charles river

FINAL REPORT

Test Facility Study No. 5002158

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 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:
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QUALITY ASSURANCE STATEMENT

Study Number: 5002158

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

		Dates Findings Submitted to:	
Date(s) of Audit	**Phase(s) Audited**	**Study Director**	**Study Director Management**
09-Mar-2017	Final Study Plan	10-Mar-2017	10-Mar-2017
20-Mar-2017	Addition of Study Plan to Provantis	20-Mar-2017	20-Mar-2017
20-Mar-2017	Study Plan Amendment 1	20-Mar-2017	20-Mar-2017
20-Mar-2017	Study Plan Amendment 2	20-Mar-2017	20-Mar-2017
21-Mar-2017	Dose Preparation	21-Mar-2017	21-Mar-2017
04-Apr-2017	Draize Evaluation	04-Apr-2017	04-Apr-2017
13-Apr-2017	Study Plan Amendment 3	13-Apr-2017	13-Apr-2017
28-Apr-2017	Study Plan Amendment 4	28-Apr-2017	28-Apr-2017
02-May-2017	Necropsy	02-May-2017	02-May-2017
04-May-2017	Coagulation Analysis	04-May-2017	04-May-2017
14-Jun-2017	Data Review - Necropsy	14-Jun-2017	14-Jun-2017
14-Jun-2017	Data Review - Histology	14-Jun-2017	14-Jun-2017
14-Jun-2017	Report Preparation	14-Jun-2017	14-Jun-2017
14-Jun-2017	Data Review - Shipping/Receiving	14-Jun-2017	14-Jun-2017
14-Jun-2017	Data Review - Animal Care	15-Jun-2017	15-Jun-2017
14-Jun-2017 - 15-Jun-2017	Data Review - Clinical Pathology	15-Jun-2017	15-Jun-2017
14-Jun-2017 - 15-Jun-2017	Data Review - Formulations	15-Jun-2017	15-Jun-2017
14-Jun-2017 - 15-Jun-2017	Data Review - Shipping/Receiving	15-Jun-2017	15-Jun-2017
14-Jun-2017 - 15-Jun-2017	Data Review - Technical Operations	15-Jun-2017	15-Jun-2017
14-Jun-2017	Data Review - Veterinary Services	15-Jun-2017	15-Jun-2017
14-Jun-2017	Final Phase Report - Ophthalmology	14-Jun-2017	14-Jun-2017
14-Jun-2017 - 15-Jun-2017	Report Preparation	15-Jun-2017	15-Jun-2017
15-Jun-2017	Draft Report - Materials and Methods	15-Jun-2017	15-Jun-2017
23-Jun-2017	Data Review - Bioanalysis & Immunology	27-Jun-2017	27-Jun-2017
23-Jun-2017	Final Phase Report - Immunology	27-Jun-2017	27-Jun-2017
30-Jun-2017	Study Plan Amendment 5	30-Jun-2017	30-Jun-2017
05-Jul-2017 - 07-Jul-2017	Data Review - Analytical Chemistry	07-Jul-2017	07-Jul-2017
05-Jul-2017 - 07-Jul-2017	Draft Phase Report - Dose Formulation Analysis	07-Jul-2017	07-Jul-2017
29-Aug-2017	Draft Report - Results	30-Aug-2017	30-Aug-2017
30-Aug-2017	Draft Phase Report - Deviation Log	30-Aug-2017	30-Aug-2017
30-Aug-2017	Final Report	30-Aug-2017	30-Aug-2017
18-Sep-2017	Study Plan Amendment 6	18-Sep-2017	18-Sep-2017
21-Sep-2017 - 22-Sep-2017	Final Report	22-Sep-2017	22-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.

QUALITY ASSURANCE STATEMENT

Study Number: 5002158

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	Dates Findings Submitted to: Study Director Management

The Quality Assurance Statements for the work conducted at the Test Sites were reviewed and are included in the appropriate section of this report.

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)

(b) (6)

27 Sep 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 and PBMCs were conducted using scientifically qualified methods and in accordance with all 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.

(b) (6) _____ Date: 27 sep 2017

(b) (6)

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

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

Pathology	(b) (6) Charles River Laboratories, Inc. (PAI-FDK) Frederick, MD, USA

1.4. PI at Sponsor-designated Test Site

PBMC Analysis	(b) (6) Southern Research - Cell Biology and Immunology Birmingham, AL, USA

2. SUMMARY

The objective of this study was to determine the potential toxicity of mRNA-1443, 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 (µg/dose)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1443	10 / 9.6	200	0.05 / 0.048	10	10	-	-
3	mRNA-1443	30 / 29	200	0.15 / 0.145	10	10	-	-
4	mRNA-1443	100 / 96	200	0.5 / 0.48	10	10	5	5

- : Not applicable
[a] Values based on Summary of Analysis (SoA) issued on 16 March 2017 / Values based on SoA issued on 30 May 2017 (Refer to memorandum in Appendix 2).

The following parameters and end points were evaluated in this study: clinical signs, body weights, food consumption, ophthalmology, body temperature, clinical pathology parameters (hematology, coagulation, clinical chemistry, α1-acid glycoprotein and α2-macroglubulin), cytokines analysis (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) on Days 1, 15, 29, 43 at 6 hours postdose and on Day 57, PBMC analysis on Day 44, gross necropsy findings, organ weights, and histopathologic examinations.

There were no mRNA-1443-related changes in body weights, food consumption, ophthalmology and no mRNA-1443-related mortalities.

The mRNA-1443 elicited minimal and variable CD4 and CD8 T cell responses to pp65.

The primary mRNA-1443-related findings were observed at the site of injection and included: at all doses, very slight to moderate edemas, increasing in incidence and/or severity with dose, occasional severe edemas observed at ≥ 29 µg/dose, and very slight erythemas noted in males at 96 µg/dose and very slight to mild erythemas noted in females at ≥ 29 µg/dose. Although incidence and severity were dose-dependent for both sexes (peaking generally 24 hours postdose and resolving 72 hours postdose), these findings were generally noted with a higher extent in female rats. Firm abnormal consistency, swelling, and dark or pale foci were seen at the injection site of males and females at all doses and correlated histopathologically with regional mixed cellular inflammation (characterized primarily by neutrophils and to a lesser extent macrophages and lymphocytes) with edema and varying degrees of erythrocytes present. Minimal to marked perineurial mixed-cell inflammation was also noted in the sciatic nerve and was considered an extension of regionally extensive acute inflammation occurring at the injection site. Dose-dependent minimal to moderate lymphoid hyperplasia, and minimal to mild medullary plasmacytosis were seen in the locoregional lymph nodes (i.e. popliteal and inguinal) of both sexes. These lymph node changes reflected a non-specific, secondary reactive immunologic response to local acute inflammation at the injection site. Inguinal and popliteal lymph nodes occasionally had locally extensive, minimal to mild peripheral (i.e. interstitial)

inflammation and edema. The peripheral interstitial edema and inflammation were likely a secondary extension of the local inflammatory response centered at the injection site. The relative proximal location of these lymph nodes likely contributed to the accumulation of inflammation and edema in and around the injection site. mRNA-1443-related microscopic changes observed in the inguinal and popliteal lymph nodes were nearly or fully resolved, and changes in the spleen and the bone marrow were completely resolved. The mixed cellular inflammation observed at injection sites, in the connective tissues surrounding the sciatic nerve and in inguinal and popliteal lymph node was replaced by an infiltrate of mononucluear cells indicative of continued resolution and healing of injection site inflammation. In addition, there was a decrease in incidence and severity of the hepatocellular microvesicular vacuolation noted at the end of the recovery phase, suggesting partial resolution. Clinical signs (i.e. edema and erythema) observed at the injection site and gross findings were no longer observed in recovery animals, indicating a complete recovery.

Systemic changes associated with inflammation were also observed in animals given ≥ 9.6 µg/dose and included: increases in splenic weights that reach statistical significance at ≥ 9.6 µg/dose in males and at 96 µg/dose in females; with no histological correlates, minimal decreased cellularity of the periarteriolar lymphoid sheath noted in both sexes; with females having slightly increased incidence vs. males, and dose-dependent minimal to mild increased myeloid hematopoiesis in the bone marrow of males at ≥ 9.6 µg/dose and females at ≥ 29 µg/dose; this change was likely a reactive response to the pronounced inflammation observed at the injection site. Clinical pathology changes suggestive of inflammation were also observed in all males and/or females given mRNA-1443 and included: minimal to moderate increases in neutrophil, eosinophil and/or large unstained cell (males only ≥ 9.6 µg/dose) counts with concomitant increases in white blood cell counts (males ≥ 29 µg/dose, females ≥ 9.6 µg/dose), minimal decreases in lymphocyte counts (males only ≥ 29 µg/dose), reticulocyte (males only ≥ 9.6 µg/dose) and platelet (females only ≥ 9.6 µg/dose) counts, minimal increases in activated partial thromboplastin time (males ≥ 29 µg/dose, females 96 µg/dose) and mild increases in fibrinogen, minimal decreases in albumin (males 96 µg/dose, females ≥ 29 µg/dose) and increases in globulin with concomitant decreases in A/G ratio (males and females ≥ 29 µg/dose). Slight increases in body temperature were generally noted 6 hours postdose and return to or close to predose value 24 hours postdose. Although all body temperatures were within normal ranges, temperatures tend to increase with dose levels. Elevations of protein and cytokine levels suggestive of inflammation were also observed. Increases in α1-acid glycoprotein, α2-macroglobulin, IP-10 and MCP-1 were noted at ≥ 9.6 µg/dose. At the end of the recovery period, all mRNA-1443-related changes return close to control values or were partially or fully recovered.

Additionally, liver sections displayed a periportal to midzonal microvesicular vacuolar change with minimal to moderate magnitude. While present in all groups including controls, this change demonstrated a slight dose-dependent increase in incidence and magnitude consistent with a Test Item exacerbation of a background lesion. This change was also observed within recovery animals, but with decreased magnitude and incidence which indicate a partial resolution.

In conclusion, administration of mRNA-1443 by intramuscular injection for 6 weeks (4 doses) was clinically well tolerated (no mortality, changes in body weight and food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 96 µg/dose. At ≥ 9.6 µg/dose, dose-dependent changes clinical signs (edema/erythema) at the

injection site, clinical pathology parameters, and cytokines/protein levels along with slight increase in body temperature were consistent with a systemic inflammatory response. Dose-dependent target organ effects were limited to the injection site, the tissues surrounding the sciatic nerve, the popliteal and inguinal lymph nodes, the spleen, the bone marrow and the liver of animals given mRNA-1443. At the end of the recovery period, all changes were partially or fully recovered.

3. INTRODUCTION

The objective of this study was to determine the potential toxicity of mRNA-1443, 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 November 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 20 Mar 2017 (males) and 21 Mar 2017 (females). The in-life phase of the study was completed on 03 May 2017 (Main Study animals) and on 16 May 2017 (Recovery Study animals). The experimental start date was 08 Mar 2017, and the experimental completion date was 15 Sep 2017. The study plan, study plan amendments, and deviations are presented in Appendix 1.

4. MATERIALS AND METHODS

4.1. Test and Reference Items

4.1.1. Test Item

Identification:	mRNA-1443
Batch (Lot) No.:	MTDP17017
Retest Date:	The end of use bulk Test Item analysis demonstrated that the Test Item was suitable for use during the study period.
Concentration:	2.6 / 2.5* mg/mL
Physical Description:	White to off-white lipid nanoparticle dispersion
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 30 May 2017 (Refer to memorandum in Appendix 2).

4.2. Reference Item

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

4.3. Test Item Characterization

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

4.4. Analysis of the Test Item

A sample (2 vials) of the Test Item was 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 molecular biology laboratory at the Test Facility for purity analysis.

Purity and Particle size analysis were 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) were discarded before issue of the Final Report.

4.5. Reserve Samples

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

4.6. Test and Reference Item Inventory and Disposition

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

4.7. Dose Formulation and Analysis

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.

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

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

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.

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

4.7.3.1. Analytical Method

Analyses were performed by IEX-HPLC using a validated analytical procedure (CR MTL Study No. 1801913).

4.7.3.2. Concentration and Homogeneity Analysis

On the first and the last preparation 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. On days where only concentration analysis was required, the formulation was only sampled from the middle stratum.

Concentration results were considered acceptable when mean sample concentration results were within or equal to ± 15% of theoretical concentration. Each individual sample concentration result was considered acceptable when it was within or equal to ± 20%. Homogeneity results were considered acceptable when 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 were 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 Mar 2017, one hundred and twenty Crl:CD(SD) Sprague-Dawley rats (60 males and 60 females) were received from Charles River Canada Inc., St. Constant, QC, Canada. At dosing initiation, the animals were 7 weeks old and males weighed between 223 and 260 grams and females weighed between 188 and 232 grams.

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 at least 12 days was allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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 at extremes of body weight range or with compromising background findings were not assigned to groups.

No animal were replaced before or after the initiation of dosing. All spare animals were released from the study on Day 4.

The disposition of all animals was documented in the study records.

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 unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The room 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.

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. Wet pellet were provided for few days to one animal as warranted by clinical sign.

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 were 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). Water bottles were provided to one animal as warranted by clinical sign.

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

It is considered that there were 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 to non-toxic pen used for marking the injection area was suspected for control female No. 1508 on Day 25. Consequently, no marking of the injection site was performed for this animal after that day, except on the terminal necropsy day.

4.9. Experimental Design

Text Table 3
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1443	10 / 9.6	200	0.05 / 0.048	10	10	-	-
3	mRNA-1443	30 / 29	200	0.15 / 0.145	10	10	-	-
4	mRNA-1443	100 / 96	200	0.5 / 0.48	10	10	5	5

- : Not applicable
[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 30 May 2017 (Refer to memorandum in Appendix 2).

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 thigh and Site 2 right thigh). 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. Hair may have been clipped or shaved, when required, to improve visualization of the injection sites. The injection site was documented in the raw data for each dose administered.

A low incidence of dosing reflux and/or spillage was observed for individual animals. As these events occurred only once (twice for one animal) per affected animal and were scattered in all dosing groups, including controls, they were considered to have no impact on overall animals exposure and on the study outcome.

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 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 starting on Day -1.

4.10.3. Local Irritation Assessment

All animals had the dose injection site examined for signs of erythema/edema at least 24 and 72 hours postdose (end of each group). 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 on Day -1. A fasted weight was recorded on the day of necropsy.

4.10.5. Food Consumption

Food consumption was quantitatively measured weekly starting on Day -5 (refer to Appendix 1) and continuing weekly throughout the dosing and recovery periods.

4.10.6. Ophthalmic Examinations

Animals had funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations once prior to randomization (all animals) and on Day 42 for males and Day 41 for females. As there were no Test Item-related ophthalmoscopic findings toward 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).

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-macroglubulin
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 K_3EDTA 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 the 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 a serum separator tube) 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 Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine Kinase Total bilirubin Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium 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 was 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 (Cytokine Analysis)

Blood was collected from the jugular vein of all recovery animals. 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)**	**K_3EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hrs**	**Animal Nos.**	IFN-α*	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	1011 to1015 4011 to 4015 1511 to 1515 4511 to 4515	X	X
15	6		X	X
29	6		X	X
43	6		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 number of aliquots and volumes were targets that may have been adjusted based on sample volume availability.

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 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.

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

4.11.3. Anti Therapeutic Antibody (ATA) Analysis

Before the initiation of dosing and on Day 29 (before dose administration), a 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 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.

ATA samples were ultimately not analyzed and were discarded prior to report finalization, following Study Director approval.

4.11.4. 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 the appropriate animals. Samples were shipped at controlled temperature set to maintain 21°C via overnight courier to Southern Research, Birmingham, AL, USA, for whole blood stimulation and cytokine analysis.

The PBMC samples were analyzed using a qualified method.

4.12. 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]

X = Procedure conducted
[a] See Tissue Collection and Preservation table for listing of tissues.

4.12.1. Unscheduled Deaths

No animals died during the course of the study.

4.12.2. 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.

4.12.3. Necropsy

Main 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.

4.12.4. Organ Weights

The organs identified in Text Table 10 were weighed at necropsy for all scheduled euthanasia animals. Paired organs were weighed together. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight 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.

4.12.5. 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[f]	Lung
Bone marrow smear	Lymph node, mandibular
Bone marrow	Lymph node, mesenteric
Bone, femur	Lymph node, inguinal[d]
Bone, sternum	Lymph node, popliteal[d]
Brain[e]	Small intestine, duodenum
Cervix	Small intestine, ileum
Epididymis	Small intestine, jejunum
Esophagus	Muscle, skeletal (Quatriceps[g])
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] Lymph node draining the last administration site used (unilateral examination).
[e] Seven Brain levels examined to include olfactory bulb (examined in Body cavity, nasal section level 4).
[f] Level 4 processed to slide for evaluation of olfactory bulb. Nasal structures were not examined.
[g] Biceps femoris for all recovery animals (refer to Appendix 1).

4.12.6. Histology

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

4.12.7. Histopathology

Histopathological evaluation was performed by a board-certified veterinary pathologist. Injection site, liver, spleen, bone marrow, sciatic nerve and popliteal and inguinal lymph nodes were identified by the study pathologist during microscopic evaluation as potential target tissues. They were evaluated and reported.

4.12.8. Peer Review

A pathology peer review was conducted by (b) (6) from Moderna Therapeutics.

4.12.9. 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 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

All results presented in the tables of the report were 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

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

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 have been expressed as a percentage of 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
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	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. 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.

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
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 CO2, as appropriate
Johnson Controls Metasys	MVE 7.0/4.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

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 CR MTL archive 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.

All records and reports generated from Sponsor-designated subcontractors were archive at the Southern Research's Archive.

9. RESULTS

9.1. Dose Formulation Analyses

(Appendix 3)

Dose formulation concentration results were within specification except for Day 1, Group 2 (i.e. mean: 126%). Following investigation, the cause of out of specification results could not be determined. However, this was considered to have had no impact on the overall integrity of the study since the concentration results obtained were slightly over the concentration acceptance criteria. In addition, the same procedures of preparation were performed for all occasions and on Day 43, all concentrations were within specifications.

Homogeneity testing showed that the formulation technique used produced homogeneous preparations.

9.2. End of Use Bulk Test Item Analysis

(Appendix 2 and Appendix 19)

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

The end of use bulk Test Item analysis demonstrates a purity of (b) (4), which is similar to the original results provided by the Sponsor on the Certificate of Analysis (i.e. (b) (4)

9.3. Mortality

(Appendix 4)

There were no mortalities during the course of the study.

9.4. Clinical Observations

(Table 1, Appendix 5, and Appendix 6)

There were no significant mRNA-1443-related clinical signs observed during the course of this study.

9.5. Local Irritation Assessment

(Appendix 7)

Edema and, less frequently, erythema, were noted at the injection site following dosing of males and females given ≥ 9.6 µg/dose. The edema severity scores ranged from very slight to moderate, with occasional severe edema noted at ≥ 29 µg/dose. Very slight erythemas were noted in males at 96 µg/dose while scores ranged from very slight to mild erythema in females at ≥ 29 µg/dose. The apex of severity was generally noted 24 hours postdose and decreased 72 hours postdose. Although incidence and severity were dose-dependent for both sexes, these findings were generally noted with a higher extent in female rats.

Very slight to slight edema and/or erythema were still observed 72 hours post last dose (i.e. Day 43) but they were no longer observed at the end of 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 8, and Appendix 9)

There were no significant mRNA-1443-related changes in body weights during the course of this study.

9.7. Food Consumption

(Table 4 and Appendix 10)

There were no significant mRNA-1443-related changes in food consumption during the course of this study.

9.8. Ophthalmic Examinations

(Appendix 17)

There were no mRNA-1443-related ocular changes observed during the course of the study. The findings noted were age-related or incidental in origin and expected in this population of animals.

9.9. Body Temperature

(Table 5 and Appendix 11)

Slight increases in body temperature were generally noted 6 hours postdose and return to or close to predose value 24 hours postdose. Although all body temperatures were generally within normal ranges (i.e. 36.0°C to 38.0°C), temperatures tend to increase with dose levels. On Day 43, predose body temperatures were higher than postdose temperatures, except for animals dosed at 96 µg where postdose temperatures were higher.

9.10. Hematology

(Table 6 and Appendix 12)

mRNA-1443-related hematology changes were noted for males and females at ≥ 9.6 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), reticulocyte (RETIC) and platelet (PLT) counts. These changes are illustrated in Text Table 14.

Text Table 14
Hematology Changes in Rats Administered mRNA-1443

Dose (µg/dose)	9.6		29		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
WBC						
Day 44	-	1.3	1.3	1.4	**2.0**	**2.0**
Day 57					1.3	-
NEUT						
Day 44	1.6	1.7	**3.3**	**3.6**	**9.0**	**6.8**
Day 57					-	0.74
LYMPH						
Day 44	-	-	0.91	-	0.87	-
Day 57					1.4	-
EOS						
Day 44	1.8	**2.4**	**2.0**	**3.3**	**2.8**	**4.1**
Day 57					1.4	0.69
LUC						
Day 44	1.8	-	1.6	-	**2.7**	-
Day 57					-	-
RETIC						
Day 44	0.90	-	**0.85**	-	**0.82**	-
Day 57					-	-
PLT						
Day 44	-	**0.84**	-	0.93	-	**0.77**
Day 57					-	0.93

Changes are expressed as X Fold from mean 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 these timepoint for corresponding groups.

Minimal increases in WBC counts (up to 2.0X controls) were noted in males and females given ≥ 9.6 µg/dose, mainly due to minimal to moderate increases in NEUT and EOS (up to 9.0X and 2.8X controls for males and 6.8X and 4.1X controls for females, respectively), and/or LUC (up to 2.7X controls for males only). Minimal decreases in LYMPH were noted for males only at ≥ 29 µg/dose (down to 0.87X controls).

Minimal decreases in RETIC were noted in males at ≥ 9.6 µg/dose (down to 0.82X controls) and minimal decreases in PLT were noted in females at ≥ 9.6 µg/dose (down to 0.77X controls).

Of the above changes noted during the dosing period, a partial to full recovery of the findings were noted following the 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-1443-related.

9.11. Coagulation

(Table 7 and Appendix 13)

mRNA-1443-related increases in activated partial thromboplastin time (APTT) and in fibrinogen (FIB) were noted in males and females given ≥ 9.6 µg/dose. The changes are illustrated in Text Table 15.

Text Table 15
Coagulation Changes in Rats Administered mRNA-1443

Dose (µg/dose)	9.6		29		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
APTT						
Day 44	-	-	**1.1**	-	**1.2**	**1.1**
Day 57					-	-
FIB						
Day 44	**1.6**	1.5	**2.0**	**2.1**	**2.5**	**2.4**
Day 57					-	-

Changes are expressed as X Fold from mean 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 these timepoint for corresponding groups.

Minimal increases in APTT were noted for males at ≥ 29 µg/dose (up to 1.2X controls) and females at 96 µg/dose (1.1X controls). Mild increases in FIB were noted for males and females given ≥ 9.6 µg/dose (up to 2.5X and 2.4X controls, respectively). At the end of the recovery period, values 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-1443-related.

9.12. Clinical Chemistry

(Table 8 and Appendix 14)

mRNA-1443-related decreases in albumin (ALB) and increases in globulin (GLOB) were noted for males and females and were reflected by decrease in A/G ratio. These changes are illustrated in Text Table 16.

Text Table 16
Clinical Chemistry Changes in Rats Administered mRNA-1443

Dose (µg/dose)	9.6		29		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
ALB						
Day 44	-	-	-	**0.89**	**0.89**	**0.87**
Day 57					-	-
GLOB						
Day 44	-	-	**1.2**	**1.2**	**1.3**	**1.3**
Day 57					-	-
A/G Ratio						
Day 44	-	-	**0.78**	**0.72**	**0.70**	**0.67**
Day 57					-	-

Changes are expressed as X Fold from mean 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 these timepoint for corresponding groups.

Minimal decreases in ALB were noted for males given 96 µg/dose (0.89X controls) and females given ≥ 29 µg/dose (down to 0.87X controls). Minimal increases in GLOB were noted for males and females given ≥ 29 µg/dose (up to1.3X controls, for both sexes) and affected the A/G ratio

(down to 0.70X and 0.67X controls for males and females, respectively). At the end of the recovery period, values 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-1443-related.

9.12.1. α1-acid Glycoprotein and α2-macroglobulin Analysis

(Table 9 and Appendix 15)

On Day 44, dose-dependent increases in α2-macroglobulin and α1-acid Glycoprotein were noted for males and females. These changes were statistically significant at ≥ 29 µg/dose in both genders. At the end of the recovery period (i.e. Day 57), all values returned close to control group suggesting a full recovery.

9.13. Laboratory Investigations (Cytokine Analysis)

(Table 10, Appendix 16, and Appendix 20)

When compared to the control group, higher concentrations of IP-10 were observed in animals at 96 µg/dose with the highest concentrations being generally observed on Days 29 and 43, 6 hours post dose, in both genders. These changes were statistically significant at 6 hours post dose on Days 29 and 43 for males and on Day 29 only for females. In addition, statistically significant increases in MCP-1 were also observed in females on Days 1, 15, 29 and 43, at 6 hours postdose.

At the end of the recovery period (i.e. Day 57), the concentrations of IP-10 and MCP-1 in the treated groups were generally very similar to the control group concentration suggesting full recovery.

No mRNA-1443-related changes were observed in IL-1β, IL-6, MIP1-α and TNF-α levels.

9.14. PBMC Analysis

(Appendix 18)

The T cell responses were evaluated by assessment of Interferon gamma (INFγ) producing T cells by intracellular cytokine staining and flow cytometric analysis. A summary of INFγ production responses are detailed in the following table.

Summary of Results - pp65 Specific INFγ Response

	Group	Test material	N	Dose level (µg)	pp65 specific CD4+ T cells Range (%)*;	Mean (%);	SD	pp65 specific CD8+ T cells Range (%)*;	Mean (%);	SD
Males	1	Reference	10	0	0.00 - 0.18;	0.00;	0.13	0.00 - 0.00;	0.00;	0.07
	2	mRNA-1443	10	9.6	0.00 - 0.27;	0.00;	0.12	0.00 - 1.07;	0.12;	0.34
	3	mRNA-1443	10	29	0.00 - 0.22;	0.00;	0.20	0.00 - 0.57;	0.00;	0.45
	4	mRNA-1443	9	96	0.00 - 0.10;	0.00;	0.11	0.00 - 0.41;	0.00;	0.37
Females	1	Reference	10	0	0.00 - 0.48;	0.00;	0.25	0.00 - 0.18;	0.01;	0.09
	2	mRNA-1443	10	9.6	0.00 - 0.62;	0.00;	0.56	0.00 - 0.22;	0.01;	0.11
	3	mRNA-1443	10	29	0.00 - 0.48;	0.00;	0.34	0.00 - 0.17;	0.01;	0.10
	4	mRNA-1443	10	96	0.00 - 0.68;	0.09;	0.38	0.00 - 0.55;	0.00;	0.43

*For purpose of Range and Mean calculation, values < 0.00 following Unstimulated Control subtraction were set to 0.00 for reporting.

The mRNA-1443 elicited minimal CD4 and CD8 T cell responses to pp65. Minimal and varying T cell responses for pp65 peptide library were noted at all dose levels. In male rats dosed with 96 µg/dose, the range of pp65-specific CD4 and CD8 T cells secreting IFN-α were 0 to 0.10% and 0 to 0.41%, respectively. In female rats that received 96 µg/dose, the range of pp65-specific CD4 and CD8 T cells were 0 to 0.68% and 0 to 0.55%, respectively.

In males at 29 µg/dose, the range of pp65-specific CD4 and CD8 T cells secreting IFN-α were 0 to 0.22% and 0 to 0.57%, respectively. In females at 29 µg/dose, the range of pp65-specific CD4 and CD8 T cells were 0 to 0.48% and 0 to 0.17%, respectively.

In males at 9.6 µg/dose, the range of pp65-specific CD4 and CD8 T cells secreting IFN-α were 0 to 0.27% and 0 to 1.07%, respectively. In females at 9.6 µg/dose, the range of pp65-specific CD4 and CD8 T cells were 0 to 0.62% and 0 to 0.22%, respectively.

