	0.109	0.971	--
	4509	1.225	2.087	10.246	1.455	0.083	0.587	--
	4510	1.280	2.199	9.814	1.469	0.094	0.882	--

Appendix 19

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
3F	3501	0.327	0.635
	3502	0.459	0.620
	3503	0.316	0.737
	3604	0.616	0.714
	3505	0.453	0.547
	3506	0.400	1.243
	3507	0.511MPI	0.520
	3508	0.489	0.580
	3509	0.489MPI	1.086
	3510	0.440	0.790
4F	4501	0.343	0.466
	4502	0.548	0.848
	4503	0.415	1.327
	4504	0.441	0.662
	4505	0.467	0.915
	4506	0.349	0.917
	4507	0.651	0.982
	4508	0.485	0.608
	4509	0.535	0.558
	4510	0.465	0.961

Appendix 19

Appendix 3
Individual Organ Weight Values - Relative to Body Weight (Day 44)

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1001	0.3987	0.2228	0.01214	0.00216	0.2460	0.00417	0.2973
	1002	0.4386	0.2392	0.01124	0.00222	0.2471	0.00567	0.3059
	1003	0.4364	0.2609	0.00877	0.00206	0.2689	0.00574	0.3187
	1004	0.3889	0.2000	0.01118	0.00227	0.1191	0.00386	0.2979
	1005	0.3976	0.2350	0.01306	0.00275	0.2607	0.00423	0.3103
	1006	0.3978	0.2139	0.01069	0.00218	0.2181	0.00527	0.3545
	1007	0.4517	0.2785	0.01240	0.00300	0.2750	0.00419	0.3806
	1008	0.4043	0.2282	0.01350	0.00295	0.2135	0.00308MPI	0.3359
	1009	0.3764	0.1995	0.01242	0.00308	0.2264	0.00327	0.3121
	1010	0.3706	0.2117	0.01156	0.00234	0.2142	0.00418	0.3086
2M	2001	0.4466	0.2411	0.00943	0.00254	0.2180	0.00387	0.3231
	2102	0.4467	0.2429	0.01547	0.00282	0.2893	0.00388	0.3781
	2003	0.4280	0.2480	0.01019	0.00304	0.2569	0.00366	0.3362
	2004	0.4825	0.2688	0.01350	0.00229	0.1643	0.00406	0.3731
	2005	0.3985	0.2372	0.01201	0.00231	0.2229	0.00410	0.3471
	2006	0.4190	0.2319	0.01175	0.00248	0.2491	0.00351	0.3251
	2007	0.4449	0.2814	0.01349	0.00286	0.3282	0.00416	0.3525
	2008	0.4608	0.2524	0.01098	0.00255	0.2508	0.00567	0.3229
	2009	0.4691	0.2583	0.00968	0.00258	0.3072	0.00494	0.3278
	2010	0.3702	0.2316	0.01130	0.00211	0.2019	0.00389	0.3105

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	1001	0.5219	2.7214	0.3179	--	0.1900	0.7529	0.0975
	1002	0.6141	2.8014	0.3288	--	0.1555	0.8163	0.1080
	1003	0.5623	2.6763	0.3282	--	0.1640	0.7564	0.0609
	1004	0.6174	2.8925	0.3097	--	0.1658	0.5884	0.1009
	1005	0.6609	3.1755	0.3243	--	0.1790	0.7440	0.1089
	1006	0.5695	2.4439	0.3161	--	0.2262	0.6343	0.1011
	1007	0.6023	2.5260	0.3444	--	0.1581	0.9860	0.0731
	1008	0.5723	2.5279	0.3454	--	0.1652	0.6641	0.0667
	1009	0.5437	2.5982	0.3232	--	0.1481	0.6535	0.0712MPI
	1010	0.5906	3.0175	0.2937	--	0.1955	0.6409	0.1105
2M	2001	0.5072	2.9787	0.3546	--	0.1583	0.8292	0.0712
	2102	0.6354	2.4911	0.3634	--	0.2453	0.7382	0.0757
	2003	0.7004	2.9393	0.3752	--	0.2613	0.8143	0.0932
	2004	0.6874	2.7298	0.3410	--	0.2143	0.8081	0.0816
	2005	0.5525	2.7302	0.3994	--	0.2136	0.6451	0.1108
	2006	0.5605	3.0639	0.3472	--	0.1965	0.7132	0.1292
	2007	0.5976	2.7153	0.3202	--	0.2014	0.6651MPI	0.0945
	2008	0.6896	2.8671	0.3549	--	0.1953	0.7516	0.1310
	2009	0.6381	2.7309	0.3538	--	0.2278	0.8483	0.0994
	2010	0.5721	2.6222	0.3475	--	0.2052	0.7186	0.1106

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	UTERUS %
1M	1001	--
	1002	--
	1003	--
	1004	--
	1005	--
	1006	--
	1007	--
	1008	--
	1009	--
	1010	--
2M	2001	--
	2102	--
	2003	--
	2004	--
	2005	--
	2006	--
	2007	--
	2008	--
	2009	--
	2010	--

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
3M	3001	0.4190	0.2315	0.01244	0.00238	0.2358	0.00380	0.3182
	3002	0.4637	0.2609	0.01132	0.00283	0.1587	0.00438	0.3238
	3103	0.4215	0.2264	0.01283	0.00249	0.2687	0.00330	0.3448
	3004	0.4629	0.2522	0.01439	0.00218	0.2508	0.00341	0.3469
	3005	0.4443	0.2579	0.01233	0.00256	0.2171	0.00388	0.3189
	3006	0.4476	0.2540	0.01180	0.00254	0.2082	0.00450	0.3830
	3007	0.4305	0.2211	0.01209	0.00279	0.2514	0.00461	0.3336
	3008	0.4225	0.2386	0.00991	0.00245	0.2299	0.00350	0.2996
	3009	0.3780	0.2267	0.01386	0.00236	0.1859	0.00455	0.3253
	3010	0.4473	0.2635	0.01402	0.00320	0.2414	0.00271	0.3210
4M	4001	0.4551	0.2620	0.01561	0.00242	0.2823	0.00402	0.3325
	4002	0.4081	0.2588	0.01375	0.00396	0.2033	0.00467	0.3215
	4003	0.4245	0.2466	0.01612	0.00205	0.2771	0.00448	0.3197
	4004	0.3991	0.2108	0.01368	0.00239	0.1716	0.00297	0.3277
	4005	0.4075	0.2452	0.01403	0.00266	0.2705	0.00463	0.3415
	4006	0.4339	0.2382	0.01241	0.00217	0.2435	0.00507	0.3367
	4007	0.4432	0.2467	0.01311	0.00406	0.2248	0.00628	0.3006
	4008	0.4266	0.2555	0.01657	0.00234	0.2049	0.00366	0.3144
	4009	0.4164	0.2253	0.01022	0.00309	0.1950MPI	0.00434	0.3225
	4010	0.4475	0.2126	0.01321	0.00229	0.2536	0.00375	0.3540

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
3M	3001	0.5503	2.9172	0.3301	--	0.2026	0.6986	0.0770MPI
	3002	0.5974	2.8462	0.3767	--	0.2473	0.7840	0.1054
	3103	0.5307	2.7712	0.3444	--	0.1867	0.7813	0.1056
	3004	0.5316	2.9512	0.3224	--	0.2988	0.7733	0.0694
	3005	0.6252	2.6769	0.3427	--	0.1960	0.9012	0.0845
	3006	0.5487	3.0166	0.3339	--	0.2268	0.6900	0.0609
	3007	0.6521	2.7156	0.3342	--	0.2057	0.6906	0.0945
	3008	0.5517	2.5923	0.3350	--	0.2027	0.6764	0.1241
	3009	0.5987	2.7569	0.3099	--	0.1791	0.7448	0.0854
	3010	0.5908	2.6820	0.3880	--	0.2222	0.7673	0.0606
4M	4001	0.6890	2.5242	0.3630	--	0.2075	0.7955	0.0959
	4002	0.5748	2.8088	0.3371	--	0.2621	0.7546	0.0915
	4003	0.6131	2.6237	0.3721	--	0.2468	0.8120	0.1062
	4004	0.5811	3.0310	0.3215	--	0.2133	0.6664	0.0901
	4005	0.5424	3.1540	0.3368	--	0.2388	0.6977	0.0724
	4006	0.5736	3.0522	0.3254	--	0.2023	0.6881	0.0921
	4007	0.5923	3.2580	0.3554	--	0.3123	0.8404	0.1299MPI
	4008	0.5587	2.6681	0.3492	--	0.2309	0.7622	0.0815
	4009	0.6270	3.2035	0.3922	--	0.2371	0.8007	0.1233
	4010	0.6473	2.6751	0.3669	--	0.1917	0.6396	0.1045

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	UTERUS %
3M	3001	--
	3002	--
	3103	--
	3004	--
	3005	--
	3006	--
	3007	--
	3008	--
	3009	--
	3010	--
4M	4001	--
	4002	--
	4003	--
	4004	--
	4005	--
	4006	--
	4007	--
	4008	--
	4009	--
	4010	--

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	1501	0.5489	--	0.01840	0.00511	--	0.00480	0.3737
	1502	0.6447	--	0.02431	0.00535	--	0.00544	0.4069
	1503	0.6359	--	0.01968	0.00410	--	0.00679	0.3577
	1504	0.6078	--	0.02116	0.00457	--	0.00316	0.3893
	1505	0.7122	--	0.01997	0.00575	--	0.00634	0.3868
	1506	0.5606	--	0.02160	0.00440	--	0.00537	0.4003
	1507	0.5557	--	0.02303	0.00501	--	0.00375	0.3286
	1508	0.6339	--	0.02322	0.00581	--	0.00382	0.3708
	1509	0.7291	--	0.02746	0.00612	--	0.00571	0.3634
	1510	0.7048	--	0.02236	0.00603	--	0.00503	0.3962
2F	2501	0.7348	--	0.02577	0.00581	--	0.00541	0.4122
	2502	0.6289	--	0.02231	0.00617	--	0.00432	0.3542
	2503	0.5636	--	0.01774	0.00518	--	0.00598	0.3081
	2504	0.8450	--	0.02661	0.00450	--	0.00463	0.4070
	2505	0.5425	--	0.01532	0.00532	--	0.00476	0.3699
	2506	0.6656	--	0.01966	0.00466	--	0.00537	0.4340
	2507	0.6801	--	0.02390	0.00624	--	0.00742	0.3889
	2508	0.6908	--	0.03006	0.00506	--	0.00497	0.4554
	2509	0.6368	--	0.02469	0.00491	--	0.00494	0.3215
	2510	0.6402	--	0.02542	0.00474	--	0.00446	0.4452