Overall, the analysis revealed that minimal noted antigen-specific response to the pp-65 peptide library was seen during the study.

9.15. Gross Pathology

9.15.1. Terminal Euthanasia Animals (Day 44)

(Appendix 21).

Test Item-related gross pathology findings are summarized in Text Table 17.

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

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**9.6**	**29**	**96**	**0**	**9.6**	**29**	**96**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Injection Site (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency; firm	0	2	9	10	0	2	10	10
Swelling	0	1	4	7	0	0	1	2
Focus; dark	0	0	3	1	0	0	1	1
Focus; pale	0	0	0	1	0	0	0	0
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	2	2	2	0	0	0	1
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	3	5	0	1	2	4

At the injection site, firm abnormal consistency was seen in males and females at ≥ 9.6 µg/dose with a dose-related increase in frequency; this change correlated microscopically with mixed cell inflammation. Swelling was also observed in males at ≥ 9.6 µg/dose and females at ≥ 29 µg/dose. At the injection site, dark foci were also observed in males and females at ≥ 29 µg/dose which correlated histopathologically with mixed cell inflammation with hemorrhage. In addition, one male at 96 µg/dose (No. 4004) was noted with pale foci at the injection site.

Enlargement of the popliteal and inguinal lymph nodes was seen in some treated rats which usually correlated histologically with perinodal mixed cell inflammation.

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-1443.

9.15.2. Recovery Euthanasia Animals (Day 57)

(Appendix 21)

At the end of the recovery period, no mRNA-1443-related gross findings were noted. The 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-1443.

9.16. Organ Weights

9.16.1. Terminal Euthanasia Animals (Day 44)

(Appendix 21)

mRNA-1443-related organ weight changes are summarized in Text Table 18.

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

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**9.6**	**29**	**96**	**9.6**	**29**	**96**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Spleen (No. Weighed)[a]	(10)	(10)	(10)	(10)	(10)	(10)
% diff Group 1	**16.5343**	15.7402	**22.8217**	14.0207	13.9037	20.0535
% of body weight	**21.13059**	**20.11467**	**31.40503**	9.34063	13.78629	**20.28219**
% of brain weight	14.89285	**18.35570**	**24.47485**	15.32076	13.87448	**20.57586**

[a] All values expressed as percent difference of control group means.
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – $P \leq 0.05$; refer to data tables for actual significance levels and tests used.

Statistically significant increased splenic weights were noted in males at ≥ 9.6 µg/dose and females at 96 µg/dose. There were no gross or microscopic changes that correlated to the above weight changes.

No other mRNA-1443-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective controls. However, there were 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-1443.

9.16.2. Recovery Euthanasia Animals (Day 57)

(Appendix 21)

mRNA-1443-related organ weight changes noted at the terminal euthanasia were not observed at the end of the recovery period (i.e. Day 57). There were isolated organ weight values that were statistically different from their respective controls. However, there were no patterns, trends or correlating data to suggest these values were toxicologically relevant. Thus, the organ weight differences observed were considered incidental and/or related to difference of sexual maturity and unrelated to administration of mRNA-1443.

9.17. Histopathology

9.17.1. Terminal Euthanasia (Day 44)

(Appendix 21)

mRNA-1443-related microscopic findings are summarized in Text Table 19.

Text Table 19
Summary of Microscopic Findings – Terminal Euthanasia (Day 44)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**9.6**	**29**	**96**	**0**	**9.6**	**29**	**96**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injection	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(3)[a]	(10)	(10)	(10)	(1)	(10)	(10)	(10)
Minimal	3	1	0	0	0	2	0	0
Mild	0	3	0	0	1	7	0	0
Moderate	0	6	4	0	0	1	7	0
Marked	0	0	6	10	0	0	3	10
Liver	10	10	10	10	10	10	10	10
Vacuolation, microvesicular, periportal to midzonal	(1)	(6)	(9)	(9)	(5)	(8)	(8)	(9)
Minimal	1	6	6	4	5	5	5	5
Mild	0	0	3	4	0	3	2	3
Moderate	0	0	0	1	0	0	1	1
Spleen	10	10	10	10	10	10	10	10
Decreased cellularlity, lymphoid, periarteriolar sheath	(0)	(2)	(1)	(1)	(0)	(1)	(1)	(4)
Minimal	0	2	1	1	0	1	1	4
Lymph node, inguinal	10	10	10	10	10	9	9	10
Inflammation, mixed cell; perinodal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Mild	0	0	0	1	0	0	0	0
Plasmacytosis	(0)	(1)	(0)	(7)	(0)	(0)	(0)	(3)
Minimal	0	1	0	5	0	0	0	3
Mild	0	0	0	2	0	0	0	0
Hyperplasia; lymphoid	(1)	(6)	(4)	(5)	(0)	(5)	(7)	(4)
Minimal	1	2	2	3	0	3	2	3
Mild	0	3	1	2	0	1	5	1
Moderate	0	1	1	0	0	1	0	0
Lymph node, popliteal	9	10	10	10	10	10	10	10
Inflammation, mixed cell; perinodal	(0)	(9)	(10)	(6)	(0)	(9)	(9)	(7)
Minimal	0	3	6	1	0	5	3	2
Mild	0	6	2	4	0	4	5	4
Moderate	0	0	2	1	0	0	1	1
Plasmacytosis	(1)	(0)	(0)	(3)	(1)	(1)	(1)	(5)
Minimal	1	0	0	3	1	1	1	2
Mild	0	0	0	0	0	0	0	3
Hyperplasia; lymphoid	(0)	(9)	(8)	(5)	(0)	(8)	(9)	(8)
Minimal	0	6	5	3	0	3	6	5
Mild	0	3	3	2	0	5	3	3
Sciatic nerve	10	10	10	10	10	10	10	10
Inflammation, mixed cell; perineurial	(0)	(10)	(10)	(10)	(5)	(10)	(9)	(10)
Minimal	0	1	4	0	5	0	4	2
Mild	0	5	3	8	0	6	3	7
Moderate	0	3	3	2	0	3	2	1
Marked	0	1	0	0	0	1	0	0
Bone marrow	10	10	10	10	10	10	10	10
Increased hematopoiesis; myeloid	(0)	(2)	(2)	(5)	(1)	(0)	(4)	(4)
Minimal	0	2	2	4	1	0	4	4
Mild	0	0	0	1	0	0	0	0

[a] Numbers in parentheses represent the number of animals with the finding.

At the injection site, a dose-dependent, minimal to marked mixed cellular inflammation accompanied by edema was noted in males and females at ≥ 9.6 µg/dose. This change was characterized by a stereotypic acute inflammatory milieu comprising increased clear space expanding the interstitium (i.e. edema) accompanied by numerous neutrophils variably admixed with foamy macrophages, lymphocytes, and rare plasma cells and hemosiderophages, as well as variable quantities of extravasated erythrocytes (i.e. hemorrhage).

In the sciatic nerve, a dose-dependent, minimal to marked mixed cellular inflammation of the perineurial tissue was observed and was variably accompanied by edema. Of note, the sciatic nerve contained no changes within the nerve fibers, inflammation did not broach the epidneurium, and inflammation/edema was generally of a lesser severity than the injection site proper.

Similar to the sciatic nerve, minimal to moderate mixed cellular inflammation surrounded the inguinal and/or popliteal lymph node in males and females at ≥ 9.6 µg/dose. These changes were reflected by perinodal interstitial mixed cell inflammation variably accompanied by small amounts of edema. Inflammation did not extend into the lymph node capsule. The inguinal lymph node site generally had less incidence and severity of peripheral inflammation vs. the popliteal site.

Intrinsic lymph node changes included lymphoid hyperplasia and medullary plasmacytosis; these changes were orderly and of a character and magnitude that would be expected of reactive lymph nodes that are a non-specific and appropriate secondary consequence of injection site inflammation. These non-specific reactive changes were observed in relevant locoregional injection site lymph nodes (i.e. inguinal, popliteal) at a higher rate and slightly higher magnitude than controls.

In the spleen of males and females at ≥ 9.6 µg/dose, slightly increased incidence of a minimally decreased cellularity of the periarteriolar lymphoid sheath was noted. Although males did not display any evident dose-dependent trend, increased incidence in females at 96 µg/dose may indicate a dose-dependent effect. Microscopically, this change was characterized by subtle attrition of periarteriolar lymphocytes and variably accompanied by a slight increase in tingible body macrophages.

In the bone marrow of males at ≥ 9.6 µg/dose and females at ≥ 29 µg/dose, increased incidence of minimal to mild increased myeloid hematopoiesis (i.e. myeloid hyperplasia) with a distinctive appearance were noted. Incidence in males and females generally trends upward with increasing dose, suggesting a dose-dependent effect. Microscopically, this change was consistently characterized by multifocal aggregates of precursor cells predominantly composed of early myeloid lineage and typically found adjacent to the cortex and/or trabeculae.

Liver of control and treated males and females display microvescular hepatocelluar vacuolation without nuclear displacement throughout periportal to midzonal regions. However, this change demonstrated a dose-dependent increase in incidence and magnitude at ≥ 9.6 µg/dose in both genders, consistent with a Test Item exacerbation of a background lesion.

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-1443.

9.17.2. Recovery Euthanasia (Day 57)

(Appendix 21)

Microscopic findings noted at the terminal euthanasia were observed at the end of the recovery period (i.e. Day 57) and are summarized in Text Table 20.

Text Table 20
Summary of Microscopic Findings – Recovery Euthanasia (Day 57)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**9.6**	**29**	**96**	**0**	**9.6**	**29**	**96**
No. Animals Examined	**5**	**-**	**-**	**5**	**5**	**-**	**-**	**5**
Injection site	5	-	-	5	5	-	-	5
Infiltration, mononuclear cell	(1)[a]	-	-	(4)	(0)	-	-	(4)
Minimal	1	-	-	4	0	-	-	4
Liver	5	-	-	5	5	-	-	5
Vacuolation, microvesicular, periportal to midzonal	(0)	-	-	(1)	(2)	-	-	(4)
Minimal	0	-	-	0	2	-	-	1
Mild	0	-	-	1	0	-	-	3
Lymph node, inguinal	5	-	-	5	5	-	-	5
Plasmacytosis	(1)	-	-	(2)	(0)	-	-	(0)
Minimal	1	-	-	2	0	-	-	0
Hyperplasia; lymphoid	(2)	-	-	(3)	(1)	-	-	(1)
Minimal	2	-	-	2	1	-	-	1
Mild	0	-	-	1	0	-	-	0
Lymph node, popliteal	5	-	-	5	5	-	-	5
Infiltration, mononuclear cell; perinodal	(0)	-	-	(1)	(0)	-	-	(1)
Minimal	0	-	-	1	0	-	-	1
Plasmacytosis	(2)	-	-	(3)	(0)	-	-	(2)
Minimal	2	-	-	2	0	-	-	0
Mild	0	-	-	1	0	-	-	2
Hyperplasia; lymphoid	(1)	-	-	(3)	(0)	-	-	(5)
Minimal	0	-	-	3	0	-	-	5
Mild	1	-	-	0	0	-	-	0
Sciatic nerve	5	-	-	5	5	-	-	5
Infiltration, mononuclear cell; perineurial	(0)	-	-	(5)	(1)	-	-	(4)
Minimal	0	-	-	5	1	-	-	2
Mild	0	-	-	0	0	-	-	2

[a] Numbers in parentheses represent the number of animals with the finding.

At the injections site, there was a resolution of edema and acute mixed cellular inflammation in animals at 96 µg/dose at the end of the recovery period (i.e. Day 57) when compared with main animals at 96 µg/dose on Day 44. When present, the interstitial to perivascular inflammatory population was minimal and comprises a mixture of lymphocytes and macrophages with rare plasma cells and is consistent with a healing process.

In the sciatic nerve, minimal to mild infiltration of mononuclear cells was noted in both sexes. This change suggests a partial recovery from the mixed cellular inflammation observed by the end of the Recovery period.

In the inguinal/popliteal lymph nodes, perinodal mixed-cell inflammation was absent in males and females at 96 µg/dose following recovery. As part of the resolving/resolved acute

inflammation, a minimal mononuclear cell infiltration was occasionally present within the interstitium and/or perivascularly, albeit with much decreased frequency and incidence when compared with initial perinodal inflammation on Day 44.

Intrinsic lymph node changes including lymphoid hyperplasia and medullary plasmacytosis had decreased incidence and magnitude following recovery and were consistent with a resolving/resolved inflammatory response.

In the liver of control and treated males and females, microvescular hepatocellular vacuolation were noted throughout the periportal to midzonal regions. This change occurred at decreased incidence and magnitude when compared with Main Study (i.e. Day 44) animals indicating improvement. Amongst recovery animals, this change was observed in two control females (minimal), and one male (mild) and four (1 minimal, 3 mild) females at 96 µg/dose. However, the higher incidence in the 96 µg/dose recovery animals suggests that this Test Item effect has not fully resolved.

Microscopic findings noted in the bone marrow and the spleen at terminal euthanasia were no longer observed at the end of the recovery period and therefore were considered completely recovered.

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-1443.

10. CONCLUSION

In conclusion, administration of mRNA-1443 by intramuscular injection for 6 weeks (4 doses) was clinically well tolerated (no mortality, changes in body weight and food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 96 µg/dose. At ≥ 9.6 µg/dose, dose-dependent changes clinical signs (edema/erythema) at the injection site, clinical pathology parameters, and cytokines/protein levels along with slight increase in body temperature were consistent with a systemic inflammatory response. Dose-dependent target organ effects were limited to the injection site, the tissues surrounding the sciatic nerve, the popliteal and inguinal lymph nodes, the spleen, the bone marrow and the liver of animals given mRNA-1443. At the end of the recovery period, all changes were partially or fully recovered.

Figure 1

Summary of Body Weights - Males

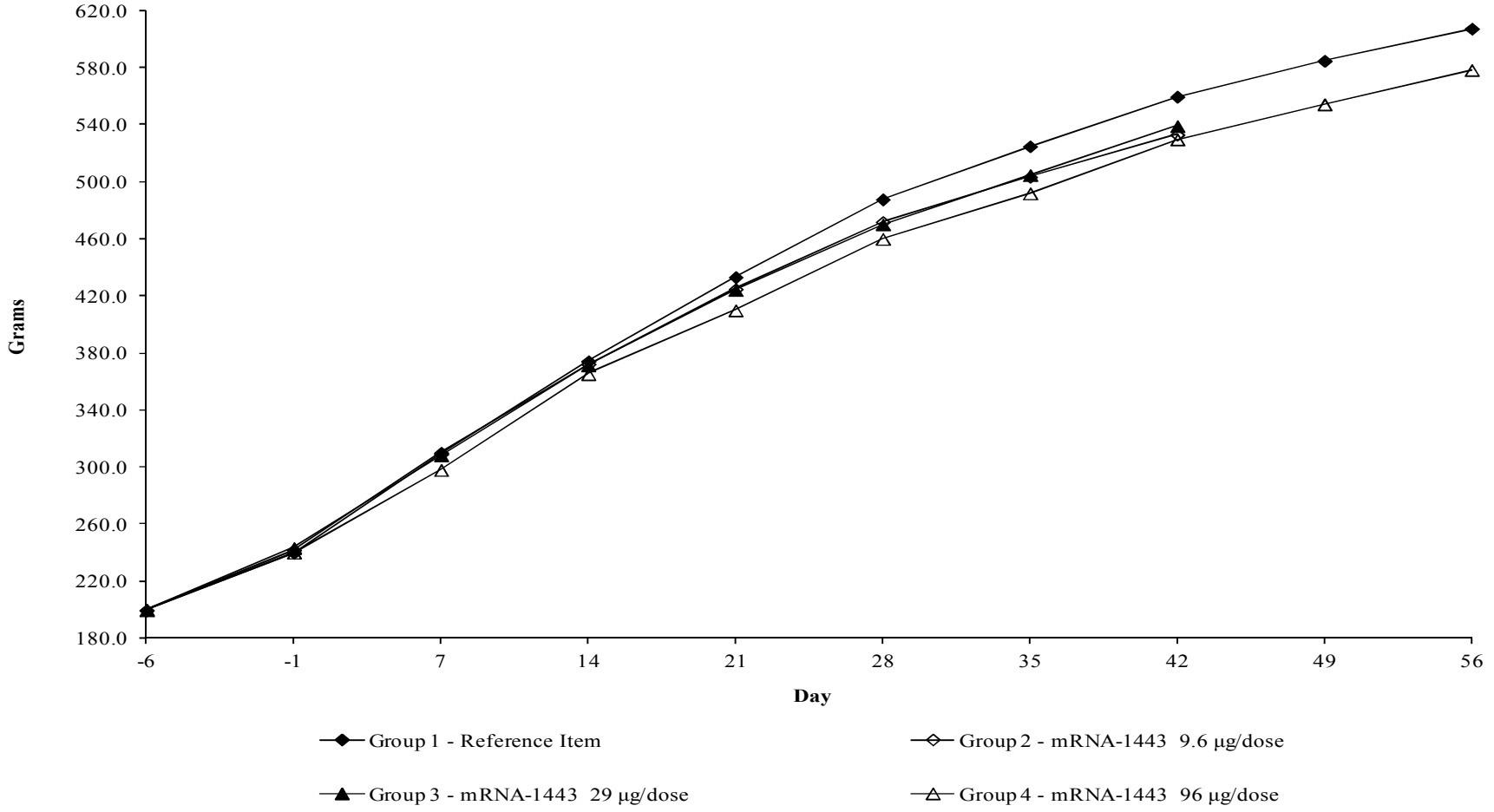

Figure 2

Summary of Body Weights - Females

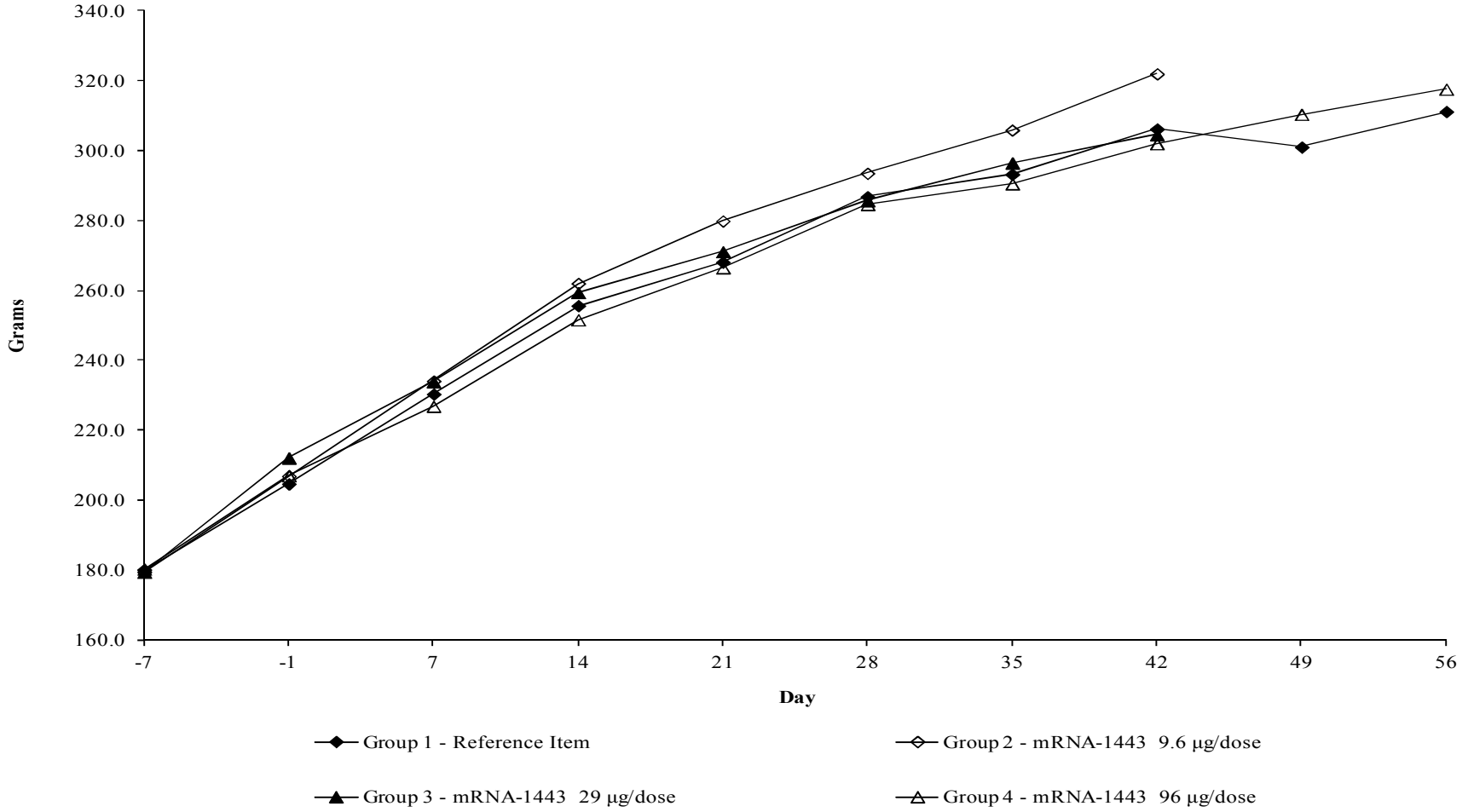

Table 1

Summary of Clinical Observations

5002158

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	9.6 ug/dose	29 ug/dose	96 ug/dose
Skin, Red				
Number of Observations	.	1	.	2
Number of Animals	.	1	.	1
Days from - to	.	28 28	.	14 21
Skin, Lesion w/ Discharge				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	-1 -1	.
Skin, Scab				
Number of Observations	9	6	7	2
Number of Animals	6	4	4	2
Days from - to	-1 44	21 44	28 44	35 35
Fur, Staining, Black				
Number of Observations	3	.	.	.
Number of Animals	1	.	.	.
Days from - to	-1 14	.	.	.
Fur, Staining, Red				
Number of Observations	24	13	9	19
Number of Animals	8	5	5	11
Days from - to	-1 57	7 44	28 44	14 57
Fur, Staining, Yellow				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	28 28
Fur, Thin Cover				
Number of Observations	3	.	3	2
Number of Animals	2	.	1	1
Days from - to	14 28	.	35 44	56 57

Table 1

Summary of Clinical Observations

5002158

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	9.6 ug/dose	29 ug/dose	96 ug/dose
Auditory Canal, Discharge Liq				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Mouth, Discharge Liquid				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Muzzle, Discharge Liquid				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Sneezing				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Breathing, Deep				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Breathing, Labored				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Skin Staining				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.

Table 1

Summary of Clinical Observations

5002158

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	9.6 ug/dose	29 ug/dose	96 ug/dose
Pinna Partly Missing				
Number of Observations	4	.	.	.
Number of Animals	1	.	.	.
Days from - to	-11 44	.	.	.

Table 1

Summary of Clinical Observations

5002158

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	9.6 ug/dose	29 ug/dose	96 ug/dose
Skin, Red				
Number of Observations	2	.	.	1
Number of Animals	2	.	.	1
Days from - to	28 49	.	.	-1 -1
Skin, Dry				
Number of Observations	3	.	.	1
Number of Animals	1	.	.	1
Days from - to	21 44	.	.	-1 -1
Skin, Scab				
Number of Observations	5	3	.	7
Number of Animals	4	3	.	3
Days from - to	-1 49	14 28	.	14 44
Fur, Staining, Red				
Number of Observations	23	11	15	31
Number of Animals	9	6	7	11
Days from - to	7 57	14 44	14 44	21 57
Fur, Thin Cover				
Number of Observations	3	2	.	1
Number of Animals	2	1	.	1
Days from - to	42 44	42 44	.	56 56
Pinna Partly Missing				
Number of Observations	.	.	8	.
Number of Animals	.	.	1	.
Days from - to	.	.	-1 44	.
Mass Present				
Number of Observations	.	5	.	.
Number of Animals	.	1	.	.
Days from - to	.	21 44	.	.

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day -6	-1	7	14	21	28	35
1M	Mean	199.4	239.7	309.0	374.3	433.2	487.7	525.0
	SD	7.6	11.1	17.9	25.4	31.6	34.3	35.7
	N	15	15	15	15	15	15	15
2M	Mean	199.7	241.8	309.9	372.1	424.8	471.8	503.6
	SD	4.6	8.0	13.1	17.6	20.9	22.8	26.9
	N	10	10	10	10	10	10	10
	%Diff G1	0.2	0.9	0.3	-0.6	-1.9	-3.3	-4.1
3M	Mean	200.0	243.2	308.2	371.2	424.1	470.2	504.7
	SD	5.0	11.6	20.8	29.0	37.0	43.5	53.0
	N	10	10	10	10	10	10	10
	%Diff G1	0.3	1.4	-0.3	-0.8	-2.1	-3.6	-3.9
4M	Mean	199.4	239.9	297.9	365.2	409.9	459.9	491.9
	SD	7.4	10.4	18.5	28.8	37.4	43.3	50.0
	N	15	15	15	15	15	15	15
	%Diff G1	0.0	0.1	-3.6	-2.4	-5.4	-5.7	-6.3

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day 42	Day 49	Day 56
1M	Mean	559.7	585.0	607.4
	SD	38.2	46.3	46.0
	N	15	5	5
2M	Mean	533.1	--	--
	SD	31.7	--	--
	N	10	--	--
	%Diff G1	-4.7	--	--
3M	Mean	539.1	--	--
	SD	55.5	--	--
	N	10	--	--
	%Diff G1	-3.7	--	--
4M	Mean	529.8	554.4	578.4
	SD	56.1	41.7	41.5
	N	15	5	5
	%Diff G1	-5.3	-5.2	-4.8

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day -7	-1	7	14	21	28	35
1F	Mean	180.1	204.7	230.4	255.7	268.1	286.8	293.3
	SD	8.0	11.2	13.4	15.4	18.3	19.1	18.8
	N	15	15	15	15	15	15	15
2F	Mean	179.5	206.9	234.1	262.0	279.9	293.5	305.9
	SD	5.9	9.9	15.1	18.8	24.6	26.7	30.1
	N	10	10	10	10	10	10	10
	%Diff G1	-0.4	1.1	1.6	2.5	4.4	2.3	4.3
3F	Mean	179.4	212.1	233.9	259.4	271.1	285.7	296.5
	SD	5.7	8.1	11.4	13.0	19.9	22.4	24.4
	N	10	10	10	10	10	10	10
	%Diff G1	-0.4	3.6	1.5	1.5	1.1	-0.4	1.1
4F	Mean	180.3	207.0	226.9	251.6	266.5	284.6	290.5
	SD	7.8	12.3	17.6	23.3	24.4	26.7	26.0
	N	15	15	15	15	15	15	15
	%Diff G1	0.1	1.1	-1.5	-1.6	-0.6	-0.8	-1.0

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day 42	Day 49	Day 56
1F	Mean	306.2	301.0	311.2
	SD	21.7	11.4	8.5
	N	15	5	5
2F	Mean	322.0	--	--
	SD	31.8	--	--
	N	10	--	--
	%Diff G1	5.2	--	--
3F	Mean	304.6	--	--
	SD	24.9	--	--
	N	10	--	--
	%Diff G1	-0.5	--	--
4F	Mean	302.0	310.4	317.6
	SD	28.8	18.6	20.0
	N	15	5	5
	%Diff G1	-1.4	3.1	2.1

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day Change -6 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1M	Mean	40.3	69.3	65.3	58.9	54.5	37.3	34.7
	SD	5.3	9.3	9.7	8.4	7.7	5.2	7.7
	N	15	15	15	15	15	15	15
2M	Mean	42.1	68.1	62.2	52.7	47.0a	31.8	29.5
	SD	7.1	6.9	6.3	5.1	4.9	6.2	9.9
	N	10	10	10	10	10	10	10
3M	Mean	43.2	65.0	63.0	52.9	46.1a	34.5	34.4
	SD	7.8	10.4	9.1	8.4	7.5	10.0	4.2
	N	10	10	10	10	10	10	10
4M	Mean	40.5	57.9b	67.3	44.7c	49.9	32.1	37.9
	SD	5.7	9.2	11.2	10.2	8.7	7.9	7.9
	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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day Change -1 - 42	Change 42 - 49	Change 49 - 56	Change 42 - 56
1M	Mean	319.9	20.8	22.4	43.2
	SD	33.0	4.0	4.2	2.6
	N	15	5	5	5
2M	Mean	291.3	--	--	--
	SD	27.0	--	--	--
	N	10	--	--	--
3M	Mean	295.9	--	--	--
	SD	45.0	--	--	--
	N	10	--	--	--
4M	Mean	289.9	21.2	24.0	45.2
	SD	47.9	5.9	4.9	6.5
	N	15	5	5	5

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day Change -7 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1F	Mean	24.5	25.7	25.3	12.5	18.7	6.5	12.9
	SD	6.8	8.5	3.8	5.1	7.3	8.2	6.7
	N	15	15	15	15	15	15	15
2F	Mean	27.4	27.2	27.9	17.9	13.6	12.4	16.1
	SD	8.6	8.9	6.3	8.0	6.0	6.1	5.7
	N	10	10	10	10	10	10	10
3F	Mean	32.7	21.8	25.5	11.7	14.6	10.8	8.1
	SD	9.5	9.9	7.8	10.1	5.9	7.5	8.8
	N	10	10	10	10	10	10	10
4F	Mean	26.7	19.9	24.7	14.9	18.1	5.9	11.5
	SD	7.5	8.0	8.2	4.3	8.5	9.0	9.2
	N	15	15	15	15	15	15	15

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day Change -1 - 42	Change 42 - 49	Change 49 - 56	Change 42 - 56
1F	Mean	101.5	3.4	10.2	13.6
	SD	16.2	4.7	7.0	9.8
	N	15	5	5	5
2F	Mean	115.1	--	--	--
	SD	25.3	--	--	--
	N	10	--	--	--
3F	Mean	92.5	--	--	--
	SD	24.8	--	--	--
	N	10	--	--	--
4F	Mean	95.0	10.4	7.2	17.6
	SD	21.0	7.0	11.0	16.2
	N	15	5	5	5

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day (From/To)						
		-5/1	1/8	8/15	15/22	22/29	29/36	36/43
1M	Mean	30.27	31.11	34.52	35.89	36.27	36.60	36.43
	SD	1.84	1.40	1.94	2.44	2.08	1.91	1.36
	N	15	15	15	15	15	15	15
2M	Mean	30.10	31.33	33.98	34.74	34.13	34.33	34.23
	SD	1.07	0.74	0.72	0.48	1.22	1.74	1.78
	N	10	10	10	10	10	10	10
	%Diff G1	-0.57	0.72	-1.56	-3.20	-5.91	-6.20	-6.03
3M	Mean	29.98	30.92	34.39	34.54	35.05	34.66	34.60
	SD	2.47	2.23	2.11	2.31	2.45	2.49	2.24
	N	10	10	10	10	10	10	10
	%Diff G1	-0.97	-0.60	-0.38	-3.75	-3.37	-5.30	-5.01
4M	Mean	28.85	27.91	33.82	32.37	34.96	33.25	35.29
	SD	1.46	1.30	1.84	2.48	2.37	2.50	2.98
	N	15	15	15	15	15	15	15
	%Diff G1	-4.69	-10.27	-2.03	-9.81	-3.62	-9.14	-3.13

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day (From/To) 43/50	50/56
1M	Mean	35.32	36.64
	SD	0.44	0.60
	N	5	5
2M	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
3M	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
4M	Mean	33.66	36.48
	SD	1.04	0.93
	N	5	5
	%Diff G1	-4.70	-0.44

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day (From/To)						
		-5/1	1/8	8/15	15/22	22/29	29/36	36/43
1F	Mean	19.91	21.43	21.87	22.86	22.30	21.59	22.38
	SD	1.02	1.18	1.19	1.42	1.31	0.90	1.29
	N	15	15	15	15	15	15	15
2F	Mean	21.83	22.27	23.50	24.42	24.24	24.17	24.58
	SD	0.62	1.14	1.36	2.01	2.09	1.86	2.04
	N	10	10	10	10	10	10	10
	%Diff G1	9.63	3.94	7.44	6.82	8.70	11.93	9.83
3F	Mean	21.21	21.74	21.66	22.23	22.27	22.08	22.07
	SD	1.66	1.54	1.03	1.49	1.87	1.59	1.63
	N	10	10	10	10	10	10	10
	%Diff G1	6.51	1.46	-0.98	-2.76	-0.13	2.25	-1.39
4F	Mean	19.90	20.78	21.86	22.27	22.73	21.67	22.91
	SD	0.58	0.96	0.91	0.43	0.82	0.63	1.32
	N	15	15	15	15	15	15	15
	%Diff G1	-0.07	-3.02	-0.06	-2.60	1.91	0.34	2.38

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day (From/To) 43/50	50/56
1F	Mean	20.68	21.80
	SD	0.38	0.82
	N	5	5
2F	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
3F	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
4F	Mean	21.66	23.56
	SD	0.22	0.60
	N	5	5
	%Diff G1	4.74	8.07

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1 (pr)	Day 1 (p)	Day 2	Day 43 (pr)	Day 43 (p)	Day 44
1M	Mean	36.76	36.09	36.85	37.11	37.06	36.83
	SD	0.71	0.43	0.35	0.61	0.64	0.66
	N	15	15	15	15	15	15
2M	Mean	36.95	36.63a	36.79	37.65	36.95	36.77
	SD	0.41	0.72	0.25	0.71	0.54	0.24
	N	10	10	10	10	10	10
	%Diff G1	0.52	1.51	-0.17	1.46	-0.30	-0.15
3M	Mean	37.27	37.41c	36.74	38.38c	37.28	37.22
	SD	0.68	0.43	0.32	0.54	0.70	0.59
	N	10	10	10	10	10	10
	%Diff G1	1.39	3.67	-0.31	3.43	0.59	1.07
4M	Mean	36.91	37.74c	37.46c	37.49	38.15c	37.85c
	SD	0.67	0.47	0.51	0.78	0.95	0.53
	N	15	15	15	15	15	15
	%Diff G1	0.42	4.58	1.65	1.04	2.93	2.77

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

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1 (pr)	Day 1 (p)	Day 2	Day 43 (pr)	Day 43 (p)	Day 44
1F	Mean	36.85	37.00	37.12	38.13	37.51	36.81
	SD	0.69	0.53	0.41	0.62	0.58	0.60
	N	15	15	15	15	15	15
2F	Mean	36.75	37.23	36.80	38.17	37.46	36.81
	SD	0.49	0.45	0.47	0.39	0.75	0.60
	N	10	10	10	10	10	10
	%Diff G1	-0.26	0.62	-0.86	0.11	-0.14	-0.01
3F	Mean	37.29	37.48a	36.88	38.41	37.97	36.79
	SD	0.52	0.48	0.63	0.43	0.71	0.38
	N	10	10	10	10	10	10
	%Diff G1	1.20	1.30	-0.65	0.74	1.22	-0.06
4F	Mean	37.07	37.77c	37.35	38.55	38.71c	37.27
	SD	0.58	0.33	0.64	0.40	0.46	0.65
	N	15	15	15	15	15	15
	%Diff G1	0.60	2.09	0.63	1.12	3.18	1.23

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	9.447	1.274	7.657	0.282	0.085	0.017	0.129
	SD	2.590	0.648	2.004	0.117	0.024	0.011	0.060
	N	10	10	10	10	10	10	10
2M	Mean	10.602	2.000	7.853	0.353	0.152	0.020	0.227
	SD	3.116	0.637	2.436	0.105	0.031	0.011	0.109
	N	10	10	10	10	10	10	10
	%Diff G1	12.226	56.986	2.560	25.177	78.824	17.647	75.969
3M	Mean	11.923	4.252b	6.995	0.273	0.172a	0.020	0.211
	SD	2.505	1.498	1.834	0.107	0.060	0.008	0.067
	N	10	10	10	10	10	10	10
	%Diff G1	26.209	233.752	-8.646	-3.191	102.353	17.647	63.566
4M	Mean	18.818f	11.404c	6.639	0.234	0.240c	0.025	0.349f
	SD	3.082	3.929	1.893	0.102	0.105	0.015	0.120
	N	10	10	10	10	10	10	8
	%Diff G1	99.196	795.133	-13.295	-17.021	182.353	47.059	170.349

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.837	14.27	43.08	55.00	18.22	33.13	12.48
	SD	0.308	0.54	1.60	1.30	0.60	0.46	0.65
	N	10	10	10	10	10	10	10
2M	Mean	7.878	13.99	41.85	53.09b	17.78	33.46	12.41
	SD	0.357	0.70	2.06	0.69	0.34	0.52	0.64
	N	10	10	10	10	10	10	10
	%Diff G1	0.523	-1.96	-2.86	-3.47	-2.41	1.00	-0.56
3M	Mean	7.788	13.83	41.70	53.53a	17.76	33.15	12.60
	SD	0.415	0.70	2.50	1.36	0.38	0.52	0.39
	N	10	10	10	10	10	10	10
	%Diff G1	-0.625	-3.08	-3.20	-2.67	-2.52	0.06	0.96
4M	Mean	8.075	14.09	42.97	53.22b	17.46b	32.79	13.45c
	SD	0.451	0.77	2.32	0.90	0.38	0.37	0.33
	N	10	10	10	10	10	10	10
	%Diff G1	3.037	-1.26	-0.26	-3.24	-4.17	-1.03	7.77

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1120.6	238.18
	SD	107.9	34.31
	N	10	10
2M	Mean	1121.1	213.58
	SD	129.9	26.11
	N	10	10
	%Diff G1	0.0	-10.33
3M	Mean	1019.3	201.37a
	SD	175.8	11.88
	N	10	10
	%Diff G1	-9.0	-15.45
4M	Mean	1061.7	196.20b
	SD	100.1	30.46
	N	10	10
	%Diff G1	-5.3	-17.63

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	5.567	0.926	4.359	0.138	0.068	0.006	0.070
	SD	2.216	0.689	1.536	0.066	0.024	0.005	0.046
	N	10	10	10	10	10	10	10
2F	Mean	7.284	1.603	5.270	0.133	0.165a	0.009	0.102
	SD	2.047	0.554	1.605	0.064	0.053	0.006	0.066
	N	10	10	10	10	10	10	10
	%Diff G1	30.842	73.110	20.899	-3.623	142.647	50.000	45.714
3F	Mean	8.004	3.359f	4.212	0.110	0.227c	0.006	0.090
	SD	2.409	1.207	1.520	0.034	0.075	0.007	0.061
	N	10	10	10	10	10	10	10
	%Diff G1	43.776	262.743	-3.372	-20.290	233.824	0.000	28.571
4F	Mean	10.868f	6.310f	4.047	0.126	0.277c	0.012	0.097
	SD	2.513	1.333	1.334	0.076	0.102	0.004	0.051
	N	10	10	10	10	10	10	10
	%Diff G1	95.222	581.425	-7.158	-8.696	307.353	100.000	38.571

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.457	13.50	40.25	54.00	18.14	33.58	11.33
	SD	0.215	0.31	1.04	1.30	0.40	0.46	0.22
	N	10	10	10	10	10	10	10
2F	Mean	7.399	13.58	40.41	54.61	18.35	33.63	11.20
	SD	0.314	0.63	1.81	1.23	0.44	0.20	0.50
	N	10	10	10	10	10	10	10
	%Diff G1	-0.778	0.59	0.40	1.13	1.16	0.15	-1.15
3F	Mean	7.158	13.01a	38.78a	54.16	18.19	33.59	11.82a
	SD	0.163	0.38	1.11	0.74	0.38	0.51	0.42
	N	10	10	10	10	10	10	10
	%Diff G1	-4.010	-3.63	-3.65	0.30	0.28	0.03	4.32
4F	Mean	7.363	13.42	39.86	54.17	18.25	33.65	12.32c
	SD	0.319	0.38	1.20	1.82	0.60	0.28	0.35
	N	10	10	10	10	10	10	10
	%Diff G1	-1.261	-0.59	-0.97	0.31	0.61	0.21	8.74

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1155.8	202.09
	SD	112.7	31.48
	N	10	10
2F	Mean	970.3a	207.10
	SD	148.6	29.60
	N	10	10
	%Diff G1	-16.0	2.48
3F	Mean	1071.8	191.92
	SD	173.2	25.17
	N	10	10
	%Diff G1	-7.3	-5.03
4F	Mean	887.6c	184.22
	SD	142.2	35.06
	N	10	10
	%Diff G1	-23.2	-8.84

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-1443 96 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	9.192	1.204	7.520	0.198	0.072	0.022	0.178
	SD	0.687	0.588	0.796	0.090	0.037	0.004	0.070
	N	5	5	5	5	5	5	5
4M	Mean	12.290	1.372	10.320	0.308	0.098	0.026	0.164
	SD	3.447	0.595	2.822	0.086	0.023	0.015	0.036
	N	5	5	5	5	5	5	5
	%Diff G1	33.703	13.953	37.234	55.556	36.111	18.182	-7.865

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.610	14.40	40.98	53.92	18.92	35.06	13.16
	SD	0.643	1.23	2.97	2.15	1.15	0.89	0.86
	N	5	5	5	5	5	5	5
4M	Mean	7.990	14.62	42.56	53.34	18.36	34.44	14.04
	SD	0.566	0.58	1.93	1.93	0.67	0.71	0.29
	N	5	5	5	5	5	5	5
	%Diff G1	4.993	1.53	3.86	-1.08	-2.96	-1.77	6.69

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1003.8	242.88
	SD	187.0	47.23
	N	5	5
4M	Mean	1201.6	243.54
	SD	79.2	24.07
	N	5	5
	%Diff G1	19.7	0.27

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	4.554	0.776	3.488	0.124	0.094	0.006	0.066
	SD	1.476	0.260	1.492	0.025	0.023	0.005	0.015
	N	5	5	5	5	5	5	5
4F	Mean	4.053	0.573	3.228	0.125	0.065	0.003	0.058
	SD	1.543	0.096	1.327	0.097	0.034	0.005	0.029
	N	4	4	4	4	4	4	4
	%Diff G1	-11.012	-26.224	-7.468	0.806	-30.851	-58.333	-12.879

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.252	13.28	38.68	53.34	18.34	34.34	11.38
	SD	0.372	0.48	1.64	0.89	0.68	0.78	0.26
	N	5	5	5	5	5	5	5
4F	Mean	7.068	13.20	38.53	54.53	18.70	34.33	12.73c
	SD	0.189	0.36	1.44	1.21	0.36	0.56	0.29
	N	4	4	4	4	4	4	4
	%Diff G1	-2.544	-0.60	-0.40	2.22	1.96	-0.04	11.82

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-1443 96 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1080.2	165.32
	SD	181.5	43.83
	N	5	5
4F	Mean	1009.3	193.65
	SD	36.2	34.22
	N	4	4
	%Diff G1	-6.6	17.14

Table 7

Summary of Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	16.64	15.92	281.9
	SD	0.66	0.76	14.3
	N	10	10	10
2M	Mean	16.29	16.77	445.9c
	SD	0.40	0.75	30.9
	N	10	10	10
	%Diff G1	-2.10	5.34	58.2
3M	Mean	16.13	17.73c	550.4c
	SD	0.82	1.09	56.3
	N	9	9	9
	%Diff G1	-3.04	11.39	95.3
4M	Mean	16.24	18.75c	701.8c
	SD	0.56	1.01	39.3
	N	10	10	10
	%Diff G1	-2.40	17.78	149.0

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	16.92	16.04	214.3
	SD	0.48	1.04	23.9
	N	10	10	10
2F	Mean	16.99	15.93	327.4
	SD	0.50	0.59	41.1
	N	10	10	10
	%Diff G1	0.41	-0.69	52.8
3F	Mean	17.00	16.81	455.1c
	SD	0.45	0.74	48.5
	N	10	10	10
	%Diff G1	0.47	4.80	112.4
4F	Mean	17.65d	18.30f	508.9c
	SD	0.89	0.70	29.1
	N	10	10	10
	%Diff G1	4.31	14.09	137.5

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 7

Summary of Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	18.72	16.08	298.8
	SD	1.29	0.34	93.8
	N	5	5	5
4M	Mean	18.92	15.58	272.8
	SD	0.38	0.47	33.5
	N	5	5	5
	%Diff G1	1.07	-3.11	-8.7

Table 7

Summary of Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	18.04	15.54	201.8
	SD	0.62	1.42	17.3
	N	5	5	5
4F	Mean	17.40	14.98	194.5
	SD	1.10	0.81	27.7
	N	4	4	4
	%Diff G1	-3.55	-3.64	-3.6

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	90.0	32.6	115.6	2.0	414.5	0.063	13.6
	SD	22.9	4.1	21.7	0.0	229.2	0.016	2.1
	N	10	10	10	10	10	10	10
2M	Mean	79.0	38.8	119.2	2.0	290.2	0.051	12.9
	SD	21.7	6.8	13.9	0.0	221.2	0.026	1.7
	N	10	10	10	10	10	10	10
	%Diff G1	-12.2	19.0	3.1	0.0	-30.0	-19.048	-5.1
3M	Mean	101.1	42.4b	106.3	2.0	494.3	0.061	14.3
	SD	24.3	6.4	17.1	0.0	279.9	0.019	2.9
	N	10	10	10	10	10	10	10
	%Diff G1	12.3	30.1	-8.0	0.0	19.3	-3.175	5.1
4M	Mean	99.8	32.6	103.2	2.0	605.2	0.069	13.9
	SD	26.5	7.4	17.4	0.0	388.5	0.025	2.2
	N	10	10	10	10	10	10	10
	%Diff G1	10.9	0.0	-10.7	0.0	46.0	9.524	2.2

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	0.38	149.3	70.2	70.0	5.97	3.81	2.16
	SD	0.04	25.8	13.6	30.5	0.16	0.13	0.14
	N	10	10	10	10	10	10	10
2M	Mean	0.32b	127.1	61.6	66.8	5.91	3.58c	2.33
	SD	0.04	17.9	10.7	26.5	0.14	0.12	0.09
	N	10	10	10	10	10	10	10
	%Diff G1	-15.79	-14.9	-12.3	-4.6	-1.01	-6.04	7.87
3M	Mean	0.39	139.7	65.5	67.7	6.04	3.48c	2.56c
	SD	0.03	21.9	16.0	32.7	0.27	0.11	0.21
	N	10	10	10	10	10	10	10
	%Diff G1	2.63	-6.4	-6.7	-3.3	1.17	-8.66	18.52
4M	Mean	0.40	153.2	65.4	71.1	6.12	3.38c	2.74c
	SD	0.05	27.0	12.9	18.7	0.23	0.13	0.18
	N	10	10	10	10	10	10	10
	%Diff G1	5.26	2.6	-6.8	1.6	2.51	-11.29	26.85

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.77	10.52	7.71	142.3	5.31	102.9
	SD	0.16	0.22	0.47	1.3	0.41	1.2
	N	10	10	10	10	10	10
2M	Mean	1.55c	10.64	7.92	142.3	5.07	103.0
	SD	0.07	0.21	0.71	1.2	0.26	1.5
	N	10	10	10	10	10	10
	%Diff G1	-12.43	1.14	2.72	0.0	-4.52	0.1
3M	Mean	1.38c	10.61	7.82	141.7	5.30	102.2
	SD	0.11	0.38	0.64	0.9	0.24	1.4
	N	10	10	10	10	10	10
	%Diff G1	-22.03	0.86	1.43	-0.4	-0.19	-0.7
4M	Mean	1.24c	10.50	8.53a	141.1	5.44	101.0a
	SD	0.10	0.21	0.66	1.2	0.31	2.1
	N	10	10	10	10	10	10
	%Diff G1	-29.94	-0.19	10.64	-0.8	2.45	-1.8

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	93.3	31.2	61.1	2.0	381.2	0.081	13.9
	SD	22.0	5.8	16.0	0.0	250.1	0.037	1.4
	N	10	10	10	10	10	10	10
2F	Mean	103.3	31.3	61.8	2.0	501.1	0.060	16.0
	SD	14.9	5.1	11.8	0.0	235.6	0.015	2.5
	N	10	10	10	10	10	10	10
	%Diff G1	10.7	0.3	1.1	0.0	31.5	-25.926	15.1
3F	Mean	117.6	39.6	62.1	2.0	499.2	0.062	15.7
	SD	45.3	23.6	12.2	0.0	346.7	0.018	2.8
	N	10	10	10	10	10	10	10
	%Diff G1	26.0	26.9	1.6	0.0	31.0	-23.457	12.9
4F	Mean	116.6	47.1	69.0	2.0	470.7	0.098	16.0
	SD	28.6	31.4	14.7	0.0	390.8	0.029	2.4
	N	10	10	10	10	10	10	10
	%Diff G1	25.0	51.0	12.9	0.0	23.5	20.988	15.1

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	0.41	156.1	75.6	50.3	6.52	4.61	1.91
	SD	0.06	30.8	11.6	11.1	0.37	0.37	0.17
	N	10	10	10	10	10	10	10
2F	Mean	0.40	128.4	83.0	55.3	6.23	4.15b	2.08
	SD	0.05	22.4	22.7	30.3	0.29	0.30	0.20
	N	10	10	10	10	10	10	10
	%Diff G1	-2.44	-17.7	9.8	9.9	-4.45	-9.98	8.90
3F	Mean	0.47a	126.6	77.4	42.6	6.41	4.09b	2.32c
	SD	0.05	14.9	12.1	8.1	0.29	0.30	0.15
	N	10	10	10	10	10	10	10
	%Diff G1	14.63	-18.9	2.4	-15.3	-1.69	-11.28	21.47
4F	Mean	0.48a	134.6	67.7	52.0	6.47	4.03b	2.44c
	SD	0.06	13.7	22.5	16.9	0.44	0.35	0.13
	N	10	10	10	10	10	10	10
	%Diff G1	17.07	-13.8	-10.4	3.4	-0.77	-12.58	27.75

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.45	10.63	6.95	141.7	4.73	103.4
	SD	0.30	0.25	1.19	1.3	0.25	2.1
	N	10	10	10	10	10	10
2F	Mean	2.02	10.73	7.85	142.4	4.73	103.7
	SD	0.30	0.41	0.69	0.8	0.32	1.8
	N	10	10	10	10	10	10
	%Diff G1	-17.55	0.94	12.95	0.5	0.00	0.3
3F	Mean	1.77c	10.69	7.46	142.1	4.77	103.7
	SD	0.21	0.24	0.80	1.4	0.22	1.6
	N	10	10	10	10	10	10
	%Diff G1	-27.76	0.56	7.34	0.3	0.85	0.3
4F	Mean	1.65c	10.76	7.31	142.1	4.80	103.1
	SD	0.10	0.44	1.25	0.9	0.30	1.4
	N	10	10	10	10	10	10
	%Diff G1	-32.65	1.22	5.18	0.3	1.48	-0.3

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

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	101.2	60.4	132.8	2.0	496.8	0.090	18.0
	SD	37.7	9.8	21.7	0.0	438.4	0.034	2.7
	N	5	5	5	5	5	5	5
4M	Mean	77.0	36.4b	110.2	2.0	426.8	0.082	16.4
	SD	30.0	9.3	26.1	0.0	488.3	0.020	3.0
	N	5	5	5	5	5	5	5
	%Diff G1	-23.9	-39.7	-17.0	0.0	-14.1	-8.889	-8.9

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-1443 96 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	0.36	226.8	78.4	143.2	5.86	3.72	2.14
	SD	0.05	37.8	12.5	69.6	0.17	0.26	0.34
	N	5	5	5	5	5	5	5
4M	Mean	0.32	191.6	72.2	88.2	5.98	3.88	2.10
	SD	0.04	33.1	13.0	16.0	0.24	0.16	0.24
	N	5	5	5	5	5	5	5
	%Diff G1	-11.11	-15.5	-7.9	-38.4	2.05	4.30	-1.87

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.78	10.72	7.32	139.4	5.44	100.8
	SD	0.35	0.19	0.63	1.1	0.38	1.5
	N	5	5	5	5	5	5
4M	Mean	1.90	10.92	7.56	140.0	5.20	101.4
	SD	0.24	0.40	0.66	0.7	0.31	1.1
	N	5	5	5	5	5	5
	%Diff G1	6.74	1.87	3.28	0.4	-4.41	0.6

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	126.8	42.0	48.8	2.0	863.8	0.068	15.8
	SD	19.8	8.7	11.0	0.0	236.3	0.024	2.7
	N	5	5	5	5	5	5	5
4F	Mean	89.6a	39.4	57.2	2.0	197.2c	0.062	14.8
	SD	27.4	10.3	14.7	0.0	44.0	0.026	1.3
	N	5	5	5	5	5	5	5
	%Diff G1	-29.3	-6.2	17.2	0.0	-77.2	-8.824	-6.3

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-1443 96 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	137.8	74.2	73.4	6.40	4.58	1.82
	SD	0.04	25.8	11.2	44.0	0.31	0.36	0.11
	N	5	5	5	5	5	5	5
4F	Mean	0.40	144.8	77.6	51.2	6.30	4.38	1.92
	SD	0.07	18.7	19.5	8.5	0.41	0.39	0.08
	N	5	5	5	5	5	5	5
	%Diff G1	-4.76	5.1	4.6	-30.2	-1.56	-4.37	5.49

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	11.02	6.06	139.6	4.70	101.6
	SD	0.30	0.24	0.92	0.9	0.14	1.3
	N	5	5	5	5	5	5
4F	Mean	2.28	10.86	6.58	139.8	4.66	102.6
	SD	0.22	0.43	0.78	0.4	0.24	2.1
	N	5	5	5	5	5	5
	%Diff G1	-10.24	-1.45	8.58	0.1	-0.85	1.0

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	68.251	19.900
	SD	14.318	4.283
	N	10	10
2	Mean	166.674	28.669
	SD	39.974	16.938
	N	10	10
	% Diff (G1)	144	44
3	Mean	294.610 F	158.635 E
	SD	55.663	130.148
	N	10	10
	% Diff (G1)	332	697
4	Mean	467.607 F	1180.908 F
	SD	51.225	516.141
	N	10	10
	% Diff (G1)	585	5834

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-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	39.036	23.679
	SD	24.230	6.360
	N	10	10
2	Mean	130.096	32.994
	SD	33.274	21.332
	N	10	10
	% Diff (G1)	233	39
3	Mean	251.813 F	52.681
	SD	58.668	24.036
	N	10	10
	% Diff (G1)	545	122
4	Mean	449.381 F	261.184 F
	SD	93.459	158.723
	N	10	10
	% Diff (G1)	1E3	1003

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 4 - mRNA-1443 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	144.768	20.964
	SD	137.871	6.791
	N	5	5
4	Mean	88.570	36.180
	SD	22.372	15.887
	N	5	5
	% Diff (G1)	-39	73

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 4 - mRNA-1443 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	50.728	27.554
	SD	6.036	19.138
	N	5	5
4	Mean	58.860	36.956
	SD	5.834	19.806
	N	5	5
	% Diff (G1)	16	34

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-1443 96 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	144.712	48.938	21.000	18.972	20.558
	SD	190.687	77.310	21.734	19.162	20.142
	N	5	5	5	5	5
4	Mean	5.850	93.748	5.850	11.078	91.646
	SD	0.000	134.613	0.000	11.690	131.767
	N	5	5	5	5	5
	% Diff (G1)	-96	92	-72	-42	346

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-1443 96 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	5	5	5	5	5
4	Mean	176.000	176.000	176.000	444.630	176.000
	SD	0.000	0.000	0.000	371.335	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	153	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-1443 96 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	2.490	2.490	2.372	2.430
	SD	0.000	2.281	2.281	2.017	2.147
	N	5	5	5	5	5
4	Mean	2.710	2.710	3.052	3.828	1.470
	SD	2.773	2.773	3.537	3.356	0.000
	N	5	5	5	5	5
	% Diff (G1)	84	9	23	61	-40

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-1443 96 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	201.838	146.606	110.802	167.726	209.122
	SD	87.765	49.771	36.821	160.721	295.657
	N	5	5	5	5	5
4	Mean	170.262	222.820	308.492 d	484.112 a	100.256
	SD	42.451	102.577	198.023	149.175	23.377
	N	5	5	5	5	5
	% Diff (G1)	-16	52	178	189	-52

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-1443 96 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	5	5	5	5	5
4	Mean	5.850	5.850	5.850	5.850	5.850
	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

MCP-1 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	303.614	295.866	439.954	280.644	174.794
	SD	148.431	130.748	122.121	194.300	143.055
	N	5	5	5	5	5
4	Mean	465.994	328.254	467.394	450.566	70.500
	SD	102.423	151.067	103.422	103.609	0.000
	N	5	5	5	5	5
	% Diff (G1)	53	11	6	61	-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

IL-1β (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	33.063	15.046	5.850	16.698	16.956
	SD	54.425	20.563	0.000	24.257	24.834
	N	4	5	5	5	5
4	Mean	12.602	5.850	9.962	5.850	38.250
	SD	15.098	0.000	9.195	0.000	72.449
	N	5	5	5	5	5
	% Diff (G1)	-62	-61	70	-65	126

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-1443 96 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	317.472	176.000
	SD	0.000	0.000	0.000	316.341	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	80	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-1443 96 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	1.470	1.470	1.470	1.470
	SD	0.000	0.000	0.000	0.000	0.000
	N	4	5	5	5	5
4	Mean	1.470	1.470	1.470	3.856	1.470
	SD	0.000	0.000	0.000	3.267	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	162	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

IP-10 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	108.658	99.730	84.002	82.884	80.284
	SD	19.848	21.463	26.730	17.756	9.052
	N	4	5	5	5	5
4	Mean	122.778	196.752	522.986 d	566.746	87.108
	SD	21.355	172.662	359.718	487.335	39.147
	N	5	5	5	5	5
	% Diff (G1)	13	97	523	584	8

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-1443 96 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	5.850	5.850	5.850	9.546	5.850
	SD	0.000	0.000	0.000	8.265	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	63	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-1443 96 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	70.500	236.046	326.604	158.990	128.104
	SD	0.000	155.429	176.570	121.308	128.806
	N	4	5	5	5	5
4	Mean	519.054 b	440.528 d	544.322 a	439.100 d	70.500
	SD	251.811	76.306	90.075	64.682	0.000
	N	5	5	5	5	5
	% Diff (G1)	636	87	67	176	-45

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. 5002158

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 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 Mar 2017

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA 1443, 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

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)

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)

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Pathology Will be added 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)

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-1443

Supplier: Moderna Therapeutics, Inc.