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	1501	0.5677	2.9154	0.4074	0.0294	0.2091	--	0.1434
	1502	0.6802	2.4887	0.4579	0.0296	0.2217	--	0.1616
	1503	0.5609	2.4654	0.4192	0.0285	0.2035	--	0.1266
	1504	0.6737	2.6916	0.4499	0.0260	0.1534	--	0.1170
	1505	0.6352	2.7355	0.4293	0.0279	0.2105	--	0.1324
	1506	0.6146	2.3840	0.4069	0.0297	0.2197	--	0.1166
	1507	0.5050	2.4401	0.3496	0.0275	0.1812	--	0.0975
	1508	0.6209	2.9189	0.3940	0.0256	0.1631	--	0.1159
	1509	0.6310	2.5127	0.4437	0.0321	0.1716	--	0.1194
	1510	0.6332	2.6490	0.4438	0.0315	0.1671	--	0.1675
2F	2501	0.6409	2.9129	0.4971	0.0272	0.2427	--	0.1154
	2502	0.6399	2.7269	0.5019	0.0302	0.2169	--	0.1295
	2503	0.5776	2.6402	0.3922	0.0350	0.2119	--	0.1235
	2504	0.6236	2.8136	0.4798	0.0372	0.1979	--	0.1417
	2505	0.5896	2.8031	0.3992	0.0279	0.1915	--	0.1611
	2506	0.5696	2.5123	0.4058	0.0310	0.2316	--	0.1448
	2507	0.5843	2.5592	0.4021	0.0362	0.1962	--	0.2101
	2508	0.6834MPI	4.5646	0.4799	0.0322	0.2787	--	0.0990
	2509	0.6914	2.8012	0.4482	0.0466	0.2684	--	0.1426
	2510	0.6443	2.8440	0.4415	0.0294	0.2375	--	0.1130

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	UTERUS %
1F	1501	0.1123
	1502	0.1362
	1503	0.1481
	1504	0.1540
	1505	0.2010
	1506	0.2943
	1507	0.1535
	1508	0.1645
	1509	0.4034
	1510	0.1818
2F	2501	0.4394
	2502	0.1675
	2503	0.1318
	2504	0.4145
	2505	0.2777
	2506	0.1509
	2507	0.3613
	2508	0.1965
	2509	0.2408
	2510	0.1700

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
3F	3501	0.6795	--	0.02304	0.00618	--	0.00512	0.3819
	3502	0.6666	--	0.02609	0.00493	--	0.00444	0.4493
	3503	0.6791	--	0.02399	0.00598	--	0.00617	0.3672
	3604	0.5472	--	0.01927	0.00429	--	0.00450	0.3609
	3505	0.5891	--	0.01826	0.00489	--	0.00437	0.3763
	3506	0.6574	--	0.02338	0.00456	--	0.00584	0.3708
	3507	0.7639	--	0.02885	0.00688	--	0.00608	0.3927
	3508	0.6579	--	0.02320	0.00538	--	0.00472	0.4120
	3509	0.5861	--	0.02111	0.00605	--	0.00560	0.3114
	3510	0.7272	--	0.02430	0.00509	--	0.00381	0.4128
4F	4501	0.5951	--	0.01805	0.00421	--	0.00515	0.3655
	4502	0.6804	--	0.02273	0.00430	--	0.00559	0.3899
	4503	0.6677	--	0.01834MPI	0.00539	--	0.00765	0.3545
	4504	0.7326	--	0.02514	0.00652	--	0.00716	0.4426
	4505	0.6136	--	0.02048	0.00569	--	0.00636	0.3337
	4506	0.7188	--	0.02634	0.00523	--	0.00627	0.3676
	4507	0.6382	--	0.02602	0.00681	--	0.00563	0.3467
	4508	0.5889	--	0.02383	0.00526	--	0.00520	0.4134
	4509	0.6488	--	0.02163	0.00516	--	0.00616	0.3828
	4510	0.6502	--	0.02465	0.00486	--	0.00541	0.3914

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
3F	3501	0.6355	2.7437	0.4594	0.0365	0.2867	--	0.1116
	3502	0.6884	2.9997	0.4364	0.0321	0.2308	--	0.1520
	3503	0.7360	2.9248	0.4887	0.0373	0.2559	--	0.1016
	3604	0.5555	2.6760	0.4040	0.0224	0.2173	--	0.1660
	3505	0.5780	2.8857	0.4474	0.0266	0.2103	--	0.1294
	3506	0.5977	2.6889	0.4262	0.0328	0.2472	--	0.1311
	3507	0.6236	2.8750	0.4382	0.0413	0.2049	--	0.1774MPI
	3508	0.6307	2.7225	0.4218	0.0342	0.2756	--	0.1547
	3509	0.6122	2.7355	0.4077	0.0338	0.2483	--	0.1389MPI
	3510	0.6774	3.0008	0.5000	0.0453	0.2272	--	0.1660
4F	4501	0.5881	2.8631	0.3756	0.0341	0.1811	--	0.1046
	4502	0.5458	2.7829	0.4185	0.0280	0.2315	--	0.1916
	4503	0.6624	2.8361	0.4480	0.0270	0.2630	--	0.1301
	4504	0.7110	3.0950	0.5546	0.0379	0.3177	--	0.1564
	4505	0.6777	2.7970	0.4494	0.0313	0.2783	--	0.1407
	4506	0.6491MPI	2.9955	0.4746	0.0307	0.3185	--	0.1216
	4507	0.6072	3.0118	0.4431	0.0457	0.2188	--	0.2141
	4508	0.6474	3.2900	0.4431	0.0311	0.2774	--	0.1386
	4509	0.6522	3.2019	0.4547	0.0259	0.1834	--	0.1672
	4510	0.6725	3.0012	0.4492	0.0287	0.2697	--	0.1422

Appendix 19

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	UTERUS %
3F	3501	0.2167
	3502	0.2053
	3503	0.2370
	3604	0.1925
	3505	0.1563
	3506	0.4075
	3507	0.1806
	3508	0.1835
	3509	0.3085
	3510	0.2981
4F	4501	0.1421
	4502	0.2965
	4503	0.4160
	4504	0.2348
	4505	0.2756
	4506	0.3195
	4507	0.3230
	4508	0.1737
	4509	0.1744
	4510	0.2939

Appendix 19

Appendix 4
Individual Organ Weight Values - Relative to Brain Weight (Day 44)

Appendix 19

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1001	55.8837	3.04407	0.54066	61.6992	1.04498	74.5570	130.8950
	1002	54.5373	2.56147	0.50514	56.3254	1.29191	69.7363	140.0089
	1003	59.7860	2.01070	0.47258	61.6139	1.31520	73.0272	128.8453
	1004	51.4259	2.87489	0.58418	30.6348	0.99356	76.5869	158.7397
	1005	59.0989	3.28521	0.69116	65.5731	1.06299	78.0402	166.2292
	1006	53.7659	2.68603	0.54900	54.8094	1.32486	89.1107	143.1488
	1007	61.6697	2.74446	0.66421	60.8856	0.92712	84.2712	133.3487
	1008	56.4494	3.33796	0.73047	52.7970	0.76283MPI	83.0791	141.5626
	1009	53.0000	3.30000	0.81739	60.1304	0.86957	82.9130	144.4348
	1010	57.1226	3.11792	0.63208	57.7830	1.12736	83.2547	159.3396
2M	2001	53.9835	2.11081	0.56777	48.8095	0.86538	72.3443	113.5531
	2102	54.3836	3.46239	0.63195	64.7530	0.86782	84.6462	142.2341
	2003	57.9304	2.38138	0.70944	60.0090	0.85404	78.5359	163.6240
	2004	55.7156	2.79740	0.47398	34.0613	0.84108	77.3234	142.4721
	2005	59.5327	3.01402	0.57944	55.9346	1.02804	87.1028	138.6449
	2006	55.3563	2.80518	0.59292	59.4420	0.83707	77.5785	133.7818
	2007	63.2437	3.03217	0.64346	73.7770	0.93433	79.2420	134.3323
	2008	54.7660	2.38298	0.55319	54.4255	1.22979	70.0851	149.6596
	2009	55.0587	2.06414	0.55104	65.4923	1.05239	69.8735	136.0434
	2010	62.5643	3.05317	0.57033	54.5455	1.05060	83.8765	154.5455

Appendix 19

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	1001	682.5080	79.7365	--	47.6602	188.8233	24.4434	--
	1002	638.6679	74.9665	--	35.4493	186.0975	24.6312	--
	1003	613.2858	75.2118	--	37.5836	173.3393	13.9545	--
	1004	743.7443	79.6228	--	42.6403	151.2879	25.9430	--
	1005	798.7314	81.5836	--	45.0131	187.1391	27.3841	--
	1006	614.2922	79.4465	--	56.8512	159.4374	25.4083	--
	1007	559.2712	76.2454	--	35.0092	218.3118	16.1900	--
	1008	625.2427	85.4369	--	40.8692	164.2626	16.5049	--
	1009	690.2174	85.8696	--	39.3478	173.6087	18.9130MPI	--
	1010	814.1509	79.2453	--	52.7358	172.9245	29.8113	--
2M	2001	666.9414	79.3956	--	35.4396	185.6685	15.9341	--
	2102	557.6324	81.3529	--	54.9177	165.2425	16.9559	--
	2003	686.6697	87.6638	--	61.0484	190.2395	21.7804	--
	2004	565.7528	70.6784	--	44.4238	167.4721	16.9145	--
	2005	685.0935	100.2336	--	53.5981	161.8692	27.8037	--
	2006	731.2407	82.8600	--	46.8859	170.2043	30.8421	--
	2007	610.3129	71.9700	--	45.2622	149.4932MPI	21.2428	--
	2008	622.2128	77.0213	--	42.3830	163.1064	28.4255	--
	2009	582.2042	75.4291	--	48.5547	180.8491	21.1834	--
	2010	708.4048	93.8679	--	55.4460	194.1252	29.8885	--