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Batch (Lot) Number:	MTDP17017
Concentration:	Will be added by amendment
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.

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.

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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 to the Sponsor on dry ice (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

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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.

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1801913).

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.

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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
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.

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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.

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)

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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.

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

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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.

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-1443	10	200	0.05	10	10	-	-
3	mRNA-1443	30	200	0.15	10	10	-	-
4	mRNA-1443	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 thigh and Site 2 right thigh). 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

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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.

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

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of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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

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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 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.

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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 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

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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 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)
Project Leader
Cell Biology and Immunology
Southern Research
2000 Ninth Ave S
Birmingham AL 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
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	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	IFN-α 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) _____ Date: 08 Mar 2017

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SPONSOR APPROVAL

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

(b) (6)

(b) (6) Date: 09Mar17

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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 site used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration site 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 the 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 1

Test Facility Study No. 5002158

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 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: 08-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 as per sponsor request.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
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.
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 1443, 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:	**25 Aug 2017~~29 Aug 2017~~** (Last date data are collected from the study)
Animal Arrival:	08 Mar 2017
Initiation of Dosing:	**20 Mar 2017~~22 Mar 2017~~** (Male) **21 Mar 2017~~23 Mar 2017~~** (Female)
Completion of In-life:	**03 May 2017~~05 May 2017~~** (Main) **16 May 2017~~18 May 2017~~** (Recovery) (Last date of necropsy)
Unaudited Draft Report:	**13 Jul 2017~~17 Jul 2017~~**
Audited Draft Report:	**18 Aug 2017~~22 Aug 2017~~**
Final Report:	**25 Aug 2017~~29 Aug 2017~~**

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)

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)

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Pathology Will be added 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)

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-1443

Supplier: Moderna Therapeutics, Inc.

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Batch (Lot) Number:	MTDP17017
Concentration:	Will be added by amendment
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.

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.

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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 to the Sponsor on dry ice (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

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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.

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1801913).

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.

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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**~~**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
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.

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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.

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)

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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.

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

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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.

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-1443	10	200	0.05	10	10	-	-
3	mRNA-1443	30	200	0.15	10	10	-	-
4	mRNA-1443	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 thigh and Site 2 right thigh). 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

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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.

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

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of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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

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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 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	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.

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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 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 **allowed to clot at 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)
Project Leader
Cell Biology and Immunology
Southern Research
2000 Ninth Ave S
Birmingham AL 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
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	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	IFN-α 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)

Date: 15 mai 2017

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SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 14 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 site used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration site 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 the 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 2

Test Facility Study No. 5002158

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 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: 08-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 as per sponsor request.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
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.
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: 17-Mar-2017**
1. OBJECTIVE(S)	To correct a typographical error.
8.1. Test Item	To add the concentration of the bulk Test Item.
11.3. Environmental Acclimation	To correct due to schedule modification.
15.2. Laboratory Ivestigations (Cytokine Analysis)	To include clarification for sample processing.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1443, 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:	25 Aug 2017 (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:	13 Jul 2017
Audited Draft Report:	18 Aug 2017
Final Report:	25 Aug 2017

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)

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)

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Pathology Will be added 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)

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-1443

Supplier: Moderna Therapeutics, Inc.

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Batch (Lot) Number:	MTDP17017
Concentration:	**2.6 mg/mL**~~**Will be added by amendment**~~
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.

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.

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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 to the Sponsor on dry ice (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

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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.

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1801913).

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.

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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
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.

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11.3. Environmental Acclimation

A minimum acclimation period of **12**~~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.

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)

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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.

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

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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.

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-1443	10	200	0.05	10	10	-	-
3	mRNA-1443	30	200	0.15	10	10	-	-
4	mRNA-1443	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 thigh and Site 2 right thigh). 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

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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.

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

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of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a study plan amendment.

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

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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 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.

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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 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 allowed to clot at 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
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 AL 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
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	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	IFN-α 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: 17mar2017

(b) (6)

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SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 17 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 site used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration site 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 the 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 3

Test Facility Study No. 5002158

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 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: 08-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 as per sponsor request.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
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.
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: 17-Mar-2017**
1. OBJECTIVE(S)	To correct a typographical error.
8.1. Test Item	To add the concentration of the bulk Test Item.
11.3. Environmental Acclimation	To correct due to schedule modification.
15.2. Laboratory Ivestigations (Cytokine Analysis)	To include clarification for sample processing.
Amendment 3	**Date: 12-Apr-2017**
7. RESPONSIBLE PERSONNEL	To add the email address of the management contact and to assign a pathologist from PAI-FDK.
5.2. Test Facility-designated Subcontractor(s)	To add the histopathology phase as it will be audited by PAI-FDK.
8.4. Analysis of Test Item	To correct the storage conditions for samples transfer.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To correct the shipping contact information and to add a blood collection occasion on Day 29.
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-1443, 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:	25 Aug 2017 (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:	13 Jul 2017
Audited Draft Report:	18 Aug 2017
Final Report:	25 Aug 2017

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 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** **Will be added 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. (PAI-FDK)
15 Worman's Mill Ct., Suite I
Frederick, MD 21701, USA
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-1443
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17017
Concentration:	2.6 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

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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 ~~**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 to the Sponsor on dry ice (after completion of dosing).

Appendix 1

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 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.

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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. 1801913).

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.

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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 12 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.

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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).

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.

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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-1443	10	200	0.05	10	10	-	-
3	mRNA-1443	30	200	0.15	10	10	-	-
4	mRNA-1443	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 thigh and Site 2 right thigh). 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 allowed to clot at 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~~21 Firstfield Road~~
Suite **300~~100~~**
Rockville, MD 20850, USA~~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 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 AL 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
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	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	IFN-α 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: 12 Apr 2017

(b) (6) Date: 12 Apr 2017

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SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 12 Apr 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 site used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration site 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 the 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 4

Test Facility Study No. 5002158

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 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: 08-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 as per sponsor request.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
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.
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: 17-Mar-2017**
1. OBJECTIVE(S)	To correct a typographical error.
8.1. Test Item	To add the concentration of the bulk Test Item.
11.3. Environmental Acclimation	To correct due to schedule modification.
15.2. Laboratory Ivestigations (Cytokine Analysis)	To include clarification for sample processing.
Amendment 3	**Date: 12-Apr-2017**
7. RESPONSIBLE PERSONNEL	To add the email address of the management contact and to assign a pathologist from PAI-FDK.
5.2. Test Facility-designated Subcontractor(s)	To add the histopathology phase as it will be audited by PAI-FDK.
8.4. Analysis of Test Item	To correct the storage conditions for samples transfer.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To correct the shipping contact information and to add a blood collection occasion on Day 29.
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 4	**Date: 25-Apr-2017**
4. REGULATORY COMPLIANCE	To remove the ATA analysis.
7. RESPONSIBLE PERSONNEL	To remove the PI responsible for the ATA analysis.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To remove the terminal blood collections and to clarify that ATA samples will not be analyzed.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1443, 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:	25 Aug 2017 (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:	13 Jul 2017
Audited Draft Report:	18 Aug 2017
Final Report:	25 Aug 2017

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 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)

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. (PAI-FDK)
15 Worman's Mill Ct., Suite I
Frederick, MD 21701, USA
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-1443
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17017
Concentration:	2.6 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

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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 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 to the Sponsor on dry ice (after completion of dosing).

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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 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.

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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. 1801913).

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.

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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 12 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.

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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).

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.

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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-1443	10	200	0.05	10	10	-	-
3	mRNA-1443	30	200	0.15	10	10	-	-
4	mRNA-1443	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 thigh and Site 2 right thigh). 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 allowed to clot at 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:**~~

ATA samples will not be analyzed and will be discarded prior to report finalization, following Study Director approval.

~~**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.**~~

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~~**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 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 AL 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:

(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
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	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	IFN-α 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: 25 Apr 2017

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SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 25 Apr 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 site used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration site 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 the 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 5

Test Facility Study No. 5002158

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 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: 08-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 as per sponsor request.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
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.
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: 17-Mar-2017**
1. OBJECTIVE(S)	To correct a typographical error.
8.1. Test Item	To add the concentration of the bulk Test Item.
11.3. Environmental Acclimation	To correct due to schedule modification.
15.2. Laboratory Ivestigations (Cytokine Analysis)	To include clarification for sample processing.
Amendment 3	**Date: 12-Apr-2017**
7. RESPONSIBLE PERSONNEL	To add the email address of the management contact and to assign a pathologist from PAI-FDK.
5.2. Test Facility-designated Subcontractor(s)	To add the histopathology phase as it will be audited by PAI-FDK.
8.4. Analysis of Test Item	To correct the storage conditions for samples transfer.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To correct the shipping contact information and to add a blood collection occasion on Day 29.
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 4	**Date: 25-Apr-2017**
4. REGULATORY COMPLIANCE	To remove the ATA analysis.
7. RESPONSIBLE PERSONNEL	To remove the PI responsible for the ATA analysis.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To remove the terminal blood collections and to clarify that ATA samples will not be analyzed.
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.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1443, 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:	25 Aug 2017 (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:	13 Jul 2017
Audited Draft Report:	18 Aug 2017
Final Report:	25 Aug 2017

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 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 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)

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. (PAI-FDK)
15 Worman's Mill Ct., Suite I
Frederick, MD 21701, USA
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)

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-1443
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17017
Concentration:	2.6 **/ 2.5*** 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

*** Concentration based on Summary of Analysis (SoA) released on 16 Mars 2017 / Concentration based on SoA released on 30 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

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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 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 to the Sponsor on dry ice (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
800 Technology Sq, 8th Floor
Cambridge MA 02476

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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 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.

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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. 1801913).

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.

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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 12 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.

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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).

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.

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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)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1443	10 / **9.6**	200	0.05 / **0.048**	10	10	-	-
3	mRNA-1443	30 / **29**	200	0.15 / **0.145**	10	10	-	-
4	mRNA-1443	100 / **96**	200	0.5 / **0.48**	10	10	5	5

- : Not applicable

[a] **Values based on SoA issued on 16 Mars 2017 / Values based on SoA issued on 30 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 thigh and Site 2 right thigh). 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
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).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and allowed to clot at 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.

ATA samples will not be analyzed and will be discarded prior to report finalization, following Study Director approval.

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

Appendix 1

Birmingham AL 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:

(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
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	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	IFN-α 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: 29 Jun 2017

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SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 28 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 site used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration site 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 the 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 6

Test Facility Study No. 5002158

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 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: 08-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 as per sponsor request.
7. RESPONSIBLE PERSONNEL	To update the contact information of the ATA PI.
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.
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: 17-Mar-2017**
1. OBJECTIVE(S)	To correct a typographical error.
8.1. Test Item	To add the concentration of the bulk Test Item.
11.3. Environmental Acclimation	To correct due to schedule modification.
15.2. Laboratory Ivestigations (Cytokine Analysis)	To include clarification for sample processing.
Amendment 3	**Date: 12-Apr-2017**
7. RESPONSIBLE PERSONNEL	To add the email address of the management contact and to assign a pathologist from PAI-FDK.
5.2. Test Facility-designated Subcontractor(s)	To add the histopathology phase as it will be audited by PAI-FDK.
8.4. Analysis of Test Item	To correct the storage conditions for samples transfer.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To correct the shipping contact information and to add a blood collection occasion on Day 29.
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 4	**Date: 25-Apr-2017**
4. REGULATORY COMPLIANCE	To remove the ATA analysis.
7. RESPONSIBLE PERSONNEL	To remove the PI responsible for the ATA analysis.
15.3. Anti Therapeutic Antibody (ATA) Analysis	To remove the terminal blood collections and to clarify that ATA samples will not be analyzed.
Amendment 5	**Date: 29-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.
Amendment 6	
8.1. Test Item	To correct a typographical error.
13. EXPERIMENTAL DESIGN	To correct a typographical error.

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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-1443, 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:	25 Aug 2017 (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:	13 Jul 2017
Audited Draft Report:	18 Aug 2017
Final Report:	25 Aug 2017

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 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 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)

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. (PAI-FDK)
15 Worman's Mill Ct., Suite I
Frederick, MD 21701, USA
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)

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-1443
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17017
Concentration:	2.6 / 2.5* 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

* Concentration based on Summary of Analysis (SoA) released on 16 **March**~~**Mars**~~ 2017 / Concentration based on SoA released on 30 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

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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 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 to the Sponsor on dry ice (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
800 Technology Sq, 8th Floor
Cambridge MA 02476

Appendix 1

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 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.

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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. 1801913).

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.

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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 12 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.

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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).

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.

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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)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1443	10 / 9.6	200	0.05 / 0.048	10	10	-	-
3	mRNA-1443	30 / 29	200	0.15 / 0.145	10	10	-	-
4	mRNA-1443	100 / 96	200	0.5 / 0.48	10	10	5	5

- : Not applicable
[a] Values based on SoA issued on 16 **March**~~**Mars**~~ 2017 / Values based on SoA issued on 30 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 thigh and Site 2 right thigh). 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
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 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).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and allowed to clot at 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.

ATA samples will not be analyzed and will be discarded prior to report finalization, following Study Director approval.

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

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Southern Research
2000 Ninth Ave S
Birmingham AL 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.

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.

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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.

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.

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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.

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:

(b) (6)
Moderna Therapeutics
200 Technology Square, 3rd Floor
Cambridge, MA 02116

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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.

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
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	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

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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.

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	IFN-α data collection
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using

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	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 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.

Appendix 1

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.

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: 13 Sep 2017

Appendix 1

SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 13 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 site used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration site 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 the 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 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

- Due to a change in the date of initiation of dosing, food consumption was measured starting on Day -5 instead of Day -7 as required in the per Study Plan. This deviation has no impact on the study integrity since sufficient data were available for interpretation.

Postmortem and Pathology

- During necropsies of all recovery animals, the biceps femoris was submitted as a regular section of the muscle skeletal instead of the quadriceps due to a technical error. This deviation had no impact on the pathology evaluation since this tissue did not include the injection site.
- Some miscellaneous tissues were not available for microscopic evaluation. This deviation had no impact on the pathology evaluation since missing tissues were scattered in male and female groups.
- Tissues that were supposed to be microscopically evaluated were not available on slides and therefore, were not evaluated. Tissues are listed in the Individual Animal Data of the Pathology report as not present. This deviation had no impact on the study integrity since sufficient tissues were examined.

Appendix 2

Memorandum

moderna

To: (b) (6), Charles River Laboratory, Montréal ULC

From: (b) (6)

Date: 13Jun17

Subject: Revised mRNA concentration determination for mRNA-1443 reference standard lot MTDS16032, and subsequent revised final concentration of mRNA-1443 drug product lot MTDP17017

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 5002158. Both the original and revised Summary of Analysis documents reporting the concentration of MTDP17017 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-1443 is -4%, 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 5002158 were revised based on the updated concentration reported for the mRNA-1443 lot MTDP17017 (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-1443 Dose Levels based on Ref Standard MTDS16032(reference[2]) **and drug product lot MTDP17017** (reference[3])

Dose Group	Original Dose (ug)	Revised Dose (ug)
2	10	9.6
3	30	29
4	100	96

References

1. mRNA-1443 MTDP17017 DPAD-TM-00054.1 30May17
2. mRNA-1443 MTDS16032 DSAD-SOA-0008 13Apr17
3. mRNA-1443 MTDP17017 0.5ml Fill, T0, DPAD-SOA-0001v003 30May17

Approvals

Name/Title/Company/Role	Signature	Date

Appendix 2

Memorandum

moderna

(b) (6) (b) (6) 20 June 2017

Non-Clinical Sciences

Moderna Therapeutics

Indicates authorship of memo

(b) (6) (b) (6) 20 June 2017

Non-Clinical Sciences

Moderna Therapeutics

Indicates second person review of verifiable facts and calculations

Appendix 2

Memorandum
moderna

To: (b) (6), Charles River Laboratory, Montréal ULC

From: (b) (6)

Date: 13Jun17

Subject: Revised mRNA concentration determination for mRNA-1443 reference standard lot MTDS16032, and subsequent revised final concentration of mRNA-1443 drug product lot MTDP17017

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1. mRNA-1443 MTDP17017 DPAD-TM-00054.1 30May17
2. mRNA-1443 MTDS16032 DSAD-SOA-0008 13Apr17
3. mRNA-1443 MTDP17017 0.5ml Fill, T0, DPAD-SOA-0001v003 30May17

Approvals

Name/Title/Company/Role	Signature	Date

Appendix 2

Memorandum

moderna

(b) (6) (b) (6) 1 Sept 2017

Non-Clinical Sciences

Moderna Therapeutics

Indicates second person review of verifiable facts and calculations

Appendix 2

Number: DPAD-00019 Version: 3.0 Effective Date: 8/30/2017
mRNA-1443 MTDP17017 Concentration Adjustment Memo

Memorandum

moderna
messenger therapeutics

To: (b) (6)
From: (b) (6)
Cc: (b) (6)
Date: 30 Aug 2017
Subject: Revised mRNA concentration determination for mRNA-1443 reference standard lot MTDS16032, and subsequent revised final concentration of mRNA-1443 drug product lot MTDP17017.

(b) (4)

Appendix 2

Memorandum

moderna
messenger therapeutics

Appendix 2

Number: DPAD-00019 Version: 3.0 Effective Date: 8/30/2017
mRNA-1443 MTDP17017 Concentration Adjustment Memo

Memorandum

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Reference	Description
1	CX-005128 MTDS16032 SOA Version 2
2	CX-005128 MTDS16032 SOA Version 3
3	Drug Product SOA: DPAD-SOA-0001.2
4	Drug Product SOA: DPAD-SOA-0001.3
5	CX-005128 MTDS16032 SOA Version 4
6	Drug Product Target Adjustment Memo: DPAD-TM-044 Version 1
7	Drug Product Target Adjustment Memo DPAD-TM-054 Version 1
8	"Revised mRNA Concentration Determination for mRNA-1443 reference standard Lot MTDS16032, and subsequent revised final concentration of mRNA-1443 drug product lot MTDP17017," (b) (6)
9	Drug Product SOA: DPAD-SOA-0001.1

Appendix 2

Number: DPAD-00017 Version: 5.0 Effective Date: 8/30/2017
DPAD-SOA-0001_mRNA-1443 MTDP17017

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messenger therapeutics

200 Tech Square • Cambridge, MA 02139
phone 617-714-6500 • fax 617-583-1998

Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	30 Aug 2017
Revision	005
Product name	**mRNA-1443 Test Article**
Product description	mRNA-1443 LNP in 93mM Tris, 60mM NaCl, 7% PG
Lot No.	**MTDP 17017**
Drug Substance (API)	CX000479 Lot MTDS16032
Date of Manufacture	23-Feb-2017
Re-test Date	23-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	Sanger Sequencing	Macrogen	Sequence matches 100% of the coding region		Conforms
Total RNA Content	(b) (4)	2017_03_12-003	(b) (4)		
mRNA Purity	(b) (4)	2017_03_16-006	Report % Pre-Main Peak Area		(b) (4)
			Report % Post-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		(b) (4)
Lipid Content	UPLC-CAD	2017_03_12-002	Lipid	Conc. (mg/mL)	Conc. (mg/mL)
			SM-102	(b) (4)	

Appendix 2

Number: DPAD-00017 Version: 5.0 Effective Date: 8/30/2017
DPAD-SOA-0001_mRNA-1443 MTDP17017

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			Cholesterol	(b) (4)
			DSPC	
			PEG-DMG	
Lipid Impurities	UPLC-CAD	2017_03_12-002	Report Result RRT and %Area	RRT / % Area: (b) (4); Total Impurities: (b) (4)
pH	USP <791>	2017_03_16-005	(b) (4)	
Osmolality	USP <785>	2017_03_16-005	Report result	(b) (4)
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 MTDP17015. The analytical lab provider assumed these lots were to be combined for this test.

Appendix 2

Number: DPAD-00017 Version: 5.0 Effective Date: 8/30/2017
DPAD-SOA-0001_mRNA-1443 MTDP17017

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phone 617-714-6500 • fax 617-583-1998

Revision #	Change Details	Author
1.0	Introduction of a New Document	(b) (6)
2.0	Updated drug product concentration to reflect Drug Substance SoA v.03 (used for drug product calculation of concentration)	(b) (6)
3.0	Updated drug product concentration to reflect Drug Substance SoA v.04 (used for drug product calculation of concentration)	(b) (6)
4.0	Updated to include all other release test data	(b) (6)
5.0	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 impurity data	(b) (6)

Appendix 2

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Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	16 Mar 2017
Revision	001
Product\Test Article	mRNA-1443 (CMV 7) in 100 mM TRIS 60 mM NaCl 7% (w/v PG) 2.6 mg/mL , 0.5mL Fill volume
Lot No.	MTDP17017
Moderna Protocol	DPAD-PRO-0002
Drug Substance (API)	CX005282 Lot MTDS16032
Date of Manufacture	21 Feb 2017
Stability Initiation Date	13 Mar 2017
Stability Time Point	T=0, Release

Test	Method	Testing Reference	Target Attributes	Results
mRNA Content	(b) (4)	2017_03_12-003	(b) (4)	
Endotoxin	USP <85>	0317-022 (ACCI)		
Bioburden	USP <61>	949975-S01 (Nelson Labs)		

Author: (b) (6) (b) (6) 16 Mar 2017

Data reviewed: (b) (6) (b) (6) ate 16 Mar 2017

Data generated in accordance with standard Moderna Therapeutics laboratory Practices and have been verified for accuracy

Appendix 2

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Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	30 May 2017
Revision	003
Product\Test Article	mRNA-1443 (CMV 7) in 100 mM TRIS 60 mM NaCl 7% (w/v PG) 2.4 mg/mL , 0.5mL Fill volume
Lot No.	MTDP17017
Moderna Protocol	DPAD-PRO-0002
Drug Substance (API)	CX000479 Lot MTDS16032
Date of Manufacture	23 Feb 2017
Stability Initiation Date	13 Mar 2017
Stability Time Point	T=0, Release

Test	Method	Testing Reference	Target Attributes	Results
mRNA Content	(b) (4)	2017_03_12-003	(b) (4)	
Endotoxin	USP <85>	0317-022 (ACCI)		
Bioburden	USP <61>	949975-S01 (Nelson Labs)		

*Original reported results was (b) (4) results changes with the updated Drug Substance SOA v 3.

Author: (b) (6) (b) (6) Date: 31 May 2017

Data reviewed: (b) (6) Date: 31-MAY-2017

Revision	Date	Description
1	17 Mar 2017	Original
2	03Apr2017	Concentration updated to reflect Drug Substance SoA v 3 (that was used for reference standard)
3	30May2017	Concentration updated to reflect Drug Substance SoA v 4 (that was used for reference standard)

Data generated in accordance with standard Moderna Therapeutics laboratory Practices and have been verified for accuracy

Appendix 2

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Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	15 Jun 2017
Revision	004
Product name	**mRNA-1443 Test Article**
Product description	mRNA-1443 LNP in 100mM Tris, 60mM NaCl, 7% PG
Lot No.	**MTDP 17017**
Drug Substance (API)	CX000479 Lot MTDS16032
Date of Manufacture	23-Feb-2017
Re-test Date	23-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	Sanger Sequencing	Outsourced	Sequence matches standard	Conforms
mRNA Content	(b) (4)	2017_03_12-003	(b) (4)	
mRNA Purity	(b) (4)	2017_03_16-006	(b) (4)	
% Encapsulation	(b) (4)	2017_03_12-007		
Particle Size	Dynamic Light Scattering	2017_03_12-005		
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 (b) (4); Total Impurity (% Area) — Report	**Lipid** / **Concentration (mg/mL)**: SM102, Cholesterol, DSPC, PEG-DMG, Total Impurity (% Area) (b) (4)

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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: (b) (4) / Target Number of Particles/mL: (b) (4)	Size: (b) (4) / *Number of Particles/mL: (b) (4)
Bioburden	USP <61>	Study Number 949975-S01	TAMC (b) (4) / TYMC (b) (4)	TAMC (b) (4) / TYMC (b) (4)

*Reported value is a pooled result with MTDP17015. The analytical lab provider assumed these lots were to be combined for this test.

Data Approved: (b) (6) (b) (6) **Date:** 22Jun2017

Appendix 3

FINAL REPORT

Study Phase: Analytical Chemistry

Test Facility Study No. 5002158

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)

Page 1 of 33

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-1443.

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 and by Dynamic Light Scattering (DLS) for particle size analysis.

The dose formulations were within specification, except for Day 1, Group 2 and Group 3. 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-1443 in dose formulations (phosphate-buffered saline (PBS) pH 7.2) in the bulk test item from Study 5002158.

For the work detailed in this report, the analytical phase experimental start date was 22 Mar 2017, and the analytical phase experimental completion date was 08 May 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 and particle size analysis.

At the end of the study dosing phase, one unopened vial of test item was transferred for concentration and particle size analysis.

Appendix 3

4. MATERIALS AND METHODS

4.1. Materials

4.1.1. Reference Standard

Identification:	CX-000479 mRNA
Physical Description:	Clear, colorless solution
Batch/Lot No.:	MTDS16032
Concentration:	2.47 mg/mL / 2.19 mg/mL (used for calculations) *
Retest Date:	Nov 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-1443
Physical Description:	0.5 mL per vial, white to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP17017
Concentration:	2.6 mg/mL / 2.5 mg/mL (used for calculations) **
Date of manufacture:	23 Feb 2017
Retest Date:	23 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.5002158.SP.03 (Appendix 1) and was previously validated under Study Nos. 1801913. Concentration stability data were generated by the department of Analytical Chemistry, Charles River, CR MTL for 1 day, 5 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 0.0100 – 2.50 mg/mL, under Study No. 1801913.

The method for particle size analysis is documented in Analytical Procedure AP.5002158.DLS.02 (Appendix 1).

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, except for Day 1, Group 2 (mean: 126%, respectively); therefore as part the the investigation the retention samples were analyzed and confirmed the initial results. It was concluded that the concentration for Day 1, Group 2 formulations was out of specification. 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 and the particle size was measured. Concentration and particle size results were consistent with the initial Certificate of Analysis provided by the Sponsor. Results are presented in Table 2 and Table 3.