Appendix 19

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
3M	3001	55.2555	2.97011	0.56895	56.2681	0.90646	75.9402	131.3404
	3002	56.2646	2.44061	0.61015	34.2338	0.94551	69.8184	128.8309
	3103	53.7169	3.04481	0.59063	63.7475	0.78411	81.8228	125.9165
	3004	54.4974	3.10847	0.47178	54.1887	0.73633	74.9559	114.8589
	3005	58.0616	2.77627	0.57518	48.8678	0.87409	71.7844	140.7156
	3006	56.7382	2.63591	0.56647	46.5053	1.00503	85.5642	122.5674
	3007	51.3612	2.80853	0.64882	58.3938	1.07078	77.4955	151.4973
	3008	56.4606	2.34542	0.57996	54.4136	0.82729	70.9168	130.5757
	3009	59.9809	3.66762	0.62560	49.1882	1.20344	86.0554	158.4050
	3010	58.8960	3.13412	0.71624	53.9690	0.60675	71.7609	132.0712
4M	4001	57.5703	3.43010	0.53149	62.0366	0.88432	73.0683	151.4069
	4002	63.4167	3.36928	0.97066	49.8274	1.14323	78.7748	140.8542
	4003	58.0948	3.79634	0.48334	65.2745	1.05584	75.3168	144.4392
	4004	52.8337	3.42857	0.59953	42.9977	0.74473	82.1077	145.6206
	4005	60.1750	3.44383	0.65378	66.3904	1.13720	83.7937	133.1031
	4006	54.8894	2.85995	0.50123	56.1179	1.16953	77.5921	132.1867
	4007	55.6747	2.95800	0.91600	50.7149	1.41644	67.8284	133.6461
	4008	59.8857	3.88280	0.54788	48.0229	0.85755	73.7018	130.9671
	4009	54.1145	2.45528	0.74240	46.8247MPI	1.04204	77.4597	150.5814
	4010	47.5099	2.95284	0.51124	56.6770	0.83737	79.1097	144.6452

Appendix 19

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
3M	3001	696.2392	78.7850	--	48.3607	166.7310	18.3703MPI	--
	3002	613.7867	81.2296	--	53.3302	169.0731	22.7294	--
	3103	657.5356	81.7210	--	44.2974	185.3870	25.0509	--
	3004	637.6102	69.6649	--	64.5503	167.0635	14.9912	--
	3005	602.5362	77.1286	--	44.1123	202.8533	19.0217	--
	3006	673.8693	74.6003	--	50.6624	154.1343	13.6135	--
	3007	630.8530	77.6316	--	47.7768	160.4356	21.9601	--
	3008	613.5181	79.2751	--	47.9744	160.0853	29.3817	--
	3009	729.3696	81.9962	--	47.3734	197.0392	22.5883	--
	3010	599.5438	86.7245	--	49.6807	171.5328	13.5493	--
4M	4001	554.6673	79.7678	--	45.6007	174.8102	21.0808	--
	4002	688.2657	82.6143	--	64.2364	184.9008	22.4331	--
	4003	618.0666	87.6584	--	58.1417	191.2717	25.0117	--
	4004	759.5316	80.5621	--	53.4426	166.9789	22.5761	--
	4005	773.9871	82.6427	--	58.6096	171.2247	17.7716	--
	4006	703.4398	74.9877	--	46.6339	158.5749	21.2285	--
	4007	735.1653	80.2055	--	70.4647	189.6336	29.3119MPI	--
	4008	625.3930	81.8485	--	54.1210	178.6565	19.1043	--
	4009	769.3649	94.1860	--	56.9320	192.3077	29.6064	--
	4010	597.7523	81.9744	--	42.8383	142.9264	23.3583	--

Appendix 19

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	1501	--	3.35242	0.93181	--	0.87454	68.0895	103.4357
	1502	--	3.77073	0.82927	--	0.84390	63.1220	105.5122
	1503	--	3.09476	0.64516	--	1.06855	56.2500	88.2056
	1504	--	3.48232	0.75147	--	0.52063	64.0472	110.8546
	1505	--	2.80333	0.80724	--	0.89041	54.3053	89.1879
	1506	--	3.85321	0.78491	--	0.95821	71.4067	109.6330
	1507	--	4.14315	0.90222	--	0.67540	59.1230	90.8770
	1508	--	3.66352	0.91719	--	0.60273	58.4906	97.9560
	1509	--	3.76663	0.83930	--	0.78301	49.8465	86.5404
	1510	--	3.17298	0.85520	--	0.71429	56.2196	89.8445
2F	2501	--	3.50732	0.79024	--	0.73659	56.0976	87.2195
	2502	--	3.54672	0.98090	--	0.68663	56.3242	101.7553
	2503	--	3.14682	0.91822	--	1.06169	54.6628	102.4868
	2504	--	3.14914	0.53301	--	0.54768	48.1663	73.7897
	2505	--	2.82451	0.98131	--	0.87747	68.1724	108.6708
	2506	--	2.95392	0.70046	--	0.80645	65.2074	85.5760
	2507	--	3.51434	0.91701	--	1.09119	57.1721	85.9119
	2508	--	4.35224	0.73306	--	0.71923	65.9290	98.9396MPI
	2509	--	3.87765	0.77071	--	0.77553	50.4817	108.5742
	2510	--	3.97002	0.73985	--	0.69632	69.5358	100.6286

Appendix 19

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	1501	531.1817	74.2322	5.3618	38.1052	--	26.1322	20.4581
	1502	386.0488	71.0244	4.5854	34.3902	--	25.0732	21.1220
	1503	387.7016	65.9274	4.4859	32.0060	--	19.9093	23.2863
	1504	442.8782	74.0177	4.2731	25.2456	--	19.2534	25.3438
	1505	384.0998	60.2740	3.9139	29.5499	--	18.5910	28.2290
	1506	425.2803	72.5790	5.3007	39.1947	--	20.7951	52.4975
	1507	439.0625	62.9032	4.9395	32.6109	--	17.5403	27.6210
	1508	460.4822	62.1593	4.0356	25.7338	--	18.2914	25.9434
	1509	344.6264	60.8495	4.4012	23.5415	--	16.3767	55.3224
	1510	375.8503	62.9738	4.4704	23.7123	--	23.7609	25.8017
2F	2501	396.4390	67.6585	3.7073	33.0244	--	15.7073	59.8049
	2502	433.6087	79.8141	4.8012	34.4863	--	20.5989	26.6391
	2503	468.4362	69.5839	6.2171	37.5897	--	21.9034	23.3859
	2504	332.9584	56.7726	4.4010	23.4230	--	16.7726	49.0465
	2505	516.6667	73.5722	5.1402	35.3063	--	29.6989	51.1942
	2506	377.4194	60.9677	4.6544	34.7926	--	21.7512	22.6728
	2507	376.2807	59.1189	5.3279	28.8422	--	30.8914	53.1250
	2508	660.8114	69.4790	4.6565	40.3412	--	14.3384	28.4463
	2509	439.8844	70.3757	7.3218	42.1484	--	22.3988	37.8131
	2510	444.1973	68.9555	4.5938	37.0890	--	17.6499	26.5474

Appendix 19

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
3F	3501	--	3.39026	0.90909	--	0.75339	56.2029	93.5208
	3502	--	3.91456	0.74019	--	0.66567	67.4118	103.2787
	3503	--	3.53220	0.88068	--	0.90909	54.0720	108.3807
	3604	--	3.52217	0.78325	--	0.82266	65.9606	101.5271
	3505	--	3.09893	0.82929	--	0.74200	63.8700	98.1086
	3506	--	3.55611	0.69327	--	0.88778	56.4090	90.9227
	3507	--	3.77727	0.90000	--	0.79545	51.4091	81.6364
	3508	--	3.52573	0.81770	--	0.71669	62.6263	95.8634
	3509	--	3.60155	1.03248	--	0.95492	53.1265	104.4595
	3510	--	3.34198	0.70057	--	0.52413	56.7722	93.1500
4F	4501	--	3.03279	0.70697	--	0.86578	61.4242	98.8217
	4502	--	3.34018	0.63207	--	0.82220	57.2970	80.2158
	4503	--	2.74648MPI	0.80751	--	1.14554	53.0986	99.2019
	4504	--	3.43175	0.89061	--	0.97773	60.4066	97.0474
	4505	--	3.33824	0.92784	--	1.03584	54.3937	110.4566
	4506	--	3.66457	0.72710	--	0.87252	51.1391	90.3054MPI
	4507	--	4.07732	1.06701	--	0.88144	54.3299	95.1546
	4508	--	4.04658	0.89277	--	0.88307	70.2086	109.9466
	4509	--	3.33333	0.79480	--	0.94894	59.0077	100.5299
	4510	--	3.79116	0.74788	--	0.83255	60.2070	103.4337