6. CONCLUSION

The dose formulations were within specification, except for Day 1, Group 2. 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) _____ 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 (20 Mar 2017)	1	(b) (4)	Middle	(b) (4)	-	-
					-	
			Mean		-	-
	2		Top	(b) (4)	(b) (4)	
			Middle			
			Bottom			
			Mean			
	3		Top			
			Middle			
			Bottom			
			Mean			
	4		Top			
			Middle			
			Bottom			
			Mean			
Day 1 (20 Mar 2017) (Retentions)	2		Top			
			Middle			
			Bottom			
			Mean			
(b) (4)						

[a] Re-calculated theoretical dose concentration as per SoA issued on 31 May 2017.
[b] Out of acceptance criteria.

Appendix 3

Table 1 Study Samples - Concentration and Homogeneity (Cont'd)

Occasion (Sampling Date)	Group	Theoretical Concentration (mg/mL)	Sampling Location	Measured Concentration (mg/mL)	Percent of Theoretical	RSD (%)
Day 1 (20 Mar 2017) (Retentions) [b]	3	(b) (4)	Top	(b) (4)		(b) (4)
			Middle			
			Bottom			
			Mean			
Day 43 (02 May 2017)	1		Middle			-
			Mean			
	2		Middle			-
			Mean			
	3		Middle			-
			Mean			
	4		Middle			-
			Mean			

ND = None detected.

[a] Re-calculated theoretical dose concentration as per SoA issued on 31 May 2017.

[b] Retention samples analyzed since initial results were out of acceptance criteria; re-processed results using latest SoA values were within acceptance criteria.

Appendix 3

Table 2 Bulk Test Item - Concentration

Occasion (Analysis Date)	Theoretical Concentration (mg/mL)	Measured Concentration (mg/mL)	Percent of Theoretical	Mean Measured Concentration (mg/mL)
End of study (08 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	% RSD	Mean Measured Diameter (nm)
End of study (08 May 2017)	(b) (4)					

[a] % Difference between duplicate was not within 5%; therefore all four measurements were reported.

Appendix 3

Appendix 1
Analytical Procedures

Appendix 3

Analytical Procedure (AP.5002158.SP.03)

Determination of mRNA-1443 in Dose Formulations by Ion Exchange High Performance Chromatography Using Ultraviolet/Visible Detection

Reference Standard, Reference Material and Vehicle

Reference Standard	CX-000479 mRNA
Lot number	MTDS16032
Concentration (actual)	2.19 mg/mL
Reference material	mRNA-1443
Description	White dispersion in lipid nanoparticles
Lot number	MTDP17017
Concentration (nominal)	2.5 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 1801913.

Appendix 3

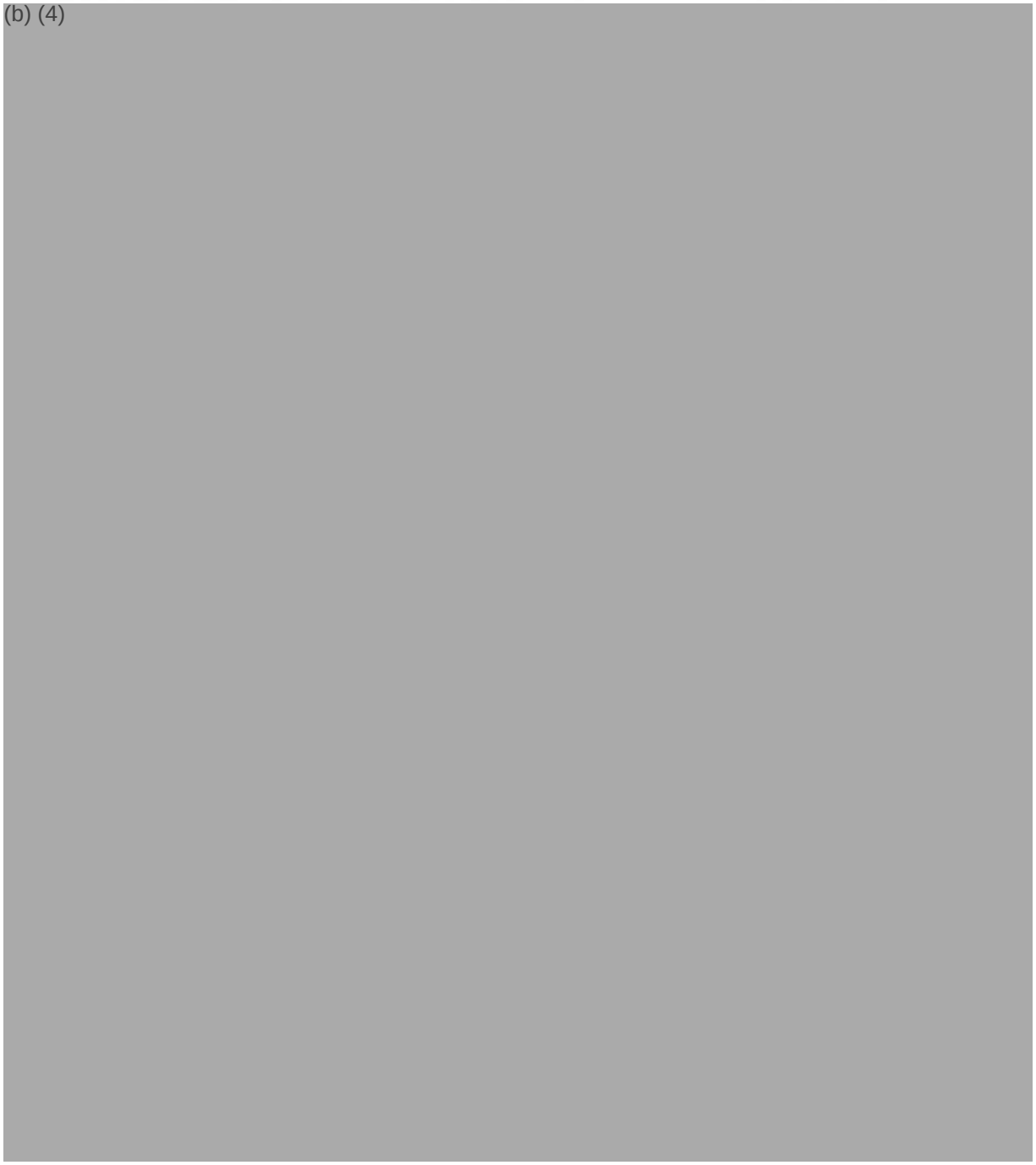
(b) (4)

Appendix 3

(b) (4)

Appendix 3

(b) (4)

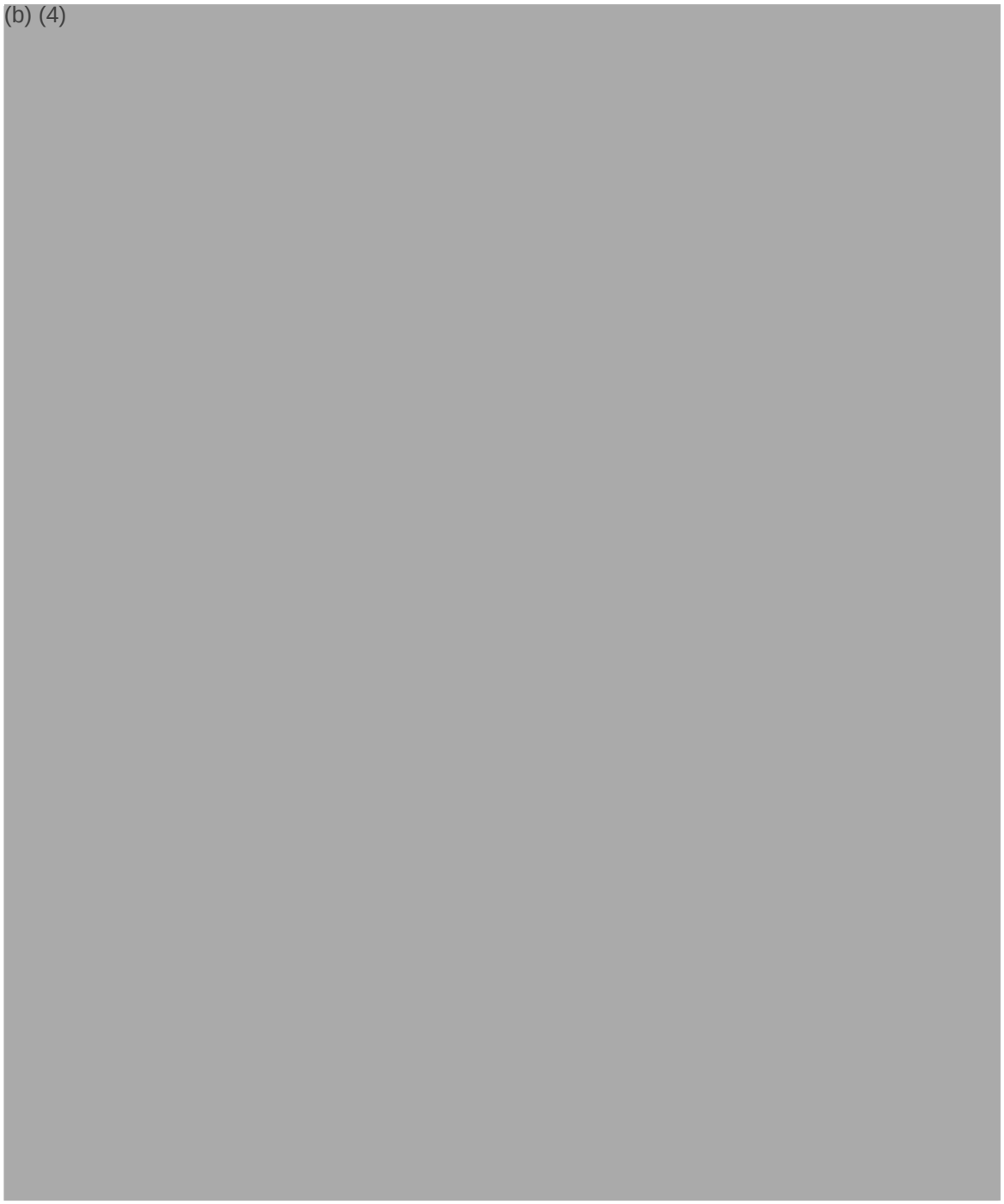


Appendix 3

(b) (4)

Appendix 3

(b) (4)



Appendix 3

(b) (4)

Acceptance criteria

Unless specified in the following or in the Study Plan, refer to SOP CAD-002 and SOP CAD-003 for acceptance criteria.

Appendix 3

AP Version Control

First update:
- Updated actual concentration of the reference standard and reference material as per latest certificate of analysis; updated concentrations throughout the AP accordingly.
- Updated sample concentrations in Table 3 and 4 as per Study Plan amendment 05.
- Corrected the sonication time for the bulk test item analysis.
- Included all missing expiry periods.

Second update:
- Included missing expiry period for standards.

Verified by (b) (6) Date 07 Jul 2017

Approved by Date 07 Jul 2017

Authorized b Date 07 Jul 2017

Scientific Director

Appendix 3

Analytical Procedure (AP.5002158.DLS.02)

Determination of the Particle Size Distribution of mRNA-1443 Drug Product by Dynamic Light Scattering (DLS) using Wyatt DynaPro NanoStar.

Bulk Test Item

Identity	mRNA-1443
Description	White dispersion in lipid nanoparticles
Lot number	MTDP17017
Concentration (nominal)	2.5 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

Analytical Procedure (AP.5002158.DLS.02)

Instrument Parameters for Sample Reading

Save all settings as a preset on location D:\Dynamics\Projects\5002158.

(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 (b) (6) Date 30 Jun 2017

Approved by (b) (6) Date 30 Jun 2017

Authorized by (b) (6) Date 30 Jun 2017

Scientific Director ☑

Appendix 3

Appendix 2
Certificates of Analysis

Appendix 3

Document Number: DSAD-SOA-0008 Version: 4.0 Final Date: 13 Apr 2017
CX-000479 MTDS16032 SoA

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SUMMARY OF ANALYSIS

Sample Description:	**CX-000479 mRNA** (GLP tox enabling batch)
mRNA length:	(b) (4)
SCC:	33.86 µg/mL
Plasmid ID:	PL-012371
Lot or Batch No:	**MTDS16032**
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	November 2016
Date of Analysis:	November 2016
Storage:	Shipping Temperature: ≤ -15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	November 2017

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Appearance	SOP-0045, v1.0	Clear, colorless solution, no visible particulates	Clear, colorless solution, no visible particulates	2016_12_14-048-(b) (6)
Identity	RT/Sanger Sequencing TSOP134.03	Sequence matches 100% description of the coding region	Sequence matches 100% description of the coding region	209-TSOP134-144.00
Total RNA content	DSAD-TM-0019*	(b) (4)		2017_02_22-019-(b) (6)
Purity	DSAD-TM-0010			2016_12_14-048-(b) (6)
Product related impurities	DSAD-TM-0010	Report % Pre-main peak % Post-main areas	(b) (4)	2016_12_14-048-(b) (6)
pH	SOP-0046, v1.0	(b) (4)		2016_12_14-048-(b) (6)
Residual DNA template	qPCR TSOP344.01			209-TSOP344-137.00 (MTDS 16032)

CX-000479 Page 1 of 2 version 04

Appendix 3

Document Number: DSAD-SOA-0008 Version: 4.0 Final Date: 13 Apr 2017
CX-000479 MTDS16032 SoA

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Residual total protein	SOP-0182, v0.1	(b) (4)	2016_11_28-033-(b) (6)
Residual solvents TEA	SOP-0185, v0.1	Report results	2016_11_28-004-(b) (6)
IPA	SOP-0183, v0.1		2016_11_28-004-(b) (6)
Ethanol	SOP-0183, v0.1		2016_11_28-004-(b) (6)
Hexylene glycol	SOP-0184, v0.1		2016_12_06-019-(b) (6)
% Poly A tailed RNA (% Tailless RNA)	DSAD-TM-0013	Report % main peak area	2016_12_14-048-(b) (6)
% 5' Capped	DSAD-TM-0021	(b) (4)	2016_11_30-006-(b) (6)
Bacterial Endotoxins	USP<85>		Result provided by PD
Bioburden	USP<61>		16-12798

(b) (4)
(b) (4) (Reference: 2017_02_22-019 (b) (6)

Signatures:

(b) (6)
Generated by: (b) (6) 12 Apr 17 Date:

(b) (6)
Reviewed by: (b) (6) 12 APR 2017 Date:

Appendix 3

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SUMMARY OF ANALYSIS

Sample Description:	**CX-000479 mRNA** (GLP tox enabling batch)
Lot or Batch No:	MTDS16032
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	November 2016
Date of Analysis:	November 2016
Storage:	Shipping Temperature: ≤ 15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	November 2017

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Appearance	SOP-0045, v1.0	Clear, colorless solution, no visible particulates	Clear, colorless solution, no visible particulates	2016_12_14-048-(b) (6)
Identity	RT/Sanger Sequencing TSOP134.03	Sequence matches 100% description of the coding region	Sequence matches 100% description of the coding region	209-TSOP134-144.00
Total RNA content	DSAD-TM-0019*	(b) (4)		2017_02_22-019-(b) (6)
Purity	SOP-0067, v1.0 (Capillary electrophoresis)			2016_12_14-048-(b) (6)
Product related impurities	SOP-0067, v1.0 (Capillary electrophoresis)	Report % Pre-main peak % Post-main areas	(b) (4)	2016_12_14-048-(b) (6)
pH	SOP-0046, v1.0	(b) (4)		2016_12_14-048-(b) (6)
Residual DNA template	qPCR TSOP344.01			209-TSOP344-137.00 (MTDS 16032)
Residual total protein	SOP-0182, v0.1			2016_11_28-033-(b) (6)

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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_11_28-004-(b) (6) 2016_11_28-004-(b) (6) 2016_11_28-004-(b) (6) 2016_12_06-019-(b) (6)
% Poly A tailed RNA (% Tailless RNA)	SOP-0089, v0.3 (RP-HPLC)	Report % main peak area	(b) (4)	2016_12_14-048-(b) (6)
% 5' Capped	SOP-0123, v0.1	(b) (4)		2016_11_30-006-(b) (6)
Bacterial Endotoxins	USP<85>			Result provided by PD
Bioburden	USP<61>			16-12798

(b) (4)
(b) (4)
(Reference: 2017_02_22-019 (b) (6)

Signatures:

(b) (6)
Generated by: (b) (6)
17 Mar 17
Date:

(b) (6)
Reviewed by: (b) (6)
17 MAR 2017
Date:

CX-000479 Page 2 of 2 version 03

Appendix 3

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Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	16 Mar 2017
Revision	001
Product\Test Article	mRNA-1443 (CMV 7) in 100 mM TRIS 60 mM NaCl 7% (w/v PG) 2.6 mg/mL , 0.5mL Fill volume
Lot No.	MTDP17017
Moderna Protocol	DPAD-PRO-0002
Drug Substance (API)	CX005282 Lot MTDS16032
Date of Manufacture	21 Feb 2017
Stability Initiation Date	13 Mar 2017
Stability Time Point	T=0, Release

Test	Method	Testing Reference	Target Attributes	Results
mRNA Content	(b) (4)	2017_03_12-003	(b) (4)	
Endotoxin	USP <85>	0317-022 (ACCI)		
Bioburden	USP <61>	949975-S01 (Nelson Labs)		

Author: (b) (6) (b) (6) 8 Mar 2017

Data reviewed: (b) (6) (b) (6) Date 16 Mar 2017

Data generated in accordance with standard Moderna Therapeutics laboratory Practices and have been verified for accuracy

Doc: DPAD-SOA-0001 *Page 1 of 1*

Appendix 3

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Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	30 May 2017
Revision	003
Product\Test Article	mRNA-1443 (CMV 7) in 100 mM TRIS 60 mM NaCl 7% (w/v PG) 2.4 mg/mL , 0.5mL Fill volume
Lot No.	MTDP17017
Moderna Protocol	DPAD-PRO-0002
Drug Substance (API)	CX000479 Lot MTDS16032
Date of Manufacture	23 Feb 2017
Stability Initiation Date	13 Mar 2017
Stability Time Point	T=0, Release

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)		

*Original reported results (b) , results changes with the updated Drug Substance SOA v 3.

Author: (b) (6) (b) (6) May 2017

Data reviewed: (b) (6) May-2017

Revision	Date	Description
1	17 Mar 2017	Original
2	03Apr2017	Concentration updated to reflect Drug Substance SoA v 3 (that was used for reference standard)
3	30May2017	Concentration updated to reflect Drug Substance SoA v 4 (that was used for reference standard)

Data generated in accordance with standard Moderna Therapeutics laboratory Practices and have been verified for accuracy

Doc: DPAD-SOA-0001 *Page 1 of 1*

Appendix 3

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Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	15 Jun 2017
Revision	004
Product name	**mRNA-1443 Test Article**
Product description	mRNA-1443 LNP in 100mM Tris, 60mM NaCl, 7% PG
Lot No.	**MTDP 17017**
Drug Substance (API)	CX000479 Lot MTDS16032
Date of Manufacture	23-Feb-2017
Re-test Date	23-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	Sanger Sequencing	Outsourced	Sequence matches standard	Conforms
mRNA Content	(b) (4)	2017_03_12-003	(b) (4)	
mRNA Purity	(b) (4)	2017_03_16-006	(b) (4)	Peak / % Area Main (b) (4) Pre Post
% 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	(b) (4)
Lipid	UPLC-CAD	2017_03_12-002	Lipid / Target Concentration (mg/mL) SM102 (b) (4) Cholesterol DSPC PEG-DMG Total Impurity (% Area) Report	Lipid / Concentration (mg/mL) SM102 (b) (4) Cholesterol DSPC PEG-DMG Total Impurity (% Area)

Doc: DPAD-SOA-0001.4 *Page 1 of 2*

Appendix 3

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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	Size	*Number of Particles/mL	
			(b) (4)				
Bioburden	USP <61>	Study Number 949975-S01		(b) (4)		(b) (4)	
			TAMC		TAMC		
			TYMC		TYMC		

*Reported value is a pooled result with MTDP17015. The analytical lab provider assumed these lots were to be combined for this test.

Data Approved: (b) (6) (b) (6) Date: 22Jun2017

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

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 (µg/dose)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 4

Individual Animal Mortality

5002158

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	02MAY2017	12:16	.	.	TERM
			1002	1001	44	7	02MAY2017	12:16	.	.	TERM
			1003	1001	44	7	02MAY2017	13:33	.	.	TERM
			1004	1004	44	7	02MAY2017	13:56	.	.	TERM
			1005	1004	44	7	02MAY2017	14:50	.	.	TERM
			1006	1004	44	7	02MAY2017	15:18	.	.	TERM
			1007	1007	44	7	02MAY2017	16:14	.	.	TERM
			1008	1007	44	7	02MAY2017	18:12	.	.	TERM
			1009	1009	44	7	02MAY2017	18:50	.	.	TERM
			1010	1009	44	7	02MAY2017	19:33	.	.	TERM
			1011	1011	57	9	15MAY2017	9:25	.	.	REC
			1012	1011	57	9	15MAY2017	10:21	.	.	REC
			1013	1011	57	9	15MAY2017	11:13	.	.	REC
			1014	1014	57	9	15MAY2017	13:36	.	.	REC
			1015	1014	57	9	15MAY2017	14:33	.	.	REC
1	0 ug/dose	Female	1501	1501	44	7	03MAY2017	11:46	.	.	TERM
			1502	1501	44	7	03MAY2017	11:45	.	.	TERM
			1503	1501	44	7	03MAY2017	13:00	.	.	TERM
			1504	1504	44	7	03MAY2017	13:04	.	.	TERM
			1505	1504	44	7	03MAY2017	14:13	.	.	TERM
			1506	1504	44	7	03MAY2017	14:18	.	.	TERM
			1507	1507	44	7	03MAY2017	15:18	.	.	TERM
			1508	1507	44	7	03MAY2017	15:35	.	.	TERM
			1509	1509	44	7	03MAY2017	17:52	.	.	TERM
			1510	1509	44	7	03MAY2017	18:12	.	.	TERM
			1511	1511	57	9	16MAY2017	8:42	.	.	REC
			1512	1511	57	9	16MAY2017	9:29	.	.	REC
			1513	1511	57	9	16MAY2017	10:14	.	.	REC
			1514	1514	57	9	16MAY2017	11:00	.	.	REC
			1515	1514	57	9	16MAY2017	13:43	.	.	REC
2	9.6 ug/dose	Male	2001	2001	44	7	02MAY2017	13:13	.	.	TERM
			2002	2001	44	7	02MAY2017	13:31	.	.	TERM
			2003	2001	44	7	02MAY2017	14:29	.	.	TERM
			2004	2004	44	7	02MAY2017	14:58	.	.	TERM
			2005	2004	44	7	02MAY2017	15:54	.	.	TERM

Appendix 4

Individual Animal Mortality

5002158

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
2	9.6 ug/dose	Male	2006	2004	44	7	02MAY2017	17:49	.	.	TERM
			2007	2007	44	7	02MAY2017	18:29	.	.	TERM
			2008	2007	44	7	02MAY2017	19:15	.	.	TERM
			2009	2009	44	7	02MAY2017	19:53	.	.	TERM
			2010	2009	44	7	02MAY2017	20:28	.	.	TERM
2	9.6 ug/dose	Female	2501	2501	44	7	03MAY2017	12:45	.	.	TERM
			2502	2501	44	7	03MAY2017	12:46	.	.	TERM
			2503	2501	44	7	03MAY2017	13:56	.	.	TERM
			2504	2504	44	7	03MAY2017	13:59	.	.	TERM
			2505	2504	44	7	03MAY2017	15:01	.	.	TERM
			2506	2504	44	7	03MAY2017	15:17	.	.	TERM
			2507	2507	44	7	03MAY2017	17:35	.	.	TERM
			2508	2507	44	7	03MAY2017	17:52	.	.	TERM
			2509	2509	44	7	03MAY2017	18:45	.	.	TERM
			2510	2509	44	7	03MAY2017	19:09	.	.	TERM
3	29 ug/dose	Male	3001	3001	44	7	02MAY2017	12:55	.	.	TERM
			3002	3001	44	7	02MAY2017	13:04	.	.	TERM
			3003	3001	44	7	02MAY2017	14:09	.	.	TERM
			3004	3004	44	7	02MAY2017	14:38	.	.	TERM
			3005	3004	44	7	02MAY2017	15:34	.	.	TERM
			3006	3004	44	7	02MAY2017	16:03	.	.	TERM
			3007	3007	44	7	02MAY2017	18:09	.	.	TERM
			3008	3007	44	7	02MAY2017	18:55	.	.	TERM
			3009	3009	44	7	02MAY2017	19:32	.	.	TERM
			3010	3009	44	7	02MAY2017	20:11	.	.	TERM
3	29 ug/dose	Female	3501	3501	44	7	03MAY2017	12:26	.	.	TERM
			3502	3501	44	7	03MAY2017	12:26	.	.	TERM
			3503	3501	44	7	03MAY2017	13:35	.	.	TERM
			3504	3504	44	7	03MAY2017	13:42	.	.	TERM
			3505	3504	44	7	03MAY2017	14:44	.	.	TERM
			3506	3504	44	7	03MAY2017	14:54	.	.	TERM
			3507	3507	44	7	03MAY2017	17:16	.	.	TERM
			3508	3507	44	7	03MAY2017	17:31	.	.	TERM
			3509	3509	44	7	03MAY2017	18:28	.	.	TERM

Appendix 4

Individual Animal Mortality

5002158

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
3	29 ug/dose	Female	3510	3509	44	7	03MAY2017	18:51	.	.	TERM
4	96 ug/dose	Male	4001	4001	44	7	02MAY2017	12:37	.	.	TERM
			4002	4001	44	7	02MAY2017	12:42	.	.	TERM
			4003	4001	44	7	02MAY2017	13:51	.	.	TERM
			4004	4004	44	7	02MAY2017	14:17	.	.	TERM
			4005	4004	44	7	02MAY2017	15:12	.	.	TERM
			4006	4004	44	7	02MAY2017	15:39	.	.	TERM
			4007	4007	44	7	02MAY2017	17:48	.	.	TERM
			4008	4007	44	7	02MAY2017	18:35	.	.	TERM
			4009	4009	44	7	02MAY2017	19:10	.	.	TERM
			4010	4009	44	7	02MAY2017	19:50	.	.	TERM
			4011	4011	57	9	15MAY2017	9:54	.	.	REC
			4012	4011	57	9	15MAY2017	10:48	.	.	REC
			4013	4011	57	9	15MAY2017	13:12	.	.	REC
			4014	4014	57	9	15MAY2017	14:03	.	.	REC
			4015	4014	57	9	15MAY2017	14:58	.	.	REC
4	96 ug/dose	Female	4501	4501	44	7	03MAY2017	12:06	.	.	TERM
			4502	4501	44	7	03MAY2017	12:07	.	.	TERM
			4503	4501	44	7	03MAY2017	13:17	.	.	TERM
			4504	4504	44	7	03MAY2017	13:23	.	.	TERM
			4505	4504	44	7	03MAY2017	14:29	.	.	TERM
			4506	4504	44	7	03MAY2017	14:36	.	.	TERM
			4507	4507	44	7	03MAY2017	15:31	.	.	TERM
			4508	4507	44	7	03MAY2017	17:10	.	.	TERM
			4509	4509	44	7	03MAY2017	18:10	.	.	TERM
			4510	4509	44	7	03MAY2017	18:32	.	.	TERM
			4511	4511	57	9	16MAY2017	9:05	.	.	REC
			4512	4511	57	9	16MAY2017	9:51	.	.	REC
			4513	4511	57	9	16MAY2017	10:37	.	.	REC
			4514	4514	57	9	16MAY2017	11:24	.	.	REC
			4515	4514	57	9	16MAY2017	14:08	.	.	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 (µg/dose)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11 Vet Aid	-1 DE	7 DE	14 DE	21 DE	28 DE
1	m	1001	Skin, Scab	Cranium	.	.	.	.	X	.
			Fur, Thin Cover	Cranium	.	.	.	.	X	X
		1003	Fur, Staining, Red	Periorbital, Left	.	.	.	.	.	.
			Fur, Thin Cover	Urogenital	.	.	.	X	.	.
			Fur, Thin Cover	Scrotum	.	.	.	X	.	.
		1004	Fur, Staining, Red	Muzzle	.	.	.	.	X	X
		1007	Fur, Staining, Red	Muzzle	.	.	.	X	X	X
			Pinna Partly Missing	Right	X	.	.	.	.	.
		1008	Skin, Scab	Hindlimb, Right	.	.	.	.	.	.
		1009	Skin, Scab	Tail	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	X	X	.
		1010	Skin, Scab	Prepuce	.	X	.	.	.	.
		1011	Fur, Staining, Black	Periorbital, Right	.	X	X	X	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
		1012	Skin, Scab	Hindlimb, Left	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	X	X	.	.	X
		1013	Fur, Staining, Red	Muzzle	.	.	.	X	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
		1014	Skin, Scab	Inguinal, Left	.	.	.	.	.	X
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	.

Severity Codes: X = Present; 9 = Red

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 Unsc PreRx	35 DE	42 DE	44 DE	49 DE	56 DE
1	m	1001	Skin, Scab	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
		1003	Fur, Staining, Red	Periorbital, Left	.	.	X	.	.	.
			Fur, Thin Cover	Urogenital	.	.	.	.	.	.
			Fur, Thin Cover	Scrotum	.	.	.	.	.	.
		1004	Fur, Staining, Red	Muzzle	.	.	.	.	.	.
		1007	Fur, Staining, Red	Muzzle	.	.	.	.	.	.
			Pinna Partly Missing	Right	.	X	X	X	.	.
		1008	Skin, Scab	Hindlimb, Right	.	X	X	X	.	.
		1009	Skin, Scab	Tail	.	X	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.
		1010	Skin, Scab	Prepuce	.	.	.	.	.	.
		1011	Fur, Staining, Black	Periorbital, Right	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
		1012	Skin, Scab	Hindlimb, Left	.	X	.	.	.	.
			Fur, Staining, Red	Muzzle	.	X	X	.	X	.
		1013	Fur, Staining, Red	Muzzle	.	.	X	.	X	X
			Fur, Staining, Red	Cranium	.	.	.	.	.	X
		1014	Skin, Scab	Inguinal, Left	.	X	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	X	.	.	.	.

Severity Codes: X = Present; 9 = Red

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	57 DE
1	m	1001	Skin, Scab	Cranium	.
			Fur, Thin Cover	Cranium	.
		1003	Fur, Staining, Red	Periorbital, Left	.
			Fur, Thin Cover	Urogenital	.
			Fur, Thin Cover	Scrotum	.
		1004	Fur, Staining, Red	Muzzle	.
		1007	Fur, Staining, Red	Muzzle	.
			Pinna Partly Missing	Right	.
		1008	Skin, Scab	Hindlimb, Right	.
		1009	Skin, Scab	Tail	.
			Fur, Staining, Red	Muzzle	.
		1010	Skin, Scab	Prepuce	.
		1011	Fur, Staining, Black	Periorbital, Right	.
			Fur, Staining, Red	Muzzle	X
			Fur, Staining, Red	Cranium	X
		1012	Skin, Scab	Hindlimb, Left	.
			Fur, Staining, Red	Muzzle	.
		1013	Fur, Staining, Red	Muzzle	X
			Fur, Staining, Red	Cranium	X
		1014	Skin, Scab	Inguinal, Left	.
			Skin, Scab	Hindlimb, Right	.

Severity Codes: X = Present; 9 = Red

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11 Vet Aid	-1 DE	7 DE	14 DE	21 DE	28 DE
1	m	1015	Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Thoracic	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
			Auditory Canal, Discharge Liq	Right	.	.	.	.	.	.
			Mouth, Discharge Liquid		.	.	.	.	.	.
			Muzzle, Discharge Liquid		.	.	.	.	.	.
			Sneezing		.	.	.	.	.	.
			Breathing, Deep		.	.	.	.	.	.
			Breathing, Labored		.	.	.	.	.	.
			Skin Staining	Pinna, Right	.	.	.	.	.	.
			Skin Staining	Pinna, Left	.	.	.	.	.	.

Severity Codes: X = Present; 9 = Red

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 Unsc PreRx	35 DE	42 DE	44 DE	49 DE	56 DE
1	m	1015	Fur, Staining, Red	Ventral Cervical	X	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	X	X	.	.	.
			Fur, Staining, Red	Dorsal Thoracic	X	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	X	.	.	.	.	.
			Fur, Staining, Red	Cranium	X	.	.	.	.	.
			Auditory Canal, Discharge Liq	Right	9	.	.	.	.	.
			Mouth, Discharge Liquid		9	.	.	.	.	.
			Muzzle, Discharge Liquid		9	.	.	.	.	.
			Sneezing		X	.	.	.	.	.
			Breathing, Deep		X	.	.	.	.	.
			Breathing, Labored		X	.	.	.	.	.
			Skin Staining	Pinna, Right	9	.	.	.	.	.
			Skin Staining	Pinna, Left	9	.	.	.	.	.

Severity Codes: X = Present; 9 = Red

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	57 DE
1	m	1015	Fur, Staining, Red	Ventral Cervical	.
			Fur, Staining, Red	Muzzle	.
			Fur, Staining, Red	Dorsal Thoracic	.
			Fur, Staining, Red	Dorsal Cervical	.
			Fur, Staining, Red	Cranium	.
			Auditory Canal, Discharge Liq	Right	.
			Mouth, Discharge Liquid		.
			Muzzle, Discharge Liquid		.
			Sneezing		.
			Breathing, Deep		.
			Breathing, Labored		.
			Skin Staining	Pinna, Right	.
			Skin Staining	Pinna, Left	.

Severity Codes: X = Present; 9 = Red

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	7 DE	21 DE	28 DE	35 DE	42 DE	44 DE
2	m	2001	Skin, Scab	Scrotum	.	.	.	X	.	.
			Skin, Scab	Pinna, Right	.	.	.	.	X	X
			Skin, Scab	Pinna, Left	.	.	.	.	X	X
		2003	Fur, Staining, Red	Muzzle	.	.	.	X	X	.
			Fur, Staining, Red	Cranium	.	.	.	X	.	.
		2004	Fur, Staining, Red	Cranium	.	.	X	X	X	X
		2007	Skin, Scab	Hindlimb, Right	.	.	.	X	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	X	X
		2008	Skin, Scab	Pinna, Left	.	X	.	.	.	.
			Fur, Staining, Red	Muzzle	X	.	.	.	.	.
		2009	Skin, Scab	Tail	.	.	.	X	.	.
			Fur, Staining, Red	Muzzle	.	.	X	X	X	X
		2010	Skin, Red	Hindpaw, Right	.	.	X	.	.	.

Severity Codes: X = Present

Group 2 - 9.6 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	28 DE	35 DE	42 DE	44 DE
3	m	3002	Fur, Staining, Red	Cranium	.	.	X	X	.
		3003	Skin, Scab	Hindlimb, Left	.	.	X	.	.
		3004	Skin, Lesion w/ Discharge	Prepuce	1	.	.	.	.
			Fur, Staining, Red	Periorbital, Left	.	.	.	X	.
		3007	Skin, Scab	Tail	.	X	X	X	X
			Fur, Staining, Red	Cranium	.	.	.	X	X
		3008	Fur, Staining, Red	Muzzle	.	.	X	.	.
		3009	Skin, Scab	Tail	.	X	.	.	.
		3010	Skin, Scab	Cranium	.	.	X	.	.
			Fur, Staining, Red	Muzzle	.	X	X	X	.
			Fur, Staining, Red	Cranium	.	.	.	X	.
			Fur, Thin Cover	Cranium	.	.	X	X	X

Severity Codes: X = Present; 1 = Slight

Group 3 - 29 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	14 DE	21 DE	28 DE	35 DE	42 DE	44 DE	56 DE	57 DE
4	m	4001	Fur, Staining, Red	Muzzle	.	.	X	X	X	X	.	.
		4002	Fur, Staining, Red	Periorbital, Right	.	.	.	.	X	.	.	.
		4003	Fur, Staining, Red	Muzzle	X	.	.	.	X	X	.	.
		4005	Fur, Staining, Red	Muzzle	.	X	.	.	.	.	.	.
		4006	Fur, Staining, Red	Cranium	.	.	.	.	X	.	.	.
		4007	Skin, Scab	Inguinal, Left	.	.	.	X	.	.	.	.
		4008	Skin, Red	Pinna, Right	X	X	.	.	.	.	.	.
			Skin, Red	Pinna, Left	X	X	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	X	.	.	.	.	.	.
		4011	Skin, Scab	Hindlimb, Left	.	.	.	X	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	X	.	.	.
			Fur, Staining, Yellow	Cranium	.	.	X	.	.	.	.	.
		4012	Fur, Staining, Red	Muzzle	.	.	X	.	.	.	X	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	X	.
		4013	Fur, Staining, Red	Muzzle	.	.	.	.	.	.	.	X
		4014	Fur, Staining, Red	Muzzle	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	X	X
		4015	Fur, Staining, Red	Cranium	.	.	.	.	X	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	X	X
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	X	X

Severity Codes: X = Present

Group 4 - 96 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	7 DE	14 DE	21 DE	28 DE	35 DE	42 DE	44 DE	49 DE	56 DE	57 DE
1	f	1502	Skin, Scab	Pinna, Right	X	.	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	X	X	.	.	.	.
			Fur, Staining, Red	Cranium	.	X	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	.	.	.	.	.	.	X	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	X	X	.	.	.
		1503	Fur, Staining, Red	Dorsal Cervical	.	.	.	.	X	X	X	X	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.	X	.	.	.
		1504	Skin, Scab	Pinna, Left	.	X	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Muzzle	.	.	X	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	X	.	.	.
		1505	Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Muzzle	.	.	X	.	.	.	X	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	X	.	.	.	.
		1507	Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	X	X	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	X	X	X	.	.	.
		1508	Skin, Red	Hindlimb, Left	.	.	.	.	X	.	.	.	.	.	.
			Skin, Dry	Hindlimb, Right	.	.	.	X	X	.	.	X	.	.	.
			Skin, Dry	Hindlimb, Left	.	.	.	X	X	.	.	X	.	.	.
		1510	Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	X	X	.	.	.
		1511	Skin, Scab	Tail	.	.	.	.	.	.	X	.	X	.	.
			Fur, Staining, Red	Muzzle	.	X	.	.	.	.	.	.	.	.	.
		1512	Fur, Staining, Red	Muzzle	.	.	.	X	.	.	.	.	.	.	.
			Fur, Staining, Red	Mouth	.	.	.	X	.	.	.	.	.	.	.
		1514	Skin, Red	Hindlimb, Right	.	.	.	.	.	.	.	.	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	.	.	X	.	.
			Skin, Scab	Hindlimb, Left	.	.	.	.	.	X	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.	.	.	.	X	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	X	.	X	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.	X	X	X

Severity Codes: X = Present

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002158

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	Fur, Staining, Red	Dorsal Cervical	.	.	X	.	.	.
		2502	Skin, Scab	Hindlimb, Right	X	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	X
			Fur, Staining, Red	Muzzle	.	.	X	.	.	.
		2503	Skin, Scab	Tail	.	.	X	.	.	.
			Fur, Staining, Red	Muzzle	X	X	.	.	.	.
		2504	Fur, Staining, Red	Muzzle	X	X	.	.	.	.
			Mass Present		.	X	X	X	X	X
		2507	Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	X
			Fur, Staining, Red	Dorsal Cervical	.	.	X	X	.	.
		2510	Skin, Scab	Tail	.	.	X	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	X	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	X	X

Severity Codes: X = Present

Group 2 - 9.6 ug/dose

Appendix 5

Individual Clinical Observations

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	7 DE	14 DE	21 DE	28 DE	35 DE	42 DE	44 DE
3	f	3503	Fur, Staining, Red	Muzzle	.	.	X	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	X	X	X	X	X
		3505	Fur, Staining, Red	Periorbital, Left	.	.	.	.	.	.	.	X
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	X
		3506	Fur, Staining, Red	Dorsal Cervical	.	.	.	.	X	X	X	X
		3507	Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	X
		3508	Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	X	X
			Fur, Staining, Red	Muzzle	.	.	.	.	.	X	.	.
		3509	Fur, Staining, Red	Muzzle	.	.	X	.	.	.	.	X
			Fur, Staining, Red	Cranium	.	.	X	.	.	.	X	X
		3510	Fur, Staining, Red	Dorsal Cervical	.	.	.	.	X	X	.	.

Severity Codes: X = Present

Group 3 - 29 ug/dose

Appendix 5

Individual Clinical Observations

5002158

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	49 DE	56 DE	57 DE
4	f	4502	Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	X	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	X	.	.	.
		4503	Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	X	X	.	.	.
		4504	Fur, Staining, Red	Muzzle	.	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	X	.	.	.
		4506	Fur, Staining, Red	Cranium	.	.	.	.	.	X	X	.	.	.
		4507	Skin, Scab	Tail	.	.	X	X	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	X	X	.	.	.
		4508	Skin, Scab	Tail	.	.	.	X	X	X	X	.	.	.
		4510	Fur, Staining, Red	Muzzle	.	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	X	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	X	X	X	X	X	.	.	.
		4511	Fur, Staining, Red	Cranium	.	.	.	X	X	X	.	X	X	X
		4512	Fur, Staining, Red	Cranium	.	.	.	.	X	.	.	.	.	.
		4513	Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.	X	X
		4514	Skin, Red	Tail	X	.	.	.	.	.	.	.	.	.
			Skin, Dry	Tail	X	.	.	.	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	X	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Thoracic	.	.	.	.	.	.	.	X	.	.
			Fur, Staining, Red	Muzzle	.	.	.	X	X	.	.	.	X	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	.	X	X
			Fur, Staining, Red	Cranium	.	.	.	X	X	X	.	.	X	X
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.	.	X	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.	X	.
		4515	Fur, Staining, Red	Ventral Thoracic	.	.	.	.	.	.	.	X	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	.	X	.

Severity Codes: X = Present

Group 4 - 96 ug/dose

Appendix 6

Individual Palpable Masses Explanation Page

Abbreviation	Description	Abbreviation	Description
AVS	Suspected aberrant value	NR	Not recorded

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 (µg/dose)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 6

Individual Palpable Masses

5002158

Group: 2 Animal: 2504 Sex: Female

Mass	Day (Week)	Time	Location	Size	Description
1	21(3)	15:52	Abdominal	3 mm	Firm
1	28(4)	8:35	Abdominal	3 mm	Firm
1	35(5)	15:40	Abdominal	3 mm	Firm
1	42(6)	9:18	Abdominal	3 mm	Firm
1	44(7)	11:11	Abdominal	3 mm	Firm

Appendix 7

Individual Local Irritation Assessment Explanation Page

Score	Erythema (Redness) Description
0	No erythema
1	Very slight erythema (barely perceptible)
2	Well-defined erythema and/or 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 (edges of area are well-defined by definite raising)
3	Moderate edema (raised approximately 1 mm)
4	Severe edema (raised more than 1 mm and extending beyond area of exposure)

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

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)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
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	0	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	0	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	.	0	.	.
			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	0	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
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	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
		1012	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
		1013	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
		1014	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
		1015	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
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	0	0	0	0	.	0	.	0	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	2	0	0	.	0	.	.
		2002	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	1	0	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	0	0	0	0	.	0	.	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	2	0	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	0	0	0	0	.	0	.	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	2	0	0	.	0	.	.
		2005	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	1	0	0	.	0	1	0	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	1	0	0	0	.	0	.	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	1	0	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	1	0	0	0	.	0	.	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	1	0	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	1	0	0	0	.	0	.	0	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	2	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
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	0	0	0	0	.	0	.	0	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	1	0	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	0	0	0	0	.	0	.	0	.	.
			Edema	Treatment Site No.01	0	1	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
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	1	1	0	0	.	0	.	1	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	2	0	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	0	0	0	0	.	0	.	1	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	2	0	0	.	0	.	.
		3003	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	.	1	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	2	0	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	1	1	0	0	.	0	.	1	.	.
			Edema	Treatment Site No.01	0	2	0	0	.	0	2	0	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	0	1	0	0	.	0	.	2	.	.
			Edema	Treatment Site No.01	0	2	0	0	.	0	3	0	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	1	1	0	0	.	0	.	2	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	3	0	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	0	0	0	0	.	0	.	1	.	.
			Edema	Treatment Site No.01	0	2	0	0	.	0	3	0	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	1	1	0	0	.	0	.	1	.	.
			Edema	Treatment Site No.01	0	2	0	0	.	0	3	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
3	m	3009	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	.	0	.	.
			Erythema	Treatment Site No.01	1	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	0	1	0	0	.	0	3	0	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	0	0	.	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	0	.	1	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	2	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
4	m	4001	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	2	0	0	0	.	0	.	2	.	.
			Edema	Treatment Site No.01	0	2	0	0	.	0	4	0	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	2	1	0	0	.	0	.	2	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	3	0	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	0	0	.	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	0	.	2	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	3	0	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	2	0	0	0	.	0	.	2	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	4	0	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	2	0	0	0	.	0	.	2	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	3	0	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	0	0	.	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	0	.	3	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	3	0	0	.	0	.	.
		4007	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	.	0	.	.
			Erythema	Treatment Site No.01	1	1	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	0	1	0	0	.	0	3	0	0	.	0	.	.
		4008	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	0	0	0	0	.	0	4	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
4	m	4009	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	1	0	0	.	0	.	3	.	.
			Edema	Treatment Site No.01	0	2	0	0	.	0	4	0	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	0	0	0	.	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	0	.	3	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	4	0	0	.	0	.	.
		4011	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	0	2	.	2	0
			Edema	Treatment Site No.01	0	1	0	0	.	0	3	0	0	0	.	.	0
		4012	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	1	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	0	3	.	1	0
			Edema	Treatment Site No.01	0	2	0	0	.	0	3	0	0	0	.	.	0
		4013	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	0	3	.	1	0
			Edema	Treatment Site No.01	0	1	0	0	.	0	3	0	0	0	.	.	0
		4014	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	0	2	.	1	0
			Edema	Treatment Site No.01	0	2	0	0	.	0	4	0	0	0	.	.	0
		4015	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	0	3	.	2	0
			Edema	Treatment Site No.01	0	2	0	0	.	0	4	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
1	f	1501	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	.	.	.
		1502	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	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	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	.	.	.
		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	4	0	.	0	1	.	.	.
			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	.	.	.

Severity Codes: 0 = Grade 0; 1 = Grade 1; 2 = Grade 2; 3 = Grade 3; 4 = Grade 4

Group 1 - 0 ug/dose Group 2 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
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	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	.	.	.
		1511	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
		1512	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
		1513	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
		1514	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	4
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	4
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
		1515	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
2	f	2501	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	.	.
			Erythema	Treatment Site No.01	0	1	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	1	0	0	.	0	0	1	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	0	0	0	.	0	0	.	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	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	0	0	0	.	0	0	.	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	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	0	0	0	.	0	0	.	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	0	0	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	0	0	0	.	0	1	.	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	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	0	0	0	.	0	0	.	.	.
			Edema	Treatment Site No.01	0	1	0	0	.	0	0	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	0	0	0	0	.	0	1	.	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	0	0	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	0	0	0	0	.	0	1	.	.	.
			Edema	Treatment Site No.01	1	1	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
2	f	2509	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	1	0	0	0	.	0	0	0	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	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
3	f	3501	Erythema	Treatment Site No.02	0	.	0	1	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	2	1	0	0	.	0	1	.	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	0	0	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	2	1	0	0	.	0	0	.	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	0	1	0	0	.	.	.
		3503	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	2	1	0	0	.	0	1	.	.	.
			Edema	Treatment Site No.01	1	1	0	0	.	0	0	0	0	0	.	.	.
		3504	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	2	1	0	0	.	0	0	1	0	0	.	.	.
		3505	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	0	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	0	0	0	0	.	.	.
		3506	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	2	1	0	0	.	0	1	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	0	1	0	0	.	.	.
		3507	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	2	1	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	1	1	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	2	0	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	0	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
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	2	1	0	0	.	0	3	.	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	0	0	0	0	.	.	.
		3510	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	.	.
			Erythema	Treatment Site No.01	0	1	0	0	.	0	1	1	0	0	.	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	2	1	0	0	.	0	0	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
4	f	4501	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	0	0	.	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	1	0	0	0	.	.	.
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	1	1	0	0	.	.	.
		4502	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	0	1	.	.	.
			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	4	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	0	1	0	0	.	.	.
		4503	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	4	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	0	1	0	0	.	.	.
		4504	Erythema	Treatment Site No.02	0	.	0	2	0	0	0	.	0	2	.	.	.
			Erythema	Treatment Site No.01	0	1	0	0	.	0	1	0	0	0	.	.	.
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	0	1	0	0	.	.	.
		4505	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	0	0	.	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	1	1	0	0	.	.	.
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	0	2	0	0	.	.	.
		4506	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	.	.
			Erythema	Treatment Site No.01	0	1	0	0	.	0	2	1	0	0	.	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	2	1	0	0	.	.	.
		4507	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	0	1	.	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	2	1	0	0	.	.	.
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	3	2	0	0	.	0	1	0	0	0	.	.	.
		4508	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	0	1	.	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	2	1	0	0	.	.	.
			Edema	Treatment Site No.02	0	.	0	3	0	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	2	1	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 7

Individual Local Irritation Assessment

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37	44	44 DE	46	51
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	1	0	0	0	.	.	.
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	0	4	.	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	1	1	0	0	.	.	.
		4510	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	1	.	.	.
			Erythema	Treatment Site No.01	0	1	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	2	0	0	.	0	1	1	0	0	.	.	.
		4511	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	1	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	0	0	.	1	0
			Edema	Treatment Site No.01	3	0	0	0	.	0	1	1	0	0	.	.	0
		4512	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	0	4	.	1	0
			Edema	Treatment Site No.01	3	0	0	0	.	0	0	0	0	0	.	.	0
		4513	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0	1	.	0	0
			Erythema	Treatment Site No.01	0	1	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	0	4	.	1	0
			Edema	Treatment Site No.01	3	2	0	0	.	0	0	1	0	0	.	.	0
		4514	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	0	1	.	1	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	1	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	0	4	.	2	0
			Edema	Treatment Site No.01	3	1	0	0	.	0	1	2	0	0	.	.	0
		4515	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	0	1	.	0	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	0	3	0	0	0	.	0	4	.	1	0
			Edema	Treatment Site No.01	3	1	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 8

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 (µg/dose)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day -6	-1	7	14	21	28	35	42
1M	1001	197	242	312	380	446	501	536	579
	1002	192	230	301	354	417	479	508	544
	1003	203	240	301	352	397	437	475	508
	1004	212	258	330	400	472	523	570	598
	1005	203	252	325	396	459	507	544	567
	1006	206	252	336	407	467	525	563	593
	1007	212	250	323	393	457	524	560	599
	1008	194	224	281	350	404	470	512	558
	1009	198	235	293	344	390	432	473	492
	1010	191	232	295	354	404	457	496	536
	1011	206	250	315	386	437	490	523	561
	1012	200	236	318	397	460	520	561	597
	1013	189	223	286	348	404	462	500	533
	1014	199	244	330	410	481	534	573	618
	1015	189	228	289	343	403	455	481	512

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
1M	1001	--	--
	1002	--	--
	1003	--	--
	1004	--	--
	1005	--	--
	1006	--	--
	1007	--	--
	1008	--	--
	1009	--	--
	1010	--	--
	1011	577	604
	1012	618	644
	1013	553	575
	1014	645	662
	1015	532	552

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day -6	-1	7	14	21	28	35	42
2M	2001	195	239	305	372	418	471	503	527
	2002	206	254	321	383	433	471	506	536
	2003	200	246	309	370	427	473	497	546
	2004	196	238	305	367	419	467	500	528
	2005	192	236	304	368	421	471	501	532
	2006	201	255	337	411	469	523	567	605
	2007	205	243	307	360	413	454	481	491
	2008	201	229	286	343	389	435	469	497
	2009	204	240	314	381	443	489	525	551
	2010	197	238	311	366	416	464	487	518

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
2M	2001	--	--
	2002	--	--
	2003	--	--
	2004	--	--
	2005	--	--
	2006	--	--
	2007	--	--
	2008	--	--
	2009	--	--
	2010	--	--

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day -6	-1	7	14	21	28	35	42
3M	3001	199	236	293	344	385	422	446	480
	3002	201	255	339	418	479	535	583	623
	3003	208	260	331	405	467	525	574	609
	3004	199	235	288	342	386	429	458	490
	3005	194	238	310	372	425	472	507	537
	3006	196	226	284	343	389	426	456	490
	3007	203	245	307	376	430	479	518	551
	3008	205	254	326	392	456	498	536	570
	3009	192	231	282	336	381	421	438	467
	3010	203	252	322	384	443	495	531	574

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
3M	3001	--	--
	3002	--	--
	3003	--	--
	3004	--	--
	3005	--	--
	3006	--	--
	3007	--	--
	3008	--	--
	3009	--	--
	3010	--	--

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day -6	-1	7	14	21	28	35	42
4M	4001	203	249	323	406	455	510	548	587
	4002	191	228	267	316	336	360	374	392
	4003	204	239	298	355	411	461	490	530
	4004	189	231	287	353	398	446	480	519
	4005	205	249	318	389	437	482	518	551
	4006	194	226	280	335	373	422	449	481
	4007	212	245	304	370	416	468	503	548
	4008	206	256	327	416	482	540	586	635
	4009	200	238	294	365	413	463	492	528
	4010	189	226	278	337	372	428	464	510
	4011	211	258	321	399	445	507	542	585
	4012	193	235	289	362	406	462	493	536
	4013	196	239	285	345	382	434	468	496
	4014	200	247	310	385	435	482	520	562
	4015	198	233	287	345	388	433	452	487

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
4M	4001	--	--
	4002	--	--
	4003	--	--
	4004	--	--
	4005	--	--
	4006	--	--
	4007	--	--
	4008	--	--
	4009	--	--
	4010	--	--
	4011	605	623
	4012	567	591
	4013	516	542
	4014	577	608
	4015	507	528

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day -7	-1	7	14	21	28	35	42
1F	1501	172	188	211	234	247	262	263	274
	1502	178	201	241	272	285	297	314	331
	1503	181	199	232	258	269	276	288	306
	1504	189	219	250	275	292	314	323	327
	1505	190	215	228	255	268	299	299	317
	1506	183	197	221	244	247	278	286	294
	1507	173	200	225	242	263	277	290	299
	1508	168	188	214	236	247	267	274	283
	1509	191	224	262	291	314	337	329	353
	1510	190	210	241	266	280	288	305	321
	1511	177	211	229	256	263	285	289	304
	1512	169	204	227	247	259	283	280	277
	1513	174	193	225	256	265	278	297	312
	1514	187	218	229	255	266	288	294	307
	1515	180	203	221	248	257	273	269	288

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
1F	1501	--	--
	1502	--	--
	1503	--	--
	1504	--	--
	1505	--	--
	1506	--	--
	1507	--	--
	1508	--	--
	1509	--	--
	1510	--	--
	1511	302	318
	1512	287	306
	1513	312	314
	1514	312	319
	1515	292	299

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day -7	-1	7	14	21	28	35	42
2F	2501	189	201	234	258	273	286	303	313
	2502	171	207	225	245	255	280	288	297
	2503	179	209	234	260	270	283	289	307
	2504	174	191	220	243	255	265	276	291
	2505	187	224	263	297	321	338	361	372
	2506	184	215	241	262	277	286	297	311
	2507	182	210	224	260	288	303	305	329
	2508	179	215	256	294	324	341	358	384
	2509	176	196	225	252	262	264	277	296
	2510	174	201	219	249	274	289	305	320

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
2F	2501	--	--
	2502	--	--
	2503	--	--
	2504	--	--
	2505	--	--
	2506	--	--
	2507	--	--
	2508	--	--
	2509	--	--
	2510	--	--