Appendix 19

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1647 10 µg/dose
Group 3 - mRNA-1647 30 µg/dose
Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
3F	3501	403.7670	67.6042	5.3742	42.1899	--	16.4239	31.8935
	3502	450.0248	65.4744	4.8187	34.6249	--	22.8018	30.7998
	3503	430.6818	71.9697	5.4924	37.6894	--	14.9621	34.8958
	3604	489.0640	73.8424	4.0887	39.7044	--	30.3448	35.1724
	3505	489.8157	75.9457	4.5102	35.6935	--	21.9690	26.5276
	3506	409.0274	64.8379	4.9875	37.6060	--	19.9501	61.9950
	3507	376.3636	57.3636	5.4091	26.8182	--	23.2273MPI	23.6364
	3508	413.8047	64.1174	5.1948	41.8951	--	23.5209	27.8980
	3509	466.7475	69.5589	5.7683	42.3655	--	23.7033MPI	52.6418
	3510	412.6622	68.7597	6.2273	31.2403	--	22.8334	40.9964
4F	4501	481.0963	63.1148	5.7377	30.4303	--	17.5717	23.8730
	4502	408.9928	61.5108	4.1110	34.0185	--	28.1603	43.5766
	4503	424.7418	67.0892	4.0376	39.3897	--	19.4836	62.3005
	4504	422.4589	75.7018	5.1791	43.3688	--	21.3456	32.0426
	4505	455.8665	73.2450	5.1055	45.3608	--	22.9259	44.9190
	4506	416.7232	66.0204	4.2656	44.3044	--	16.9171	44.4498
	4507	471.9588	69.4330	7.1649	34.2784	--	33.5567	50.6186
	4508	558.7094	75.2547	5.2887	47.1131	--	23.5323	29.5002
	4509	493.5453	70.0867	3.9981	28.2755	--	25.7707	26.8786
	4510	461.6181	69.0969	4.4214	41.4864	--	21.8721	45.2023

Appendix 19

Appendix 5
Individual Organ Weight Values -Absolute (Day 57)

Appendix 19

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	1011	556	2.214	1.410	0.0702	0.0164	0.889	0.0279
	1012	647	2.333	1.320	0.0733	0.0205	1.008	0.0254
	1013	595	2.301	1.372	0.0620	0.0148	1.753	0.0378
	1015	594	2.335	1.519	0.0608	0.0157	1.177	0.0267
4M	4011	607	2.269	1.329	0.0740	0.0161	1.364	0.0327
	4012	577	2.258	1.337	0.0556	0.0151	1.278	0.0270
	4013	615	2.192	1.328	0.0715	0.0137	1.095	0.0277
	4014	550	2.388	1.345	0.0830	0.0161	1.275	0.0253
	4015	573	2.324	1.455	0.0713	0.0149	1.223	0.0246

Appendix 19

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	1011	1.789	2.797	16.689	1.685	--	0.834	3.515
	1012	2.205	3.333MPI	18.510	1.803	--	0.927	4.009
	1013	1.876	3.095	16.561	1.819	--	0.933	3.768
	1015	2.045	3.660	15.714	1.860	--	1.014	4.680
4M	4011	1.818	3.303	19.007	2.024	--	1.086	3.799
	4012	1.966	3.556	15.873	2.014	--	1.244	4.183
	4013	1.913	3.452	17.543	1.796	--	1.221	3.663
	4014	1.933	3.070	14.427	2.018	--	1.056	4.314
	4015	1.929	3.865	14.902	1.855	--	0.904	3.983

Appendix 19

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1M	1011	0.426	--
	1012	0.575	--
	1013	0.299	--
	1015	0.527MPI	--
4M	4011	0.507	--
	4012	0.449	--
	4013	0.369	--
	4014	0.362	--
	4015	0.381	--

Appendix 19

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1F	1511	280	1.965	--	0.0541	0.0150	--	0.0114
	1612	336	2.057	--	0.0757	0.0186	--	0.0119MPI
	1513	349	2.079	--	0.0690	0.0168	--	0.0171
	1514	341	2.161	--	0.0658	0.0178	--	0.0235
	1515	348	2.092	--	0.0573	0.0169	--	0.0167
4F	4511	324	2.110	--	0.0823	0.0170	--	0.0194
	4512	336	1.924	--	0.0673	0.0184	--	0.0164
	4513	362	2.200	--	0.0641	0.0127	--	0.0234
	4514	329	2.071	--	0.0674	0.0118	--	0.0203
	4515	284	1.916	--	0.0596	0.0150	--	0.0194

Appendix 19

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	1511	1.089	1.648	7.766	1.207	0.081	0.472	--
	1612	1.271	1.995	9.479	1.445	0.118	0.536	--
	1513	1.148	2.072	9.112	1.260	0.075	0.499	--
	1514	1.390	2.090	10.084	1.505	0.097	0.818	--
	1515	1.197	1.992	9.526	1.407	0.249MPI	0.649	--
4F	4511	1.159	2.036	8.855	1.295	0.095	0.735	--
	4512	1.213	2.276	9.163	1.348	0.092	0.586	--
	4513	1.280	1.964	9.119	1.468	0.090	0.734	--
	4514	1.182	1.662	8.214	1.409	0.087	0.536	--
	4515	1.073	1.868	7.300	1.158	0.073	0.670	--

Appendix 19

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1F	1511	0.240	0.993
	1612	0.336	0.611
	1513	0.373	0.858
	1514	0.512	0.415
	1515	0.326	0.465
4F	4511	0.382	0.571
	4512	0.285	0.982
	4513	0.615	0.452
	4514	0.394	0.501
	4515	0.339	0.596

Appendix 19

Appendix 6
Individual Organ Weight Values - Relative to Body Weight (Day 57)

Appendix 19

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1011	0.3982	0.2536	0.01263	0.00295	0.1599	0.00502	0.3218
	1012	0.3606	0.2040	0.01133	0.00317	0.1558	0.00393	0.3408
	1013	0.3867	0.2306	0.01042	0.00249	0.2946	0.00635	0.3153
	1015	0.3931	0.2557	0.01024	0.00264	0.1981	0.00449	0.3443
4M	4011	0.3738	0.2189	0.01219	0.00265	0.2247	0.00539	0.2995
	4012	0.3913	0.2317	0.00964	0.00262	0.2215	0.00468	0.3407
	4013	0.3564	0.2159	0.01163	0.00223	0.1780	0.00450	0.3111
	4014	0.4342	0.2445	0.01509	0.00293	0.2318	0.00460	0.3515
	4015	0.4056	0.2539	0.01244	0.00260	0.2134	0.00429	0.3366

Appendix 19

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	1011	0.5031	3.0016	0.3031	--	0.1500	0.6322	0.0766
	1012	0.5151MPI	2.8609	0.2787	--	0.1433	0.6196	0.0889
	1013	0.5202	2.7834	0.3057	--	0.1568	0.6333	0.0503
	1015	0.6162	2.6455	0.3131	--	0.1707	0.7879	0.0887MPI
4M	4011	0.5442	3.1313	0.3334	--	0.1789	0.6259	0.0835
	4012	0.6163	2.7510	0.3490	--	0.2156	0.7250	0.0778
	4013	0.5613	2.8525	0.2920	--	0.1985	0.5956	0.0600
	4014	0.5582	2.6231	0.3669	--	0.1920	0.7844	0.0658
	4015	0.6745	2.6007	0.3237	--	0.1578	0.6951	0.0665

Appendix 19

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	UTERUS %
1M	1011	--
	1012	--
	1013	--
	1015	--
4M	4011	--
	4012	--
	4013	--
	4014	--
	4015	--

Appendix 19

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	1511	0.7018	--	0.01932	0.00536	--	0.00407	0.3889
	1612	0.6122	--	0.02253	0.00554	--	0.00354MPI	0.3783
	1513	0.5957	--	0.01977	0.00481	--	0.00490	0.3289
	1514	0.6337	--	0.01930	0.00522	--	0.00689	0.4076
	1515	0.6011	--	0.01647	0.00486	--	0.00480	0.3440
4F	4511	0.6512	--	0.02540	0.00525	--	0.00599	0.3577
	4512	0.5726	--	0.02003	0.00548	--	0.00488	0.3610
	4513	0.6077	--	0.01771	0.00351	--	0.00646	0.3536
	4514	0.6295	--	0.02049	0.00359	--	0.00617	0.3593
	4515	0.6746	--	0.02099	0.00528	--	0.00683	0.3778

Appendix 19

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	1511	0.5886	2.7736	0.4311	0.0289	0.1686	--	0.0857
	1612	0.5938	2.8211	0.4301	0.0351	0.1595	--	0.1000
	1513	0.5937	2.6109	0.3610	0.0215	0.1430	--	0.1069
	1514	0.6129	2.9572	0.4413	0.0284	0.2399	--	0.1501
	1515	0.5724	2.7374	0.4043	0.0716MPI	0.1865	--	0.0937
4F	4511	0.6284	2.7330	0.3997	0.0293	0.2269	--	0.1179
	4512	0.6774	2.7271	0.4012	0.0274	0.1744	--	0.0848
	4513	0.5425	2.5191	0.4055	0.0249	0.2028	--	0.1699
	4514	0.5052	2.4967	0.4283	0.0264	0.1629	--	0.1198
	4515	0.6577	2.5704	0.4077	0.0257	0.2359	--	0.1194

Appendix 19

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	UTERUS %
1F	1511	0.3546
	1612	0.1818
	1513	0.2458
	1514	0.1217
	1515	0.1336
4F	4511	0.1762
	4512	0.2923
	4513	0.1249
	4514	0.1523
	4515	0.2099

Appendix 19

Appendix 7
Individual Organ Weight Values - Relative to Brain Weight (Day 57)

Appendix 19

Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1011	63.6856	3.17073	0.74074	40.1536	1.26016	80.8040	126.3324
	1012	56.5795	3.14188	0.87870	43.2062	1.08873	94.5135	142.8633MPI
	1013	59.6262	2.69448	0.64320	76.1843	1.64276	81.5298	134.5067
	1015	65.0535	2.60385	0.67238	50.4069	1.14347	87.5803	156.7452
4M	4011	58.5721	3.26135	0.70956	60.1146	1.44116	80.1234	145.5707
	4012	59.2117	2.46236	0.66873	56.5988	1.19575	87.0682	157.4845
	4013	60.5839	3.26186	0.62500	49.9544	1.26369	87.2719	157.4818
	4014	56.3233	3.47571	0.67420	53.3920	1.05946	80.9464	128.5595
	4015	62.6076	3.06799	0.64114	52.6248	1.05852	83.0034	166.3081

Appendix 19

Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	1011	753.7940	76.1066	--	37.6694	158.7624	19.2412	--
	1012	793.3991	77.2825	--	39.7342	171.8388	24.6464	--
	1013	719.7306	79.0526	--	40.5476	163.7549	12.9944	--
	1015	672.9764	79.6574	--	43.4261	200.4283	22.5696MPI	--
4M	4011	837.6818	89.2023	--	47.8625	167.4306	22.3446	--
	4012	702.9672	89.1940	--	55.0930	185.2524	19.8849	--
	4013	800.3193	81.9343	--	55.7026	167.1077	16.8339	--
	4014	604.1457	84.5059	--	44.2211	180.6533	15.1591	--
	4015	641.2220	79.8193	--	38.8985	171.3855	16.3941	--

Appendix 19

Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	1511	--	2.75318	0.76336	--	0.58015	55.4198	83.8677
	1612	--	3.68012	0.90423	--	0.57851MPI	61.7890	96.9859
	1513	--	3.31890	0.80808	--	0.82251	55.2189	99.6633
	1514	--	3.04489	0.82369	--	1.08746	64.3221	96.7145
	1515	--	2.73901	0.80784	--	0.79828	57.2180	95.2199
4F	4511	--	3.90047	0.80569	--	0.91943	54.9289	96.4929
	4512	--	3.49792	0.95634	--	0.85239	63.0457	118.2952
	4513	--	2.91364	0.57727	--	1.06364	58.1818	89.2727
	4514	--	3.25447	0.56977	--	0.98020	57.0739	80.2511
	4515	--	3.11065	0.78288	--	1.01253	56.0021	97.4948

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Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1647 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	1511	395.2163	61.4249	4.1221	24.0204	--	12.2137	50.5344
	1612	460.8167	70.2479	5.7365	26.0574	--	16.3345	29.7035
	1513	438.2876	60.6061	3.6075	24.0019	--	17.9413	41.2698
	1514	466.6358	69.6437	4.4887	37.8528	--	23.6927	19.2041
	1515	455.3537	67.2562	11.9025MPI	31.0229	--	15.5832	22.2275
4F	4511	419.6682	61.3744	4.5024	34.8341	--	18.1043	27.0616
	4512	476.2474	70.0624	4.7817	30.4574	--	14.8129	51.0395
	4513	414.5000	66.7273	4.0909	33.3636	--	27.9545	20.5455
	4514	396.6200	68.0348	4.2009	25.8812	--	19.0246	24.1912
	4515	381.0021	60.4384	3.8100	34.9687	--	17.6931	31.1065

Appendix 19

Appendix 8
Individual Animal Data Gross and Histopathology Findings

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1001	Group:	1	Sex:	Male
Species:	Rat	Strain:	Sprague-Dawley		
		Dose:	0ug/dose		
		Removal Reason:	Terminal Euthanasia		
		Day (Week) of Death:	44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1002	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LUNG : Focus; dark : 1 to 2, right middle, right caudal, right accessory. (TGL)
THYMUS : Discoloration; dark : Caudal half. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.
GLAND, ADRENAL : Examined
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Renal Pelvis
KIDNEY : Chronic progressive nephropathy; minimal
KIDNEY : Dilatation; unilateral, mild
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; mild [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LUNG : Congestion; mild [LUNG : Focus; dark : 1 to 2, right middle, right caudal, right accessory. (G)]
MUSCLE, SKELETAL : Infiltration, mononuclear cell; minimal
SITE, INJECTION : muscle
SITE, INJECTION : Degeneration; minimal, myofiber
TESTIS : Degeneration; minimal
THYMUS : Hemorrhage; moderate [THYMUS : Discoloration; dark : Caudal half. (G) | THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1003	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
KIDNEY : Dilatation; tubular, multifocal, mild
KIDNEY : Inflammation, mononuclear cell; minimal
LIVER : Infiltration, mononuclear cell; minimal
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1004	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, THYROID : Cyst
KIDNEY : Inflammation, mononuclear cell; minimal
LIVER : Vacuolation; centrilobular, microvesicular, mild
LIVER : Infiltration, mononuclear cell; minimal
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Erythrocytosis; mild, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1005	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LUNG : Focus; dark : 1, left lobe (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 2, bilateral (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PROSTATE : Infiltration, mononuclear cell; mild
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
KIDNEY : Dilatation; unilateral, minimal, pelvis
LIVER : Infiltration, mononuclear cell; minimal
LUNG : Congestion; minimal [LUNG : Focus; dark : 1, left lobe (G)]
LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : 2, bilateral (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1006	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 2, fissure, right medial. (TGL)
LUNG : Focus; dark : 1 to 6. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 2, fissure, right medial. (G)]
LUNG : Hemorrhage; focal, minimal [LUNG : Focus; dark : 1 to 6. (G)]
LYMPH NODE, MANDIBULAR : Erythrocytosis; mild, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]
NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1007	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LUNG : Focus; dark : 1 to 2, right caudal, right accessory lobes (TGL)
LYMPH NODE, INGUINAL : Enlargement : Right (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 4, right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, THYROID : Cyst
HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; multifocal, minimal [LUNG : Focus; dark : 1 to 2, right caudal, right accessory lobes (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Right (G) | LYMPH NODE, MANDIBULAR : Focus; dark : 4, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1008	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, THYROID : Small : Left. (TGL)
LIVER : Focus; pale : >10. (TGL)
LUNG : Focus; dark : 4, left lobe. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PITUITARY : Pars Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : >10. (G)]
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; minimal [LUNG : Focus; dark : 4, left lobe. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal, myofiber
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G) | GLAND, THYROID : Small : Left. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1009	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
THYMUS : Focus; dark : >10 (TGL)
THYMUS : Abnormal consistency; firm : Right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; mild
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; minimal
PANCREAS : Atrophy; acinar, focal, minimal
PANCREAS : Fibrosis; mild, islet of langerhans
PANCREAS : Hemorrhage; minimal, islet of langerhans
PANCREAS : Inflammation, mixed cell; minimal
SITE, INJECTION : Hemorrhage; mild, myofiber
SITE, INJECTION : Hemorrhage; mild, subcutaneous tissue
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10 (G) | THYMUS : Abnormal consistency; firm : Right (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1010	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 2, fissure, right medial. (TGL)
LUNG : Focus; dark : 1, edge, right caudal. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 2, fissure, right medial. (G)]
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; minimal [LUNG : Focus; dark : 1, edge, right caudal. (G)]
LYMPH NODE, INGUINAL : Erythrocytosis; minimal, sinus
SITE, INJECTION : Degeneration; minimal, myofiber
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1011	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Recovery Euthanasia	
		Day (Week) of Death:	57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PROSTATE : Infiltration, mononuclear cell; mild
GLAND, THYROID : Cyst
HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Cyst
LIVER : Infiltration, mononuclear cell; minimal
LUNG : Metaplasia; osseous, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1012	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Recovery Euthanasia	
		Day (Week) of Death:	57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Focus; raised : 1, pale, firm, cortex, medulla, right. (TGL)
LUNG : Focus; dark : 3 to 5, right cranial, right middle, right accessory, left lobe. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EPIDIDYMIS : Sperm granuloma; focal, mild
EYE : Dysplasia; unilateral, minimal, retina
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Cyst
HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Nephroblastoma, malignant; incidental [KIDNEY : Focus; raised : 1, pale, firm, cortex, medulla, right. (G)]

KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LUNG : Hemorrhage; minimal [LUNG : Focus; dark : 3 to 5, right cranial, right middle, right accessory, left lobe. (G)]

LYMPH NODE, MESENTERIC : Erythrocytosis; minimal, sinus
NERVE, OPTIC : One Of A Pair Available For Evaluation.
NERVE, OPTIC : Examined
PANCREAS : Fibrosis; focal, minimal, islet of langerhans
SITE, INJECTION : Degeneration; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; ESOPHAGUS; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1013	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Recovery Euthanasia	
		Day (Week) of Death:	57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, THYROID : Cyst
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LUNG : Hemorrhage; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1014	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Found Dead	
		Day (Week) of Death:	43 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: ANIMAL DELIVERED DEAD

Gross Pathology Observations:

GLAND, ADRENAL : Small : right. (TGL)
GLAND, ADRENAL : Abnormal consistency; soft : right. (TGL)
GLAND, ADRENAL : Discoloration; dark : right. (TGL)
KIDNEY : Discoloration; dark : corticomedullary junction, bilateral. (TGL)
LUNG : Failure to collapse (TGL)
THYMUS : Discoloration; dark (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

BONE MARROW SMEAR - Not Required By Protocol/Study Plan

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.
GLAND, ADRENAL : Examined
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
GLAND, THYROID : Cyst
LIVER : Congestion; moderate
LIVER : Infiltration, mononuclear cell; minimal
LUNG : Congestion; moderate [LUNG : Failure to collapse (G)]
THYMUS : Hemorrhage; mild [THYMUS : Discoloration; dark (G) | THYMUS : Focus; dark : >10. (G)]
NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Small : right. (G) | GLAND, ADRENAL : Abnormal consistency; soft : right. (G) | GLAND, ADRENAL : Discoloration; dark : right. (G) | KIDNEY : Discoloration; dark : corticomedullary junction, bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1015	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Recovery Euthanasia	
		Day (Week) of Death:	57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
MUSCLE, SKELETAL : Material accumulation; clot : ventral cervical extending into thymus. (TGL)
THYMUS : Focus; dark : 3. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Vacuolation; centrilobular, microvesicular, minimal
LIVER : Infiltration, mononuclear cell; minimal
MUSCLE, SKELETAL : Hemorrhage; moderate [MUSCLE, SKELETAL : Material accumulation; clot : ventral cervical extending into thymus. (G)]
MUSCLE, SKELETAL : Inflammation, neutrophilic; mild
SITE, INJECTION : Degeneration; minimal, myofiber
TRACHEA : adventitial
TRACHEA : Inflammation, mixed cell; mild
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial. (G) | THYMUS : Focus; dark : 3. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1501	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
THYMUS : Focus; dark : >10, right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
KIDNEY : Inflammation, mononuclear cell; minimal
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LUNG : Inflammation, mixed cell; minimal
VAGINA : Diestrus
NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : >10, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1502	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, INGUINAL : Focus; dark : 1, right. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.
GLAND, ADRENAL : Examined
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, INGUINAL : Erythrocytosis; minimal, sinus [LYMPH NODE, INGUINAL : Focus; dark : 1, right. (G)]