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day -7	-1	7	14	21	28	35	42
3F	3501	172	218	240	260	289	311	324	319
	3502	186	215	246	277	291	306	317	332
	3503	174	221	257	276	286	304	322	330
	3504	174	196	232	258	282	285	302	318
	3505	189	219	233	273	288	304	315	320
	3506	183	209	233	255	264	278	292	302
	3507	178	203	221	252	266	282	285	296
	3508	175	218	226	238	234	246	248	262
	3509	180	215	232	260	267	289	287	303
	3510	183	207	219	245	244	252	273	264

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
3F	3501	--	--
	3502	--	--
	3503	--	--
	3504	--	--
	3505	--	--
	3506	--	--
	3507	--	--
	3508	--	--
	3509	--	--
	3510	--	--

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day -7	-1	7	14	21	28	35	42
4F	4501	173	191	205	230	238	252	250	262
	4502	191	232	262	297	318	346	350	356
	4503	180	201	217	241	257	267	279	297
	4504	174	200	214	242	255	282	278	286
	4505	187	229	264	299	311	340	330	356
	4506	176	192	221	247	261	276	288	310
	4507	182	202	224	256	272	273	298	297
	4508	173	201	207	221	238	257	263	268
	4509	189	214	236	255	264	285	301	308
	4510	189	213	231	255	267	281	280	290
	4511	170	204	218	234	258	272	276	304
	4512	179	207	234	274	293	301	317	334
	4513	183	207	217	231	244	274	275	273
	4514	168	194	217	233	246	271	276	279
	4515	191	218	237	259	275	292	296	310

Appendix 8

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day 49	Day 56
4F	4501	--	--
	4502	--	--
	4503	--	--
	4504	--	--
	4505	--	--
	4506	--	--
	4507	--	--
	4508	--	--
	4509	--	--
	4510	--	--
	4511	309	306
	4512	336	338
	4513	292	313
	4514	294	293
	4515	321	338

Appendix 9

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 (µg/dose)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day							
		Change -6 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
1M	1001	45	70	68	66	55	35	43	--
	1002	38	71	53	63	62	29	36	--
	1003	37	61	51	45	40	38	33	--
	1004	46	72	70	72	51	47	28	--
	1005	49	73	71	63	48	37	23	--
	1006	46	84	71	60	58	38	30	--
	1007	38	73	70	64	67	36	39	--
	1008	30	57	69	54	66	42	46	--
	1009	37	58	51	46	42	41	19	--
	1010	41	63	59	50	53	39	40	--
	1011	44	65	71	51	53	33	38	16
	1012	36	82	79	63	60	41	36	21
	1013	34	63	62	56	58	38	33	20
	1014	45	86	80	71	53	39	45	27
	1015	39	61	54	60	52	26	31	20

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
1M	1001	--
	1002	--
	1003	--
	1004	--
	1005	--
	1006	--
	1007	--
	1008	--
	1009	--
	1010	--
	1011	27
	1012	26
	1013	22
	1014	17
	1015	20

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day							
		Change -6 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
2M	2001	44	66	67	46	53	32	24	--
	2002	48	67	62	50	38	35	30	--
	2003	46	63	61	57	46	24	49	--
	2004	42	67	62	52	48	33	28	--
	2005	44	68	64	53	50	30	31	--
	2006	54	82	74	58	54	44	38	--
	2007	38	64	53	53	41	27	10	--
	2008	28	57	57	46	46	34	28	--
	2009	36	74	67	62	46	36	26	--
	2010	41	73	55	50	48	23	31	--

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
2M	2001	--
	2002	--
	2003	--
	2004	--
	2005	--
	2006	--
	2007	--
	2008	--
	2009	--
	2010	--

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day							
		Change -6 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
3M	3001	37	57	51	41	37	24	34	--
	3002	54	84	79	61	56	48	40	--
	3003	52	71	74	62	58	49	35	--
	3004	36	53	54	44	43	29	32	--
	3005	44	72	62	53	47	35	30	--
	3006	30	58	59	46	37	30	34	--
	3007	42	62	69	54	49	39	33	--
	3008	49	72	66	64	42	38	34	--
	3009	39	51	54	45	40	17	29	--
	3010	49	70	62	59	52	36	43	--

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
3M	3001	--
	3002	--
	3003	--
	3004	--
	3005	--
	3006	--
	3007	--
	3008	--
	3009	--
	3010	--

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day							
		Change -6 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
4M	4001	46	74	83	49	55	38	39	--
	4002	37	39	49	20	24	14	18	--
	4003	35	59	57	56	50	29	40	--
	4004	42	56	66	45	48	34	39	--
	4005	44	69	71	48	45	36	33	--
	4006	32	54	55	38	49	27	32	--
	4007	33	59	66	46	52	35	45	--
	4008	50	71	89	66	58	46	49	--
	4009	38	56	71	48	50	29	36	--
	4010	37	52	59	35	56	36	46	--
	4011	47	63	78	46	62	35	43	20
	4012	42	54	73	44	56	31	43	31
	4013	43	46	60	37	52	34	28	20
	4014	47	63	75	50	47	38	42	15
	4015	35	54	58	43	45	19	35	20

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
4M	4001	--
	4002	--
	4003	--
	4004	--
	4005	--
	4006	--
	4007	--
	4008	--
	4009	--
	4010	--
	4011	18
	4012	24
	4013	26
	4014	31
	4015	21

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day							
		Change -7 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
1F	1501	16	23	23	13	15	1	11	--
	1502	23	40	31	13	12	17	17	--
	1503	18	33	26	11	7	12	18	--
	1504	30	31	25	17	22	9	4	--
	1505	25	13	27	13	31	0	18	--
	1506	14	24	23	3	31	8	8	--
	1507	27	25	17	21	14	13	9	--
	1508	20	26	22	11	20	7	9	--
	1509	33	38	29	23	23	-8	24	--
	1510	20	31	25	14	8	17	16	--
	1511	34	18	27	7	22	4	15	-2
	1512	35	23	20	12	24	-3	-3	10
	1513	19	32	31	9	13	19	15	0
	1514	31	11	26	11	22	6	13	5
	1515	23	18	27	9	16	-4	19	4

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
1F	1501	--
	1502	--
	1503	--
	1504	--
	1505	--
	1506	--
	1507	--
	1508	--
	1509	--
	1510	--
	1511	16
	1512	19
	1513	2
	1514	7
	1515	7

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day							
		Change -7 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
2F	2501	12	33	24	15	13	17	10	--
	2502	36	18	20	10	25	8	9	--
	2503	30	25	26	10	13	6	18	--
	2504	17	29	23	12	10	11	15	--
	2505	37	39	34	24	17	23	11	--
	2506	31	26	21	15	9	11	14	--
	2507	28	14	36	28	15	2	24	--
	2508	36	41	38	30	17	17	26	--
	2509	20	29	27	10	2	13	19	--
	2510	27	18	30	25	15	16	15	--

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
2F	2501	--
	2502	--
	2503	--
	2504	--
	2505	--
	2506	--
	2507	--
	2508	--
	2509	--
	2510	--

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day Change -7 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
3F	3501	46	22	20	29	22	13	-5	--
	3502	29	31	31	14	15	11	15	--
	3503	47	36	19	10	18	18	8	--
	3504	22	36	26	24	3	17	16	--
	3505	30	14	40	15	16	11	5	--
	3506	26	24	22	9	14	14	10	--
	3507	25	18	31	14	16	3	11	--
	3508	43	8	12	-4	12	2	14	--
	3509	35	17	28	7	22	-2	16	--
	3510	24	12	26	-1	8	21	-9	--

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
3F	3501	--
	3502	--
	3503	--
	3504	--
	3505	--
	3506	--
	3507	--
	3508	--
	3509	--
	3510	--

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day							
		Change -7 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42	Change 42 - 49
4F	4501	18	14	25	8	14	-2	12	--
	4502	41	30	35	21	28	4	6	--
	4503	21	16	24	16	10	12	18	--
	4504	26	14	28	13	27	-4	8	--
	4505	42	35	35	12	29	-10	26	--
	4506	16	29	26	14	15	12	22	--
	4507	20	22	32	16	1	25	-1	--
	4508	28	6	14	17	19	6	5	--
	4509	25	22	19	9	21	16	7	--
	4510	24	18	24	12	14	-1	10	--
	4511	34	14	16	24	14	4	28	5
	4512	28	27	40	19	8	16	17	2
	4513	24	10	14	13	30	1	-2	19
	4514	26	23	16	13	25	5	3	15
	4515	27	19	22	16	17	4	14	11

Appendix 9

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day Change 49 - 56
4F	4501	--
	4502	--
	4503	--
	4504	--
	4505	--
	4506	--
	4507	--
	4508	--
	4509	--
	4510	--
	4511	-3
	4512	2
	4513	21
	4514	-1
	4515	17

Appendix 10

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 (µg/dose)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To)						
		-5/1	1/8	8/15	15/22	22/29	29/36	36/43
1M	1001	30.1	31.0	33.7	35.8	35.6	36.8	36.7
	1002	30.1	31.0	33.7	35.8	35.6	36.8	36.7
	1003	30.1	31.0	33.7	35.8	35.6	36.8	36.7
	1004	33.3	32.8	35.9	36.9	36.4	36.6	36.1
	1005	33.3	32.8	35.9	36.9	36.4	36.6	36.1
	1006	33.3	32.8	35.9	36.9	36.4	36.6	36.1
	1007	29.5	30.6	34.6	35.5	37.6	38.8	38.3
	1008	29.5	30.6	34.6	35.5	37.6	38.8	38.3
	1009	27.8	28.6	30.4	30.4	31.7	32.4	33.5
	1010	27.8	28.6	30.4	30.4	31.7	32.4	33.5
	1011	30.7	32.2	36.4	38.4	38.1	38.0	36.8
	1012	30.7	32.2	36.4	38.4	38.1	38.0	36.8
	1013	30.7	32.2	36.4	38.4	38.1	38.0	36.8
	1014	28.6	30.1	34.9	36.6	37.6	36.2	37.0
	1015	28.6	30.1	34.9	36.6	37.6	36.2	37.0

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	35.0	36.2
	1012	35.0	36.2
	1013	35.0	36.2
	1014	35.8	37.3
	1015	35.8	37.3

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) -5/1	1/8	8/15	15/22	22/29	29/36	36/43
2M	2001	31.4	31.5	34.2	35.0	34.8	34.5	34.9
	2002	31.4	31.5	34.2	35.0	34.8	34.5	34.9
	2003	31.4	31.5	34.2	35.0	34.8	34.5	34.9
	2004	30.0	32.2	34.8	35.2	35.1	36.4	35.8
	2005	30.0	32.2	34.8	35.2	35.1	36.4	35.8
	2006	30.0	32.2	34.8	35.2	35.1	36.4	35.8
	2007	29.9	30.4	33.1	34.3	32.0	31.8	31.1
	2008	29.9	30.4	33.1	34.3	32.0	31.8	31.1
	2009	28.5	30.7	33.3	34.1	33.8	33.5	34.0
	2010	28.5	30.7	33.3	34.1	33.8	33.5	34.0

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
2M	2001	--	--
	2002	--	--
	2003	--	--
	2004	--	--
	2005	--	--
	2006	--	--
	2007	--	--
	2008	--	--
	2009	--	--
	2010	--	--

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) -5/1	1/8	8/15	15/22	22/29	29/36	36/43
3M	3001	32.9	33.4	37.1	37.0	37.7	37.5	37.1
	3002	32.9	33.4	37.1	37.0	37.7	37.5	37.1
	3003	32.9	33.4	37.1	37.0	37.7	37.5	37.1
	3004	26.9	28.0	32.0	31.8	31.8	31.7	31.7
	3005	26.9	28.0	32.0	31.8	31.8	31.7	31.7
	3006	26.9	28.0	32.0	31.8	31.8	31.7	31.7
	3007	30.5	31.4	34.6	36.1	35.9	35.9	35.4
	3008	30.5	31.4	34.6	36.1	35.9	35.9	35.4
	3009	29.7	31.1	33.7	33.4	35.1	33.6	34.4
	3010	29.7	31.1	33.7	33.4	35.1	33.6	34.4

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
3M	3001	--	--
	3002	--	--
	3003	--	--
	3004	--	--
	3005	--	--
	3006	--	--
	3007	--	--
	3008	--	--
	3009	--	--
	3010	--	--

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) -5/1	1/8	8/15	15/22	22/29	29/36	36/43
4M	4001	28.7	27.1	32.7	30.3	31.7	30.0	31.8
	4002	28.7	27.1	32.7	30.3	31.7	30.0	31.8
	4003	28.7	27.1	32.7	30.3	31.7	30.0	31.8
	4004	27.3	27.0	31.6	31.0	33.4	31.7	32.8
	4005	27.3	27.0	31.6	31.0	33.4	31.7	32.8
	4006	27.3	27.0	31.6	31.0	33.4	31.7	32.8
	4007	30.1	30.4	37.1	37.2	38.6	37.9	40.1
	4008	30.1	30.4	37.1	37.2	38.6	37.9	40.1
	4009	28.9	27.9	34.4	32.0	35.6	34.0	37.9
	4010	28.9	27.9	34.4	32.0	35.6	34.0	37.9
	4011	27.8	27.0	33.4	31.0	35.3	33.5	34.9
	4012	27.8	27.0	33.4	31.0	35.3	33.5	34.9
	4013	27.8	27.0	33.4	31.0	35.3	33.5	34.9
	4014	31.7	29.4	35.6	35.1	37.4	34.7	37.4
	4015	31.7	29.4	35.6	35.1	37.4	34.7	37.4

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	32.9	35.8
	4012	32.9	35.8
	4013	32.9	35.8
	4014	34.8	37.5
	4015	34.8	37.5

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) -5/1	1/8	8/15	15/22	22/29	29/36	36/43
1F	1501	19.2	20.7	20.8	21.6	20.9	20.9	21.6
	1502	19.2	20.7	20.8	21.6	20.9	20.9	21.6
	1503	19.2	20.7	20.8	21.6	20.9	20.9	21.6
	1504	19.6	22.6	22.8	23.1	22.8	22.5	22.4
	1505	19.6	22.6	22.8	23.1	22.8	22.5	22.4
	1506	19.6	22.6	22.8	23.1	22.8	22.5	22.4
	1507	18.2	19.7	20.6	21.6	20.7	20.3	20.6
	1508	18.2	19.7	20.6	21.6	20.7	20.3	20.6
	1509	21.4	23.3	23.2	25.9	24.6	22.8	25.1
	1510	21.4	23.3	23.2	25.9	24.6	22.8	25.1
	1511	20.7	21.3	22.9	23.2	23.0	21.9	22.7
	1512	20.7	21.3	22.9	23.2	23.0	21.9	22.7
	1513	20.7	21.3	22.9	23.2	23.0	21.9	22.7
	1514	20.5	20.8	20.5	22.1	21.9	20.9	22.1
	1515	20.5	20.8	20.5	22.1	21.9	20.9	22.1

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	20.4	22.4
	1512	20.4	22.4
	1513	20.4	22.4
	1514	21.1	20.9
	1515	21.1	20.9

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) -5/1	1/8	8/15	15/22	22/29	29/36	36/43
2F	2501	21.6	21.5	22.4	23.0	22.4	23.0	22.6
	2502	21.6	21.5	22.4	23.0	22.4	23.0	22.6
	2503	21.6	21.5	22.4	23.0	22.4	23.0	22.6
	2504	21.5	22.0	23.2	23.4	23.4	23.1	23.6
	2505	21.5	22.0	23.2	23.4	23.4	23.1	23.6
	2506	21.5	22.0	23.2	23.4	23.4	23.1	23.6
	2507	23.0	24.4	26.0	28.1	27.9	27.6	27.7
	2508	23.0	24.4	26.0	28.1	27.9	27.6	27.7
	2509	21.5	21.7	23.1	24.4	24.6	24.1	25.9
	2510	21.5	21.7	23.1	24.4	24.6	24.1	25.9

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) -5/1	1/8	8/15	15/22	22/29	29/36	36/43
3F	3501	23.4	23.9	22.9	23.9	24.8	23.9	23.9
	3502	23.4	23.9	22.9	23.9	24.8	23.9	23.9
	3503	23.4	23.9	22.9	23.9	24.8	23.9	23.9
	3504	19.9	21.3	21.5	22.6	21.7	22.5	22.6
	3505	19.9	21.3	21.5	22.6	21.7	22.5	22.6
	3506	19.9	21.3	21.5	22.6	21.7	22.5	22.6
	3507	21.5	20.3	20.1	21.4	20.0	19.9	20.0
	3508	21.5	20.3	20.1	21.4	20.0	19.9	20.0
	3509	19.6	20.6	21.6	20.0	21.6	20.9	20.6
	3510	19.6	20.6	21.6	20.0	21.6	20.9	20.6

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) 43/50	50/56
3F	3501	--	--
	3502	--	--
	3503	--	--
	3504	--	--
	3505	--	--
	3506	--	--
	3507	--	--
	3508	--	--
	3509	--	--
	3510	--	--

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	Day (From/To) -5/1	1/8	8/15	15/22	22/29	29/36	36/43
4F	4501	19.9	20.8	21.4	21.9	22.1	21.5	21.7
	4502	19.9	20.8	21.4	21.9	22.1	21.5	21.7
	4503	19.9	20.8	21.4	21.9	22.1	21.5	21.7
	4504	19.7	21.2	22.7	22.5	22.9	21.1	23.6
	4505	19.7	21.2	22.7	22.5	22.9	21.1	23.6
	4506	19.7	21.2	22.7	22.5	22.9	21.1	23.6
	4507	18.9	19.4	20.7	21.9	21.9	21.4	21.9
	4508	18.9	19.4	20.7	21.9	21.9	21.4	21.9
	4509	21.0	22.7	23.1	22.9	24.0	23.1	22.9
	4510	21.0	22.7	23.1	22.9	24.0	23.1	22.9
	4511	20.1	20.3	22.2	22.6	23.5	21.8	25.0
	4512	20.1	20.3	22.2	22.6	23.5	21.8	25.0
	4513	20.1	20.3	22.2	22.6	23.5	21.8	25.0
	4514	19.8	20.3	20.7	21.7	21.8	21.4	21.6
	4515	19.8	20.3	20.7	21.7	21.8	21.4	21.6

Appendix 10

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	21.5	24.0
	4512	21.5	24.0
	4513	21.5	24.0
	4514	21.9	22.9
	4515	21.9	22.9

Appendix 11

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	pr	Body temperature at predosing
p	Body temperature at post dosing		

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)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 11

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	36.8	36.5	36.9	37.2	37.3	36.3
	1002	36.4	36.0	37.4	38.6	36.4	36.1
	1003	37.0	35.7	37.3	37.0	37.1	35.6
	1004	36.3	35.5	36.5	36.8	36.8	36.8
	1005	36.5	35.5	36.8	36.8	36.9	37.0
	1006	36.8	35.6	36.5	36.7	36.4	36.3
	1007	36.0	36.6	36.8	38.0	36.4	36.8
	1008	37.0	36.0	36.8	36.8	36.7	36.3
	1009	36.9	35.9	36.9	37.0	36.9	37.1
	1010	37.7	36.0	36.6	36.5	37.4	37.3
	1011	35.5	36.2	36.2	36.7	36.9	36.9
	1012	36.4	36.1	36.9	38.0	38.0	38.2
	1013	36.2	36.2	37.5	36.7	37.1	37.8
	1014	37.6	36.5	36.7	36.7	36.8	37.0
	1015	38.3	37.0	37.0	37.1	38.8	36.9

Appendix 11

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	36.1	36.3	36.5	36.5	37.1	36.7
	2002	37.0	36.0	36.7	37.2	37.0	37.1
	2003	36.5	35.3	36.7	37.6	36.6	36.7
	2004	37.1	37.8	36.7	37.8	37.8	36.6
	2005	37.1	37.0	37.1	38.1	36.7	36.8
	2006	37.5	37.5	36.9	38.4	37.8	36.4
	2007	36.9	36.8	36.8	37.9	37.0	36.7
	2008	37.2	36.6	36.5	38.5	37.0	36.9
	2009	36.8	36.4	37.3	36.5	36.2	36.6
	2010	37.3	36.6	36.7	38.0	36.3	37.2

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	36.9	37.2	37.4	38.2	38.1	37.3
	3002	37.3	37.4	36.3	37.1	38.1	36.3
	3003	36.3	38.0	36.5	37.9	38.2	37.1
	3004	37.4	37.7	36.5	38.6	36.5	37.9
	3005	37.5	37.9	36.6	38.5	36.4	36.5
	3006	36.0	36.7	36.9	38.8	37.7	37.0
	3007	38.0	36.8	36.7	38.4	37.2	37.2
	3008	37.5	37.7	36.6	38.6	36.6	37.1
	3009	38.0	37.3	36.8	38.8	36.8	38.3
	3010	37.8	37.4	37.1	38.9	37.2	37.5

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	36.4	37.8	37.6	36.4	37.3	37.3
	4002	36.9	38.9	38.1	37.5	38.9	39.0
	4003	36.1	37.3	36.7	36.7	38.0	37.8
	4004	37.2	37.6	37.0	38.0	36.2	38.0
	4005	36.1	37.8	37.3	37.9	37.8	37.1
	4006	36.6	37.5	38.4	38.3	38.7	38.3
	4007	38.2	37.1	37.5	38.2	37.9	37.4
	4008	37.4	37.8	37.1	38.6	36.3	38.0
	4009	37.6	37.2	37.6	38.3	37.8	37.3
	4010	37.8	37.4	37.4	36.8	38.6	38.5
	4011	37.0	38.2	37.6	36.6	38.7	37.3
	4012	36.0	38.1	37.5	36.4	39.2	37.9
	4013	36.4	37.7	38.3	37.0	38.8	38.3
	4014	37.4	38.2	36.9	38.2	38.9	37.8
	4015	36.6	37.5	36.9	37.5	39.1	37.7

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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
1F	1501	37.7	36.8	37.2	38.6	36.8	36.3
	1502	36.0	37.1	36.8	38.4	37.5	37.1
	1503	36.8	37.3	37.7	38.2	37.0	36.2
	1504	36.5	37.0	37.2	37.8	38.3	36.2
	1505	35.8	36.4	37.6	37.0	36.9	36.5
	1506	36.2	36.8	37.6	37.2	37.2	37.0
	1507	37.6	37.1	36.2	38.7	37.2	37.9
	1508	38.0	38.1	37.0	38.5	36.8	37.4
	1509	37.1	37.5	36.6	38.4	37.0	36.7
	1510	36.5	37.0	36.9	38.3	37.4	38.0
	1511	36.2	36.5	36.9	37.6	37.9	36.7
	1512	36.7	36.5	37.0	37.1	38.0	36.9
	1513	37.5	36.2	37.5	38.8	38.4	36.4
	1514	37.6	37.9	37.4	38.7	38.2	36.9
	1515	36.5	36.8	37.2	38.6	38.1	36.0

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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
2F	2501	36.4	37.4	36.0	38.3	37.1	36.3
	2502	37.2	38.0	36.4	37.8	37.7	36.7
	2503	36.1	37.9	37.0	38.3	36.8	36.6
	2504	36.9	37.2	37.7	37.8	37.2	36.2
	2505	37.5	37.4	36.9	37.8	37.2	37.2
	2506	37.1	37.2	36.9	37.6	37.0	36.1
	2507	36.3	36.8	37.1	38.5	37.5	37.8
	2508	36.9	36.9	36.6	38.5	36.6	37.3
	2509	37.0	36.8	36.4	38.3	38.8	36.4
	2510	36.1	36.7	37.0	38.8	38.7	37.5

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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
3F	3501	37.3	36.5	36.3	38.6	37.7	37.5
	3502	36.3	37.2	36.1	38.5	37.8	36.3
	3503	37.0	37.5	36.5	37.6	38.3	36.7
	3504	37.7	37.5	37.1	38.3	38.8	37.2
	3505	37.7	37.8	36.6	38.9	39.0	37.0
	3506	38.0	37.3	37.0	38.9	38.8	36.6
	3507	36.9	37.1	37.0	37.8	37.5	36.9
	3508	37.7	38.0	36.9	38.7	37.6	36.6
	3509	36.9	38.0	36.9	38.4	36.9	36.8
	3510	37.4	37.9	38.4	38.4	37.3	36.3

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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
4F	4501	37.9	38.5	36.3	38.3	39.2	36.2
	4502	36.9	37.4	36.6	38.5	38.3	38.0
	4503	37.8	38.1	38.6	39.0	39.1	37.0
	4504	37.6	38.0	37.8	38.8	39.7	37.5
	4505	36.8	37.6	36.7	38.7	38.3	37.0
	4506	36.6	37.3	37.2	38.8	38.8	38.1
	4507	36.5	37.9	36.9	38.6	38.7	38.3
	4508	37.0	37.5	37.9	39.0	38.7	37.9
	4509	36.2	37.4	37.3	39.1	38.8	36.8
	4510	36.8	37.7	37.3	38.5	39.1	36.3
	4511	36.6	38.0	37.9	38.2	38.8	37.1
	4512	36.8	38.1	36.8	38.4	38.3	36.5
	4513	36.8	37.8	38.1	38.1	38.7	37.3
	4514	38.1	37.6	37.1	38.7	37.9	37.5
	4515	37.6	37.7	37.8	37.6	38.2	37.5

Appendix 12

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		
- Lymphocytes	LYMPH		

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- 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		
- Kurloff Cell	KURL		

Appendix 12

- 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	Manual, Wright-Giemsa stain
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 12

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: 2001, 4005 and 4009.