SITE, INJECTION : Degeneration; minimal, myofiber
VAGINA : Diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1503	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Cyst
HEART : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, mononuclear cell; minimal
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]
VAGINA : Diestrus
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1504	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, THYROID : thymus
GLAND, THYROID : Cyst
GLAND, THYROID : Ectopia
LIVER : Infiltration, mononuclear cell; minimal
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]
VAGINA : Estrus
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1505	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EYE : Dysplasia; unilateral, minimal, retina
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
LIVER : Infiltration, mononuclear cell; minimal
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]
VAGINA : Estrus

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1506	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial, papillary process of caudate. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 3 to 5, bilateral. (TGL)
SKIN : Scab; dark : 2 to 3, pinna, bilateral. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, THYROID : Cyst
LIVER : Necrosis; focal, minimal
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial, papillary process of caudate. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SKIN : Hyperkeratosis; mild [SKIN : Scab; dark : 2 to 3, pinna, bilateral. (G)]
SKIN : Exudate; epidermal, mild [SKIN : Scab; dark : 2 to 3, pinna, bilateral. (G)]
SKIN : Inflammation, mixed cell; mild
VAGINA : Proestrus
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : 3 to 5, bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

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5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1507	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 1 to >10, bilateral (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, THYROID : thymus
GLAND, THYROID : Ectopia
LIVER : Infiltration, mononuclear cell; minimal
THYMUS : Hemorrhage; minimal
VAGINA : Diestrus
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G) | LYMPH NODE, MANDIBULAR : Focus; dark : 1 to >10, bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1508	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, medial lobe. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PITUITARY : Pars Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, mild [LIVER : Focus; pale : 1, fissure, medial lobe. (G)]
LUNG : Macrophage aggregation; alveolar, focal, minimal
MUSCLE, SKELETAL : Degeneration; minimal, myofiber
SITE, INJECTION : Degeneration; minimal, myofiber
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10. (G)]
VAGINA : Estrus

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

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5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1509	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Discoloration; dark : Bilateral (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EYE : one lens available for evaluation
GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.
GLAND, ADRENAL : Examined
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal, sinus [LYMPH NODE, MANDIBULAR : Discoloration; dark : Bilateral (G)]
MUSCLE, SKELETAL : Degeneration; minimal, myofiber
SITE, INJECTION : Degeneration; mild, myofiber
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10 (G)]
VAGINA : Proestrus

Histo Pathology - The following Tissues were Within Normal Limits:

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5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1510	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.
GLAND, ADRENAL : Examined
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
SITE, INJECTION : Degeneration; minimal, myofiber
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]
VAGINA : Estrus
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

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5002034 - Individual Animal Data Gross and Histopathology Findings

None

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5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1511	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Recovery Euthanasia	
		Day (Week) of Death:	57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, SALIVARY, MANDIBULAR : Hemorrhage; moderate
GLAND, THYROID : Cyst
LIVER : Infiltration, mononuclear cell; minimal
VAGINA : Proestrus

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

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5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1612	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Recovery Euthanasia	
		Day (Week) of Death:	57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, THYROID : Small : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
KIDNEY : Inflammation, mononuclear cell; minimal
LIVER : Infiltration, mononuclear cell; minimal
LUNG : Macrophage aggregation; alveolar, focal, minimal
SKIN : Degeneration; minimal, muscularis carnosus
VAGINA : Proestrus
NO CORRELATE : No correlating lesion [GLAND, THYROID : Small : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1513	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Recovery Euthanasia	
		Day (Week) of Death:	57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Degeneration; minimal, myofiber
VAGINA : Proestrus

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1514	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Recovery Euthanasia	
		Day (Week) of Death:	57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
KIDNEY : Chronic progressive nephropathy; minimal
KIDNEY : Dilatation; tubular, focal, minimal
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, mild [LIVER : Focus; pale : 1, fissure, right medial (G)]
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10 (G)]
VAGINA : Diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	1515	Group:	1	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0ug/dose	
		Removal Reason:	Recovery Euthanasia	
		Day (Week) of Death:	57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 2, fissure, right medial (TGL)
OVARY : Cyst; pale : 1, right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.
GLAND, ADRENAL : Examined
GLAND, THYROID : Cyst
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, mild [LIVER : Focus; pale : 2, fissure, right medial (G)]
VAGINA : Diestrus
NO CORRELATE : No correlating lesion [OVARY : Cyst; pale : 1, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2001	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : 2, right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, marked
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; minimal, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : 2, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; BONE, FEMUR; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 2102	Group: 2		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 10ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

EYE : Focus; dark : 1, cornea, left, adjacent to sclera. (TGL)
LARGE INTESTINE, RECTUM : Parasite : >10.
LIVER : Focus; pale : 1, fissure, left medial. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : 1, right lobe. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 1, right lobe. (G)]
NO CORRELATE : No correlating lesion [EYE : Focus; dark : 1, cornea, left, adjacent to sclera. (G) | LIVER : Focus; pale : 1, fissure, left medial. (G) | LYMPH NODE, MANDIBULAR : Focus; dark : >10, right. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; EYE; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2003	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LUNG : Focus; dark : 2, right cranial, right accessory, right middle (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
THYMUS : Focus; dark : 1, left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LUNG : Inflammation, mixed cell; multifocal, minimal [LUNG : Focus; dark : 2, right cranial, right accessory, right middle (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, marked
SITE, INJECTION : Edema; minimal, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : 1, left (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : Right (G) | LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2004	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Focus; pale : >10, bilateral. (TGL)
LARGE INTESTINE, RECTUM : Parasite : 5.
SITE, INJECTION : Swelling : Right. (TGL)
SPLEEN : Focus; pale : >10, linear. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]

SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]
NO CORRELATE : No correlating lesion [SPLEEN : Focus; pale : >10, linear. (G) | KIDNEY : Focus; pale : >10, bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2005	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, INGUINAL : Enlargement : Right (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 1, right (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : 2, right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, marked
SITE, INJECTION : Edema; mild, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : Right (G) | LYMPH NODE, INGUINAL : Enlargement : Right (G) | LYMPH NODE, MANDIBULAR : Focus; dark : 1, right (G) | LIVER : Focus; pale : 1, fissure, right medial (G) | THYMUS : Focus; dark : 2, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2006	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, papillary process of caudate. (TGL)
LUNG : Focus; dark : 1, edge, right caudal. (TGL)
LYMPH NODE, INGUINAL : Focus; dark : 2, right. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : 6, left lobe. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, marked
SITE, INJECTION : Edema; minimal, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 6, left lobe. (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Focus; dark : 2, right. (G) | LIVER : Focus; pale : 1, papillary process of caudate. (G) | LUNG : Focus; dark : 1, edge, right caudal. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LUNG; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2007	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

EPIDIDYMIS : Focus; pale : 4, right (TGL)
TESTIS : Small : Right (TGL)
TESTIS : Abnormal consistency; soft : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EPIDIDYMIS : Cellular debris; mild
EPIDIDYMIS : Sperm granuloma; multifocal, moderate [EPIDIDYMIS : Focus; pale : 4, right (G)]
LIVER : Necrosis; focal, minimal
LIVER : Infiltration, mononuclear cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, marked
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
TESTIS : Degeneration; diffuse, severe [TESTIS : Small : Right (G) | TESTIS : Abnormal consistency; soft : Right (G)]
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2008	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Focus; pale : >10, bilateral. (TGL)
LARGE INTESTINE, RECTUM : Parasite : 6.
LIVER : Focus; pale : 1, near hilus, right medial (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]

THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10. (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right medial (G) | KIDNEY : Focus; pale : >10, bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2009	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SKIN : Scab; dark : 2 to 3, pinna, bilateral (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, INGUINAL : Erythrocytosis; mild, sinus
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Edema; mild, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue
SKIN : Hyperkeratosis; mild [SKIN : Scab; dark : 2 to 3, pinna, bilateral (G)]
SKIN : Exudate; epidermal, mild [SKIN : Scab; dark : 2 to 3, pinna, bilateral (G)]
SKIN : Inflammation, mixed cell; dermal, mild
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2010	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LUNG : Focus; dark : 1, right caudal. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LUNG : Hemorrhage; focal, mild [LUNG : Focus; dark : 1, right caudal. (G)]
LYMPH NODE, MANDIBULAR : Erythrocytosis; mild, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]

THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 2501	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 10ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Edema; mild, subcutaneous tissue
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2502	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : Focus; dark : 2, right. (TGL)
THYMUS : Discoloration; dark : Caudal half. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Focus; dark : 2, right. (G)]
THYMUS : Hemorrhage; moderate [THYMUS : Discoloration; dark : Caudal half. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2503	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Focus; dark : 1, right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Focus; dark : 1, right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2504	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]

SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 2505	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 10ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LUNG : Focus; dark : 1, left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : 3, left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Infiltration, mononuclear cell; minimal
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; multifocal, mild [LUNG : Focus; dark : 1, left (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Edema; moderate, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 3, left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2506	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1, edge, left lobe. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Degeneration; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; minimal, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1, edge, left lobe. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LUNG; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 2507	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 10ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
LYMPH NODE, POPLITEAL : Focus; dark : 3, right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LIVER : Fibrosis; capsular, focal, minimal [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (G)]

LYMPH NODE, MANDIBULAR : Erythrocytosis; mild, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G) | LYMPH NODE, POPLITEAL : Focus; dark : 3, right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2508	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, ADRENAL : Focus; dark : >10, left. (TGL)
KIDNEY : Adhesion : Right to capsule. (TGL)
LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Discoloration; dark : Caudal half, right lobe. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, ADRENAL : Hemorrhage; capsular, focal, mild [GLAND, ADRENAL : Focus; dark : >10, left. (G)]
KIDNEY : Inflammation, mononuclear cell; minimal
LIVER : Vacuolation; centrilobular, moderate [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, MANDIBULAR : Erythrocytosis; mild, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
THYMUS : Hemorrhage; moderate [THYMUS : Discoloration; dark : Caudal half, right lobe. (G) | THYMUS : Focus; dark : >10. (G)]
NO CORRELATE : No correlating lesion [KIDNEY : Adhesion : Right to capsule. (G)]

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	2509	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : 5 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; minimal, subcutaneous tissue
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : 5 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 2510	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 10ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 2, fissure, left medial. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; focal, minimal
LIVER : Necrosis; focal, minimal [LIVER : Focus; pale : 2, fissure, left medial. (G)]
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Edema; minimal, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3001	Group:	3	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)
THYMUS : Focus; raised : 2, dark, firm, left, surrounded by a pale rim (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; mild, subcutaneous tissue
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [THYMUS : Focus; raised : 2, dark, firm, left, surrounded by a pale rim (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3002	Group:	3	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LARGE INTESTINE, RECTUM : Parasite : 4.
LUNG : Focus; dark : 4, right accessory. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SPLEEN : Focus; pale : 6. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Infiltration, mononuclear cell; minimal
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; focal, minimal [LUNG : Focus; dark : 4, right accessory. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10. (G)]
NO CORRELATE : No correlating lesion [SPLEEN : Focus; pale : 6. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3103	Group:	3	Sex:	Male
Species:	Rat	Strain:	Sprague-Dawley		
		Dose:	30ug/dose		
		Removal Reason:	Terminal Euthanasia		
		Day (Week) of Death:	44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1, left lobe (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; multifocal, minimal [LUNG : Focus; dark : 1, left lobe (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Edema; moderate, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3004	Group:	3	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LARGE INTESTINE, RECTUM : Parasite : 4.
LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LUNG : Focus; dark : 1 to 3, left lobe, right middle, right accessory. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, left. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SPLEEN : Focus; pale : >10, linear. (TGL)
THYMUS : Focus; dark : 6. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Infiltration, mononuclear cell; minimal
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; multifocal, minimal [LUNG : Focus; dark : 1 to 3, left lobe, right middle, right accessory. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Swelling : Right. (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial. (G) | SPLEEN : Focus; pale : >10, linear. (G) | LYMPH NODE, MANDIBULAR : Focus; dark : >10, left. (G) | THYMUS : Focus; dark : 6. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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5002034 - Individual Animal Data Gross and Histopathology Findings

LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3005	Group:	3	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; moderate, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3006	Group:	3	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1 to 3, left lobe, right middle, right caudal. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; multifocal, minimal [LUNG : Focus; dark : 1 to 3, left lobe, right middle, right caudal. (G)]
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3007	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 30ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 1, left (TGL)
LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Swelling : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right (G) | SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (G) | LYMPH NODE, MANDIBULAR : Focus; dark : 1, left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3008	Group:	3	Sex:	Male
Species:	Rat	Strain:	Sprague-Dawley		
		Dose:	30ug/dose		
		Removal Reason:	Terminal Euthanasia		
		Day (Week) of Death:	44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LARGE INTESTINE, RECTUM : Parasite : >10.
LUNG : Focus; dark : 1, right middle, right accessory. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, right. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; focal, minimal [LUNG : Focus; dark : 1, right middle, right accessory. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : >10, right. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3009	Group:	3	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

EYE : Focus; dark : 1, sclera, right (TGL)
LUNG : Focus; dark : right cranial, right middle, right caudal (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LUNG : with hemorrhage
LUNG : Inflammation, mixed cell; multifocal, mild [LUNG : Focus; dark : right cranial, right middle, right caudal (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Edema; moderate, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [EYE : Focus; dark : 1, sclera, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; EYE; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3010	Group:	3	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1, dorsal, left lobe. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Discoloration; dark : Caudal half, right lobe. (TGL)
THYMUS : Focus; dark : 3, left lobe. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : 3, left lobe. (G) | THYMUS : Discoloration; dark : Caudal half, right lobe. (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G) | LUNG : Focus; dark : 1, dorsal, left lobe. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3501	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10, right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, MANDIBULAR : Erythrocytosis; mild, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : >10, right (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Edema; minimal, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10, right (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3502	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3503	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; moderate, subcutaneous tissue
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3604	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3505	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT; LYMPH NODE, MANDIBULAR

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3506	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, ADRENAL : Focus; dark : 4, left. (TGL)
LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; minimal, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]
NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Focus; dark : 4, left. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3507	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

MUSCLE, SKELETAL : Material accumulation; clot : Ventral cervical, extending into axillary left, adhesion to esophagus, cranial part of trachea (TGL)

SITE, INJECTION : Abnormal consistency; firm : Right (TGL)

THYMUS : Focus; dark : >10 (TGL)

THYMUS : Material accumulation; clot (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal

LIVER : Infiltration, mononuclear cell; minimal

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild

MUSCLE, SKELETAL : adventitial, adjacent to trachea and esophagus

MUSCLE, SKELETAL : Hemorrhage; moderate [MUSCLE, SKELETAL : Material accumulation; clot : Ventral cervical, extending into axillary left, adhesion to esophagus, cranial part of trachea (G)]

NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal

SITE, INJECTION : Edema; mild, subcutaneous tissue

SITE, INJECTION : Degeneration; mild, myofiber

SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

THYMUS : Hemorrhage; moderate [THYMUS : Material accumulation; clot (G) | THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3508	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, right lateral, hilus, adjacent to right lateral. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : Focus; dark : 4, right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Degeneration; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; minimal, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G) | SITE, INJECTION : Focus; dark : 4, right. (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10. (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, right lateral, hilus, adjacent to right lateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3509	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Discoloration; dark : Caudal part (TGL)
THYMUS : Abnormal consistency; firm : Caudal part (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; mild, subcutaneous tissue
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; moderate [THYMUS : Abnormal consistency; firm : Caudal part (G) | THYMUS : Discoloration; dark : Caudal part (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	3510	Group:	3	Sex: Female
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	30ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death:	44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, ADRENAL : Focus; dark : 3 to 5, bilateral. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Focus; dark : 3 to 5, bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, INGUINAL, RIGHT

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4001	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
LYMPH NODE, INGUINAL : Enlargement : Right (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Swelling : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PITUITARY : Pars Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; mild
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal [LYMPH NODE, INGUINAL : Enlargement : Right (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Degeneration; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; dermal, mild
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 4002	Group: 4		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 100ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, linear, right lateral, fissure, left medial. (TGL)
LYMPH NODE : Focus; dark : >10, mediastinal. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
THYMUS : Focus; dark : 2. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LARGE INTESTINE, CECUM : Parasitism; nematode
LIVER : Congestion; minimal
LIVER : Infiltration, mononuclear cell; minimal
LUNG : Inflammation, mixed cell; minimal
LYMPH NODE, INGUINAL : Inflammation, mixed cell; mild
LYMPH NODE, MANDIBULAR : Erythrocytosis; mild, sinus [LYMPH NODE : Focus; dark : >10, mediastinal. (G)]

NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; minimal, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath

THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 2. (G)]

NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : Right. (G) | LIVER : Focus; pale : 1, linear, right lateral, fissure, left medial. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 4003	Group: 4		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 100ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LUNG : Focus; dark : 1 to 3, right cranial, right caudal, left lobe (TGL)
LYMPH NODE, INGUINAL : Enlargement : Right (TGL)
SITE, INJECTION : Swelling : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LUNG : Hemorrhage; minimal [LUNG : Focus; dark : 1 to 3, right cranial, right caudal, left lobe (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Exudate; epidermal, minimal
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Right (G)]

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4004	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Swelling : right (TGL)
SITE, INJECTION : Abnormal consistency; firm : right (TGL)
THYMUS : Focus; dark : >10, left lobe. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; marked
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : right (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : >10, left lobe. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 4005	Group: 4		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 100ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
LYMPH NODE, POPLITEAL : Focus; dark : 1, right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
GLAND, THYROID : Cyst
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right (G) | LYMPH NODE, POPLITEAL : Focus; dark : 1, right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; mild, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4006	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, papillary process of caudate (TGL)
LUNG : Focus; dark : 1, edge, right caudal. (TGL)
LYMPH NODE, INGUINAL : Enlargement : Right. (TGL)
LYMPH NODE, INGUINAL : Focus; dark : 1, right. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
THYMUS : Focus; dark : 1, right lobe. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LARGE INTESTINE, COLON : Parasitism; nematode
LUNG : Hemorrhage; minimal [LUNG : Focus; dark : 1, edge, right caudal. (G)]
LYMPH NODE, INGUINAL : Erythrocytosis; mild, sinus [LYMPH NODE, INGUINAL : Focus; dark : 1, right. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Degeneration; neuroaxonal, mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G) | SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath

NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Right. (G) | LIVER : Focus; pale : 1, near hilus, papillary process of caudate (G) | THYMUS : Focus; dark : 1, right lobe. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4007	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, INGUINAL : Enlargement : Right (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Swelling : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)
THYMUS : Abnormal consistency; firm (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Cyst
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, INGUINAL : Inflammation, mixed cell; mild [LYMPH NODE, INGUINAL : Enlargement : Right (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10 (G) | THYMUS : Abnormal consistency; firm (G)]

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4008	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LARGE INTESTINE, RECTUM : Parasite : >10.
LUNG : Focus; dark : 1, left lobe, right accessory. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
KIDNEY : Inflammation, mononuclear cell; minimal
LARGE INTESTINE, CECUM : Parasitism; nematode
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; minimal, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1, left lobe, right accessory. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 4009	Group: 4		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 100ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, PROSTATE : Small : Ventral (TGL)
GLAND, PROSTATE : Mass; [a] : 8x5x3 mm, pale, firm, ventral (TGL)
LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (TGL)
LYMPH NODE, INGUINAL : Enlargement : Right (TGL)
SITE, INJECTION : Swelling : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PITUITARY : Pars Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; moderate [GLAND, PROSTATE : Mass; [a] : 8x5x3 mm, pale, firm, ventral (G)]
GLAND, THYROID : Cyst
LARGE INTESTINE, CECUM : Parasitism; nematode
LIVER : Vacuolation; centrilobular, microvesicular, mild
LIVER : Necrosis; focal, minimal
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
MUSCLE, SKELETAL : Degeneration; minimal, myofiber
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; dermal, mild
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Right (G) | GLAND, PROSTATE : Small : Ventral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; KIDNEY; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4010	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
LIVER : Vacuolation; microvesicular, focal, minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
MUSCLE, SKELETAL : Degeneration; minimal, myofiber
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; dermal, mild
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4011	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.
GLAND, ADRENAL : Examined
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; mild
KIDNEY : Chronic progressive nephropathy; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4012	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, INGUINAL : Enlargement : Right. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; mild, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; mild, subcutaneous tissue
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Right. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4013	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

THYMUS : Focus; dark : 4. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; moderate
HEART : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, mononuclear cell; minimal
SITE, INJECTION : Infiltration, mononuclear cell; minimal, subcutaneous tissue
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 4. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 4014	Group: 4		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 100ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death: 57 (9)		

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.
GLAND, ADRENAL : Examined
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, PROSTATE : Infiltration, mononuclear cell; mild
GLAND, THYROID : thymus
GLAND, THYROID : Ectopia
HEART : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LUNG : Inflammation, mixed cell; focal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal, subcutaneous tissue
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4015	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PROSTATE : Infiltration, mononuclear cell; mild
LIVER : Infiltration, mononuclear cell; minimal
LUNG : Metaplasia; osseous, focal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4501	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10, left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Edema; mild, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; minimal, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10, left (G)]
VAGINA : Diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4502	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : right (TGL)
SITE, INJECTION : Swelling : right (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.
GLAND, ADRENAL : Examined
GLAND, THYROID : thymus
GLAND, THYROID : Ectopia
LIVER : Necrosis; focal, minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : right (G)]
MUSCLE, SKELETAL : Degeneration; minimal, myofiber
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : right (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10. (G)]
VAGINA : Estrus

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4503	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, ADRENAL : Small : Right (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, left (TGL)
LYMPH NODE, MANDIBULAR : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, marked
SITE, INJECTION : Edema; moderate, subcutaneous tissue
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10 (G)]
VAGINA : Proestrus
NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Small : Right (G) | LYMPH NODE, MANDIBULAR : Enlargement : Left (G) | LYMPH NODE, MANDIBULAR : Focus; dark : >10, left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4504	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
SITE, INJECTION : Focus; dark : >10, right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, THYROID : Cyst
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right. (G) | SITE, INJECTION : Focus; dark : >10, right. (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G)]
VAGINA : Estrus

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4505	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Swelling : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
KIDNEY : Inflammation, mononuclear cell; minimal
KIDNEY : Cyst
LIVER : Infiltration, mononuclear cell; minimal
LUNG : Inflammation, mixed cell; focal, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10 (G)]

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

VAGINA : Proestrus
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (G) | LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4506	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, ADRENAL : Focus; dark : 2, right. (TGL)
KIDNEY : Adhesion : left to capsule (TGL)
LIVER : Focus; pale : 1, linear, left lateral. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : Focus; dark : >10, right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, THYROID : Cyst
LIVER : Necrosis; focal, mild
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
MUSCLE, SKELETAL : Degeneration; minimal, myofiber
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; mild, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Hemorrhage; mild, subcutaneous tissue [SITE, INJECTION : Focus; dark : >10, right. (G)]
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10. (G)]
VAGINA : Proestrus

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, linear, left lateral. (G) | GLAND, ADRENAL : Focus; dark : 2, right. (G) | KIDNEY : Adhesion : left to capsule (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4507	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, INGUINAL : Enlargement : Right (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, THYROID : Cyst
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; moderate, subcutaneous tissue
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; moderate [THYMUS : Focus; dark : >10 (G)]
VAGINA : Proestrus
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Right (G) | LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4508	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, medial lobe. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
THYMUS : Focus; dark : >10, left lobe. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Cyst
LARGE INTESTINE, COLON : Parasitism; nematode
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; mild, myofiber
SITE, INJECTION : Inflammation, mixed cell; mild, subcutaneous tissue
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10, left lobe. (G)]
VAGINA : Diestrus
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, medial lobe. (G) | LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4509	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 44 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10 (TGL)
SITE, INJECTION : Swelling : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Dilatation; tubular, focal, mild
LIVER : Necrosis; focal, minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
VAGINA : Diestrus
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal: 4510	Group: 4		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 100ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 44 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
SITE, INJECTION : Focus; dark : >10, right. (TGL)
THYMUS : Discoloration; dark : Caudal half, right lobe. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
KIDNEY : Hyperplasia; atypical, tubular, multifocal, mild
LARGE INTESTINE, CECUM : Parasitism; nematode
LIVER : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Edema; moderate, subcutaneous tissue [SITE, INJECTION : Swelling : Right. (G)]
SITE, INJECTION : Inflammation, mixed cell; dermal, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate, myofiber [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]
SITE, INJECTION : Inflammation, mixed cell; moderate, subcutaneous tissue [SITE, INJECTION : Abnormal consistency; firm : Right. (G) | SITE, INJECTION : Focus; dark : >10, right. (G)]
SPLEEN : Decreased cellularity; mild, periarteriolar lymphoid sheath

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10. (G) | THYMUS : Discoloration; dark : Caudal half, right lobe. (G)]

VAGINA : Proestrus

NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4511	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EYE : Dysplasia; unilateral, mild, retina
GLAND, PITUITARY : Pars Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
KIDNEY : Chronic progressive nephropathy; minimal
KIDNEY : Inflammation, mononuclear cell; minimal
KIDNEY : Cyst
LIVER : Infiltration, mononuclear cell; minimal
SITE, INJECTION : Degeneration; mild, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; mild, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal, subcutaneous tissue
VAGINA : Estrus

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4512	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, HARDERIAN : Infiltration, mononuclear cell; minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
PANCREAS : Inflammation, mononuclear cell; minimal
SITE, INJECTION : Infiltration, mononuclear cell; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal, subcutaneous tissue
VAGINA : Proestrus

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4513	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
LYMPH NODE, MANDIBULAR : Enlargement : bilateral (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, THYROID : Cyst
KIDNEY : Inflammation, mononuclear cell; minimal
KIDNEY : Pyelonephritis; unilateral, mild
LIVER : Infiltration, mononuclear cell; minimal
MUSCLE, SKELETAL : Degeneration; minimal, myofiber
SITE, INJECTION : Degeneration; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal, subcutaneous tissue
VAGINA : Diestrus
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G) | LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G) | LYMPH NODE, MANDIBULAR : Enlargement : bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4514	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, left lateral, near hilus right lateral (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PITUITARY : Pars Intermedia Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, THYROID : Cyst
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal, sinus
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Infiltration, mononuclear cell; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal, subcutaneous tissue
VAGINA : Diestrus
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, left lateral, near hilus right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 19

5002034 - Individual Animal Data Gross and Histopathology Findings

Animal:	4515	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 100ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 57 (9)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : 4 to 6, bilateral (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PITUITARY : Pars Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
LIVER : Infiltration, mononuclear cell; minimal
LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : 4 to 6, bilateral (G)]
SITE, INJECTION : Inflammation, mixed cell; minimal, subcutaneous tissue
SITE, INJECTION : Infiltration, mononuclear cell; minimal, myofiber
VAGINA : Diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 20

EPL® Experimental Pathology Laboratories, Inc.

MODERNA THERAPEUTICS, INC.
STUDY NUMBER 5002034
EPL PROJECT NUMBER A76-005

A 6-WEEK (4 DOSES) INTRAMUSCULAR INJECTION TOXICITY STUDY OF mRNA-1647 IN SPRAGUE-DAWLEY RATS FOLLOWED BY A 2-WEEK RECOVERY PERIOD

PEER REVIEW STATEMENT

A microscopic peer review was performed as follows for this study:

1. Re-examination of all tissues from 20% of the control group (Group 1) and 60% of the high-dose group (Group 4) animals per sex selected randomly from the Main and Recovery Sacrifices:

   Main Sacrifice
   Group 1 males: 1006, 1007
   Group 4 males: 4001, 4002, 4003, 4004, 4008, 4009
   Group 1 females: 1508, 1509
   Group 4 females: 4501, 4504, 4505, 4508, 4509, 4510

   Recovery Sacrifice
   Group 1 male: 1015
   Group 4 males: 4011, 4013, 4014
   Group 1 female: 1513
   Group 4 females: 4512, 4514, 4515

2. Re-examination of selected tissues from all animals that die on study to verify the probable cause of death: Group 1 male 1014.

3. Re-examination of all hyperplasias and neoplasias diagnosed by the study pathologist in all groups in both sexes.

4. Re-examination of the following potential target tissues from all animals in all groups in the Main and Recovery Sacrifices: injection site, spleen, bone marrow (femur and sternum), liver, lymph nodes (inguinal and popliteal), and sciatic nerve.

Following review of the microscopic findings reported by the study pathologist, the results were discussed and appropriate terminology and diagnoses mutually agreed on. Differences of opinion between the study and reviewing pathologists were resolved with agreement on the final diagnoses. The tables contained in the final report for the study reflect the mutually agreed-on diagnoses.

(b) (6)

Experimental Pathology Laboratories, Inc.

September 21, 2017
Date