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)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 12

Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	8.20	1.44	6.25	0.34	0.08	0.01	0.08
	1002	12.94	1.57	10.51	0.49	0.13	0.03	0.20
	1003	9.39	1.00	7.83	0.31	0.08	0.03	0.14
	1004	10.43	1.17	8.64	0.36	0.09	0.02	0.15
	1005	13.53	2.90	10.07	0.30	0.09	0.03	0.14
	1006	8.49	1.22	6.59	0.36	0.08	0.01	0.23
	1007	11.16	1.00	9.66	0.24	0.08	0.02	0.16
	1008	7.78	1.18	6.24	0.16	0.11	0.01	0.08
	1009	5.22	0.54	4.45	0.13	0.04	0.00	0.05
	1010	7.33	0.72	6.33	0.13	0.07	0.01	0.06
2M	2001	10.18	2.02	7.70	0.23	0.14	0.01	0.09
	2002	11.46	2.23	8.58	0.31	0.15	0.02	0.18
	2003	15.55	2.96	11.42	0.58	0.21	0.04	0.34
	2004	12.59	2.82	8.75	0.40	0.14	0.02	0.46
	2005	12.56	2.47	9.22	0.42	0.17	0.03	0.25
	2006	6.36	1.22	4.50	0.33	0.16	0.01	0.14
	2007	6.73	1.43	4.84	0.21	0.12	0.01	0.13
	2008	10.45	2.05	7.67	0.30	0.19	0.02	0.22
	2009	13.28	1.65	10.85	0.37	0.12	0.03	0.26
	2010	6.86	1.15	5.00	0.38	0.12	0.01	0.20

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	7.74	14.6	43.9	56.8	18.9	33.3	11.2
	1002	8.40	15.2	46.2	55.0	18.1	32.9	12.3
	1003	7.90	14.3	42.8	54.2	18.0	33.3	13.3
	1004	7.56	13.7	41.0	54.2	18.1	33.4	12.5
	1005	7.56	13.4	40.9	54.1	17.8	32.8	12.5
	1006	7.76	14.7	43.3	55.7	19.0	34.0	11.7
	1007	7.51	14.2	42.8	57.0	18.9	33.2	13.0
	1008	8.07	14.7	44.5	55.2	18.2	33.1	12.3
	1009	7.63	13.9	42.0	55.1	18.2	33.1	13.1
	1010	8.24	14.0	43.4	52.7	17.0	32.2	12.9
2M	2001	7.79	13.6	40.7	52.3	17.5	33.4	12.3
	2002	7.73	13.7	41.8	54.0	17.8	32.9	12.0
	2003	7.23	12.8	38.3	52.9	17.7	33.4	13.8
	2004	7.72	14.1	41.4	53.6	18.3	34.1	12.0
	2005	8.01	14.2	43.0	53.7	17.8	33.1	12.8
	2006	8.51	15.4	45.9	53.9	18.1	33.6	11.5
	2007	7.66	13.9	40.3	52.6	18.1	34.4	12.3
	2008	7.98	14.2	42.6	53.3	17.8	33.3	12.2
	2009	7.83	13.4	41.0	52.3	17.1	32.7	13.0
	2010	8.32	14.6	43.5	52.3	17.6	33.7	12.2

Appendix 12

Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	WBC MORPH
1M	1001	1081	202.8	--	--	--	--
	1002	1009	221.2	--	--	--	--
	1003	1217	282.1	--	--	--	--
	1004	1093	220.4	--	--	--	--
	1005	1074	206.7	--	--	--	--
	1006	1012	203.1	--	--	--	--
	1007	1182	297.1	--	--	--	--
	1008	993	232.5	--	--	--	--
	1009	1255	245.7	--	--	--	--
	1010	1290	270.2	--	--	--	--
2M	2001	1079	207.7	1+	1+	NAF	NAF
	2002	1114	236.3	--	--	--	--
	2003	919	262.1	--	--	--	--
	2004	1127	186.5	--	--	--	--
	2005	1159	211.2	--	--	--	--
	2006	1269	241.4	--	--	--	--
	2007	1007	190.3	--	--	--	--
	2008	1307	201.3	--	--	--	--
	2009	1253	217.2	--	--	--	--
	2010	977	181.8	--	--	--	--

Appendix 12

Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	8.68	4.16	3.89	0.20	0.11	0.01	0.30
	3002	15.06	6.64	7.73	0.30	0.12	0.02	0.25
	3003	14.14	4.30	9.07	0.32	0.22	0.02	0.20
	3004	11.19	6.03	4.63	0.25	0.16	0.01	0.11
	3005	12.78	3.47	8.61	0.19	0.21	0.02	0.28
	3006	14.09	5.53	7.93	0.21	0.21	0.02	0.18
	3007	8.81	2.27	5.93	0.24	0.20	0.02	0.16
	3008	12.71	3.02	8.63	0.55	0.23	0.04	0.25
	3009	13.41	4.70	7.95	0.27	0.21	0.02	0.26
	3010	8.36	2.40	5.58	0.20	0.05	0.02	0.12
4M	4001	19.83	13.68	5.16	0.27	0.32	0.03	0.38
	4002	22.32	16.88	4.52	0.23	0.19	0.04	0.46
	4003	18.07	8.86	8.32	0.27	0.25	0.04	0.33
	4004	23.08	16.46	5.76	0.32	0.26	0.04	0.23
	4005	17.51	8.23	9.11	0.00	0.18	0.00	--MDIFF
	4006	22.48	15.80	5.46	0.29	0.37	0.03	0.54
	4007	14.09	8.83	4.64	0.14	0.24	0.02	0.21
	4008	15.26	7.62	6.67	0.19	0.35	0.02	0.41
	4009	17.02	6.81	9.87	0.34	0.00	0.00	--MDIFF
	4010	18.52	10.87	6.88	0.29	0.24	0.03	0.23

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	7.79	13.7	41.4	53.1	17.6	33.2	12.9
	3002	7.07	12.7	38.4	54.3	18.0	33.1	12.5
	3003	7.34	12.8	38.3	52.2	17.4	33.3	12.5
	3004	7.62	13.9	41.1	54.0	18.2	33.7	13.2
	3005	7.44	13.7	40.8	54.8	18.3	33.5	12.9
	3006	8.20	14.7	44.0	53.7	17.9	33.3	12.3
	3007	8.12	14.4	43.7	53.8	17.8	33.0	12.7
	3008	7.86	13.8	41.3	52.5	17.6	33.5	12.0
	3009	8.11	13.8	41.5	51.1	17.0	33.1	12.9
	3010	8.33	14.8	46.5	55.8	17.8	31.8	12.1
4M	4001	8.07	14.3	43.4	53.8	17.7	32.9	13.8
	4002	8.70	15.0	45.8	52.7	17.3	32.8	13.2
	4003	8.29	14.1	43.7	52.7	17.0	32.2	13.3
	4004	8.45	14.5	44.3	52.4	17.2	32.8	13.6
	4005	7.45	12.8	39.5	53.0	17.1	32.3	13.9
	4006	8.64	15.2	45.9	53.1	17.6	33.1	13.2
	4007	7.61	13.2	40.0	52.6	17.4	33.1	13.6
	4008	8.00	13.8	42.1	52.6	17.2	32.7	13.4
	4009	8.03	14.5	44.4	55.3	18.1	32.6	12.8
	4010	7.51	13.5	40.6	54.0	18.0	33.4	13.7

Appendix 12

Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	WBC MORPH
3M	3001	846	189.4	--	--	--	--
	3002	1011	190.8	--	--	--	--
	3003	1091	191.1	--	--	--	--
	3004	965	192.5	--	--	--	--
	3005	1210	198.5	--	--	--	--
	3006	945	200.7	--	--	--	--
	3007	966	217.8	--	--	--	--
	3008	1369	210.8	--	--	--	--
	3009	1040	199.3	--	--	--	--
	3010	750	222.8	--	--	--	--
4M	4001	1128	251.7	--	--	--	--
	4002	1035	193.1	--	--	--	--
	4003	1129	197.2	--	--	--	--
	4004	1160	242.1	--	--	--	--
	4005	1145	174.7	2+	1+	NAF	NAF
	4006	872	198.7	--	--	--	--
	4007	1124	189.1	--	--	--	--
	4008	1109	194.0	--	--	--	--
	4009	950	168.1	1+	--	NAF	NAF
	4010	965	153.3	--	--	--	--

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	3.67	0.33	3.20	0.06	0.06	0.00	0.02
	1502	5.87	0.97	4.55	0.19	0.09	0.01	0.07
	1503	5.45	0.91	4.17	0.21	0.07	0.01	0.08
	1504	3.70	0.88	2.46	0.25	0.07	0.00	0.03
	1505	5.90	0.96	4.65	0.12	0.09	0.00	0.07
	1506	4.34	0.69	3.50	0.08	0.02	0.01	0.05
	1507	4.73	0.61	3.81	0.15	0.09	0.01	0.06
	1508	11.41	2.79	8.21	0.17	0.04	0.01	0.19
	1509	4.86	0.47	4.20	0.06	0.06	0.00	0.07
	1510	5.74	0.65	4.84	0.09	0.09	0.01	0.06
2F	2501	8.60	2.24	6.02	0.11	0.14	0.01	0.07
	2502	3.58	1.29	2.06	0.06	0.10	0.00	0.05
	2503	5.80	1.20	4.26	0.14	0.12	0.00	0.08
	2504	8.11	1.76	5.92	0.16	0.18	0.01	0.08
	2505	9.98	2.85	6.76	0.08	0.17	0.01	0.09
	2506	9.88	1.64	7.64	0.16	0.29	0.02	0.14
	2507	8.22	1.37	6.30	0.13	0.15	0.01	0.26
	2508	6.72	1.29	4.79	0.29	0.19	0.01	0.15
	2509	6.58	1.32	4.96	0.09	0.18	0.01	0.04
	2510	5.37	1.07	3.99	0.11	0.13	0.01	0.06

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	7.26	13.1	39.2	54.0	18.0	33.3	11.4
	1502	7.18	13.5	39.5	55.1	18.9	34.2	11.7
	1503	7.70	13.5	40.4	52.4	17.6	33.6	11.4
	1504	7.57	13.5	41.3	54.6	17.9	32.8	11.3
	1505	7.69	13.9	40.6	52.8	18.1	34.2	11.1
	1506	7.46	13.8	41.5	55.7	18.6	33.3	11.2
	1507	7.78	13.9	41.2	52.9	17.9	33.8	11.4
	1508	7.27	13.0	38.4	52.8	17.9	33.9	11.0
	1509	7.36	13.3	39.5	53.7	18.0	33.6	11.6
	1510	7.30	13.5	40.9	56.0	18.5	33.1	11.2
2F	2501	6.89	13.2	39.2	56.9	19.2	33.7	12.0
	2502	7.37	13.4	40.1	54.4	18.2	33.5	11.4
	2503	7.56	13.4	40.0	52.9	17.8	33.6	10.7
	2504	7.10	12.6	37.9	53.3	17.7	33.2	11.5
	2505	7.72	14.2	42.2	54.6	18.4	33.7	10.7
	2506	7.01	12.7	37.5	53.4	18.1	34.0	10.5
	2507	7.34	13.8	41.1	56.0	18.8	33.6	10.8
	2508	7.81	14.5	43.0	55.1	18.5	33.7	11.2
	2509	7.53	13.9	41.3	54.9	18.4	33.6	11.7
	2510	7.66	14.1	41.8	54.6	18.4	33.7	11.5

Appendix 12

Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	WBC MORPH
1F	1501	1072	157.7	--	--	--	--
	1502	1263	199.2	--	--	--	--
	1503	1036	198.1	--	--	--	--
	1504	1362	265.9	--	--	--	--
	1505	1061	175.9	--	--	--	--
	1506	1114	226.8	--	--	--	--
	1507	1048	167.7	--	--	--	--
	1508	1164	200.6	--	--	--	--
	1509	1284	220.1	--	--	--	--
	1510	1154	208.9	--	--	--	--
2F	2501	1113	161.3	--	--	--	--
	2502	875	184.2	--	--	--	--
	2503	1071	191.5	--	--	--	--
	2504	1162	214.1	--	--	--	--
	2505	1110	220.8	--	--	--	--
	2506	1038	192.8	--	--	--	--
	2507	948	197.7	--	--	--	--
	2508	852	235.0	--	--	--	--
	2509	743	268.0	--	--	--	--
	2510	791	205.6	--	--	--	--

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	8.68	3.71	4.58	0.13	0.20	0.00	0.05
	3502	6.93	3.19	3.37	0.08	0.22	0.00	0.06
	3503	5.35	2.79	2.32	0.08	0.13	0.00	0.04
	3504	8.89	3.72	4.56	0.10	0.40	0.01	0.10
	3505	12.16	4.01	7.48	0.19	0.22	0.02	0.23
	3506	10.07	5.87	3.80	0.09	0.25	0.01	0.05
	3507	8.59	2.79	5.30	0.12	0.26	0.01	0.12
	3508	4.23	1.44	2.48	0.08	0.15	0.00	0.08
	3509	5.80	2.15	3.34	0.10	0.18	0.00	0.03
	3510	9.34	3.92	4.89	0.13	0.26	0.01	0.14
4F	4501	10.43	6.27	3.65	0.14	0.25	0.01	0.11
	4502	11.77	6.84	4.48	0.10	0.25	0.01	0.09
	4503	9.58	5.56	3.63	0.08	0.18	0.01	0.13
	4504	11.35	7.77	3.15	0.12	0.23	0.01	0.08
	4505	9.60	6.12	3.12	0.08	0.23	0.01	0.04
	4506	8.81	5.33	3.09	0.05	0.27	0.01	0.05
	4507	14.62	7.90	6.00	0.11	0.36	0.02	0.22
	4508	12.72	7.42	4.46	0.26	0.48	0.01	0.09
	4509	6.11	3.44	2.37	0.06	0.14	0.01	0.09
	4510	13.69	6.45	6.52	0.26	0.38	0.02	0.07

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	7.14	13.2	38.4	53.8	18.5	34.4	11.7
	3502	7.13	13.2	39.0	54.7	18.5	33.8	12.3
	3503	7.17	12.5	37.8	52.7	17.4	33.0	11.4
	3504	7.12	13.2	38.5	54.0	18.6	34.4	11.8
	3505	7.21	13.3	39.6	54.9	18.4	33.5	11.6
	3506	6.82	12.2	36.5	53.5	18.0	33.6	11.8
	3507	7.40	13.4	40.5	54.7	18.1	33.1	11.6
	3508	7.35	13.1	39.7	54.0	17.8	33.0	11.7
	3509	7.22	13.1	39.1	54.1	18.2	33.7	11.5
	3510	7.02	12.9	38.7	55.2	18.4	33.4	12.8
4F	4501	7.76	14.1	41.9	53.9	18.1	33.6	11.9
	4502	6.94	12.8	37.4	53.9	18.5	34.3	12.8
	4503	7.21	13.3	39.7	55.1	18.5	33.5	13.0
	4504	7.29	13.2	39.2	53.7	18.1	33.7	12.1
	4505	7.21	13.1	39.2	54.3	18.2	33.4	12.0
	4506	7.32	13.6	40.0	54.7	18.6	33.9	12.5
	4507	7.90	13.3	39.6	50.1	16.8	33.6	12.2
	4508	7.20	13.5	40.2	55.8	18.7	33.5	12.2
	4509	7.72	13.9	41.1	53.2	18.0	33.7	12.3
	4510	7.08	13.4	40.3	57.0	19.0	33.3	12.2

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Individual Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	WBC MORPH
3F	3501	1232	167.2	--	--	--	--
	3502	1180	226.4	--	--	--	--
	3503	1025	201.5	--	--	--	--
	3504	1169	202.5	--	--	--	--
	3505	829	166.8	--	--	--	--
	3506	1167	213.3	--	--	--	--
	3507	1039	149.2	--	--	--	--
	3508	1127	216.7	--	--	--	--
	3509	1230	196.1	--	--	--	--
	3510	720	179.5	--	--	--	--
4F	4501	915	160.5	--	--	--	--
	4502	1077	168.6	--	--	--	--
	4503	769	166.3	--	--	--	--
	4504	962	174.2	--	--	--	--
	4505	1020	175.5	--	--	--	--
	4506	1027	230.0	--	--	--	--
	4507	820	161.9	--	--	--	--
	4508	669	203.7	--	--	--	--
	4509	699	256.6	--	--	--	--
	4510	918	144.9	--	--	--	--

Appendix 12

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	10.37	1.36	8.63	0.16	0.09	0.02	0.11
	1012	8.91	0.65	7.91	0.13	0.08	0.02	0.12
	1013	9.11	2.07	6.59	0.14	0.03	0.02	0.27
	1014	8.99	1.28	6.99	0.35	0.12	0.03	0.23
	1015	8.58	0.66	7.48	0.21	0.04	0.02	0.16
4M	4011	14.28	1.28	12.30	0.35	0.12	0.03	0.20
	4012	8.95	0.99	7.54	0.21	0.07	0.01	0.13
	4013	17.16	2.42	13.99	0.38	0.12	0.05	0.19
	4014	9.41	1.07	7.74	0.38	0.08	0.02	0.12
	4015	11.65	1.10	10.03	0.22	0.10	0.02	0.18

Appendix 12

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	7.46	14.4	41.1	55.2	19.3	35.0	13.2
	1012	7.98	15.0	42.0	52.6	18.8	35.7	13.0
	1013	7.05	12.4	36.7	52.1	17.5	33.7	14.6
	1014	8.53	15.7	44.9	52.6	18.4	34.9	12.6
	1015	7.03	14.5	40.2	57.1	20.6	36.0	12.4
4M	4011	7.54	14.0	41.0	54.4	18.6	34.2	13.9
	4012	7.36	14.0	40.4	54.9	19.1	34.8	14.4
	4013	8.26	15.0	44.9	54.4	18.2	33.4	13.8
	4014	8.77	15.2	44.1	50.2	17.3	34.5	14.3
	4015	8.02	14.9	42.4	52.8	18.6	35.3	13.8

Appendix 12

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	WBC MORPH
1M	1011	1040	277.0	--	--	--	--
	1012	982	249.9	--	--	--	--
	1013	707	285.4	--	--	--	--
	1014	1074	235.7	--	--	--	--
	1015	1216	166.4	--	--	--	--
4M	4011	1082	231.4	--	--	--	--
	4012	1268	223.3	--	--	--	--
	4013	1170	238.6	--	--	--	--
	4014	1214	285.0	--	--	--	--
	4015	1274	239.4	--	--	--	--

Appendix 12

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	6.54	0.60	5.68	0.11	0.07	0.01	0.07
	1512	3.09	0.53	2.34	0.11	0.07	0.00	0.04
	1513	3.42	0.68	2.37	0.16	0.12	0.01	0.07
	1514	4.10	1.17	2.65	0.10	0.11	0.00	0.07
	1515	5.62	0.90	4.40	0.14	0.10	0.01	0.08
4F	4511	4.05	0.50	3.36	0.06	0.07	0.01	0.05
	4512	4.97	0.65	3.96	0.17	0.11	0.00	0.08
	4513	1.88	0.48	1.32	0.03	0.03	0.00	0.02
	4514	5.31	0.66	4.27	0.24	0.05	0.00	0.08
	4515	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT

Appendix 12

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	7.18	13.1	38.4	53.5	18.3	34.2	11.5
	1512	7.47	13.4	39.9	53.4	17.9	33.5	11.6
	1513	7.74	14.0	40.8	52.7	18.2	34.4	11.1
	1514	6.76	13.2	37.0	54.7	19.5	35.6	11.6
	1515	7.11	12.7	37.3	52.4	17.8	34.0	11.1
4F	4511	7.11	12.9	38.0	53.5	18.2	34.0	12.8
	4512	7.16	13.4	38.5	53.8	18.7	34.8	12.9
	4513	6.79	12.9	37.1	54.6	19.0	34.8	12.9
	4514	7.21	13.6	40.5	56.2	18.9	33.7	12.3
	4515	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT

Appendix 12

Individual Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	WBC MORPH
1F	1511	1087	200.5	--	--	--	--
	1512	1335	215.7	--	--	--	--
	1513	1020	164.8	--	--	--	--
	1514	1126	134.9	--	--	--	--
	1515	833	110.7	--	--	--	--
4F	4511	1031	179.2	--	--	--	--
	4512	1013	174.4	--	--	--	--
	4513	957	176.1	--	--	--	--
	4514	1036	244.9	--	--	--	--
	4515	--CLOT	--CLOT	--	--	--	--

Appendix 13

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 13

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 (µg/dose)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 13

Individual Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1001	18.0	15.0	287	N
	1002	15.9	15.9	282	N
	1003	16.6	16.3	296	N
	1004	16.3	14.6	302	N
	1005	17.0	15.6	288	N
	1006	16.6	16.2	276	N
	1007	17.2	16.5	249	N
	1008	15.7	16.3	285	N
	1009	16.5	15.6	276	N
	1010	16.6	17.2	278	N
2M	2001	16.9	16.1	466	N
	2002	16.6	16.3	431	N
	2003	16.1	15.7	424	N
	2004	16.0	16.2	424	N
	2005	15.8	16.6	425	N
	2006	15.8	17.7	427	N
	2007	16.6	17.5	454	N
	2008	16.4	16.5	440	N
	2009	16.0	17.9	444	N
	2010	16.7	17.2	524	N

Appendix 13

Individual Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3M	3001	16.7	17.6	538	N
	3002	16.6	17.2	446	N
	3003	16.8	17.4	544	N
	3004	16.1	17.0	581	N
	3005	--CLOT	--CLOT	--CLOT	--CLOT
	3006	15.7	19.4	649	N
	3007	17.5	19.7	516	N
	3008	15.2	16.6	541	N
	3009	15.4	17.7	541	N
	3010	15.2	17.0	598	N
4M	4001	15.8	19.7	694	N
	4002	16.1	20.9	675	N
	4003	16.9	18.6	657	N
	4004	16.6	17.3	769	N
	4005	16.3	18.6	730	N
	4006	15.6	17.6	689	N
	4007	15.6	18.4	752	N
	4008	15.9	19.0	653	N
	4009	16.3	18.6	719	N
	4010	17.3	18.8	680	N

Appendix 13

Individual Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1501	17.7	14.0	197	N
	1502	16.7	15.4	242	N
	1503	16.6	17.0	219	N
	1504	16.0	16.7	196	N
	1505	16.7	15.9	213	N
	1506	17.1	17.2	185	N
	1507	17.5	15.8	185	N
	1508	16.8	17.0	247	N
	1509	17.0	14.9	214	N
	1510	17.1	16.5	245	N
2F	2501	16.9	17.0	277	N
	2502	17.4	16.0	312	N
	2503	17.1	16.0	309	N
	2504	16.5	15.7	373	N
	2505	16.5	16.6	390	N
	2506	18.0	16.3	356	N
	2507	16.9	15.1	266	N
	2508	17.0	15.7	306	N
	2509	16.3	15.7	360	N
	2510	17.3	15.2	325	N

Appendix 13

Individual Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3F	3501	17.0	15.9	413	N
	3502	17.5	17.1	518	N
	3503	17.5	16.5	468	N
	3504	16.8	17.0	488	N
	3505	16.5	16.9	384	N
	3506	16.9	16.0	429	N
	3507	17.4	16.6	454	N
	3508	16.6	16.7	393	N
	3509	16.3	16.8	491	N
	3510	17.5	18.6	513	N
4F	4501	17.2	18.8	491	N
	4502	18.1	17.8	511	N
	4503	17.0	18.5	462	N
	4504	18.5	18.2	493	N
	4505	17.1	17.6	513	N
	4506	17.3	17.6	508	N
	4507	16.5	19.1	506	N
	4508	17.2	19.3	516	N
	4509	18.1	18.8	511	N
	4510	19.5	17.3	578	N

Appendix 13

Individual Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1011	18.0	15.8	249	N
	1012	19.0	16.5	232	N
	1013	20.4	15.8	462	N
	1014	17.0	15.9	292	N
	1015	19.2	16.4	259	N
4M	4011	19.0	15.2	275	N
	4012	18.7	15.8	307	N
	4013	19.4	16.3	217	N
	4014	18.4	15.2	281	N
	4015	19.1	15.4	284	N

Appendix 13

Individual Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1511	17.6	17.4	187	N
	1512	18.0	13.4	203	N
	1513	17.9	15.6	215	N
	1514	19.1	15.6	222	N
	1515	17.6	15.7	182	N
4F	4511	17.1	15.1	213	N
	4512	16.0	13.8	166	N
	4513	18.0	15.5	176	N
	4514	18.5	15.5	223	N
	4515	--CLOT	--CLOT	--CLOT	--CLOT

Appendix 14

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 14

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 14

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)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 14

Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	113	42	123	2VBRR	577	0.06	14
	1002	81	32	145	2VBRR	264	0.06	12
	1003	76	34	128	2VBRR	192	0.07	11
	1004	92	32	103	2VBRR	503	0.05	13
	1005	132	35	99	2VBRR	882	0.05	16
	1006	57	27	69	2VBRR	155	0.08	12
	1007	65	33	112	2VBRR	274	0.06	16
	1008	85	32	135	2VBRR	404	0.05	13
	1009	89	30	114	2VBRR	276	0.10	17
	1010	110	29	128	2VBRR	618	0.05	12
2M	2001	129	46	131	2VBRR	860	0.03	15
	2002	81	44	117	2VBRR	263	0.09	14
	2003	82	44	88	2VBRR	253	0.04	13
	2004	96	46	135	2VBRR	422	0.04	14
	2005	85	41	108	2VBRR	327	0.04	15
	2006	57	28	129	2VBRR	113	0.08	10
	2007	69	36	116	2VBRR	190	0.00VBRR	13
	2008	56	41	119	2VBRR	133	0.06	12
	2009	65	32	118	2VBRR	168	0.06	12
	2010	70	30	131	2VBRR	173	0.07	11

Appendix 14

Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	147	61	101	5.9	3.8	2.1
	1002	0.4	132	91	74	6.2	4.0	2.2
	1003	0.3	147	56	49	5.9	3.6	2.3
	1004	0.4	128	55	69	5.7	3.8	1.9
	1005	0.4	169	77	64	6.0	3.8	2.2
	1006	0.3	161	85	130	6.2	4.0	2.2
	1007	0.4	207	69	69	6.1	3.7	2.4
	1008	0.4	154	77	83	5.9	3.9	2.0
	1009	0.4	119	79	30	5.9	3.8	2.1
	1010	0.4	129	52	31	5.9	3.7	2.2
2M	2001	0.3	149	79	114	5.9	3.5	2.4
	2002	0.3	133	57	62	6.1	3.7	2.4
	2003	0.3	135	65	48	5.9	3.4	2.5
	2004	0.4	102	41	43	5.8	3.6	2.2
	2005	0.3	99	56	44	5.9	3.6	2.3
	2006	0.3	137	73	90	6.2	3.8	2.4
	2007	0.4	117	57	37	5.7	3.4	2.3
	2008	0.3	116	59	52	5.8	3.6	2.2
	2009	0.3	150	70	88	5.9	3.6	2.3
	2010	0.3	133	59	90	5.9	3.6	2.3

Appendix 14

Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	1.8	10.5	7.4	143	5.0	103	N
	1002	1.8	10.4	7.1	143	4.7	102	N
	1003	1.6	10.2	7.5	143	5.0	103	N
	1004	2.0	10.8	8.0	142	5.1	103	N
	1005	1.7	10.7	7.9	141	5.6	102	N
	1006	1.8	10.6	7.2	144	5.2	105	N
	1007	1.5	10.4	8.2	141	5.9	102	N
	1008	2.0	10.6	8.6	144	5.7	105	N
	1009	1.8	10.8	7.6	141	5.8	102	H+
	1010	1.7	10.2	7.6	141	5.1	102	N
2M	2001	1.5	10.6	8.1	142	5.2	103	N
	2002	1.5	10.7	8.4	142	5.0	104	N
	2003	1.4	10.4	8.4	140	5.1	100	N
	2004	1.6	10.8	8.2	143	5.1	104	N
	2005	1.6	10.7	8.6	143	5.3	104	N
	2006	1.6	11.1	7.1	144	4.4	103	N
	2007	1.5	10.7	6.9	143	5.1	103	N
	2008	1.6	10.5	7.5	143	5.0	105	N
	2009	1.6	10.5	8.9	142	5.3	101	N
	2010	1.6	10.4	7.1	141	5.2	103	N

Appendix 14

Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	88	40	98	2VBRR	203	0.03	11
	3002	93	54	100	2VBRR	204	0.07	14
	3003	110	44	92	2VBRR	734	0.04	18
	3004	67	34	91	2VBRR	154	0.10	18
	3005	137	36	107	2VBRR	989	0.06	18
	3006	83	42	124	2VBRR	396	0.07	14
	3007	144	49	87	2VBRR	432	0.06	11
	3008	88	47	105	2VBRR	522	0.05	15
	3009	111	35	117	2VBRR	816	0.06	13
	3010	90	43	142	2VBRR	493	0.07	11
4M	4001	95	43	107	2VBRR	607	0.08	15
	4002	112	47	120	2VBRR	957	0.08	13
	4003	157	37	96	2VBRR	1464	0.04	19
	4004	114	29	103	2VBRR	680	0.10	12
	4005	85	26	89	2VBRR	418	0.03	14
	4006	102	30	136	2VBRR	545	0.06	13
	4007	70	26	97	2VBRR	216	0.06	11
	4008	112	27	90	2VBRR	714	0.09	13
	4009	65	28	77	2VBRR	203	0.05	14
	4010	86	33	117	2VBRR	248	0.10	15

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	0.4	122	44	33	5.8	3.3	2.5
	3002	0.3	190	68	136	5.7	3.4	2.3
	3003	0.4	122	79	48	6.0	3.4	2.6
	3004	0.4	126	45	40	5.7	3.5	2.2
	3005	0.4	164	82	90	6.3	3.5	2.8
	3006	0.4	131	62	96	5.9	3.5	2.4
	3007	0.4	123	76	64	6.1	3.4	2.7
	3008	0.4	137	88	80	6.1	3.5	2.6
	3009	0.4	137	64	38	6.4	3.6	2.8
	3010	0.4	145	47	52	6.4	3.7	2.7
4M	4001	0.4	168	80	104	6.0	3.4	2.6
	4002	0.5	126	56	42	6.5	3.6	2.9
	4003	0.4	122	68	75	6.3	3.5	2.8
	4004	0.4	144	79	73	6.1	3.5	2.6
	4005	0.4	165	78	95	6.1	3.3	2.8
	4006	0.4	133	73	57	6.3	3.3	3.0
	4007	0.4	145	62	75	6.2	3.4	2.8
	4008	0.4	139	60	63	5.9	3.4	2.5
	4009	0.3	184	59	74	6.1	3.2	2.9
	4010	0.4	206	39	53	5.7	3.2	2.5

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	9.9	7.2	143	5.3	104	N
	3002	1.5	10.2	8.1	141	5.0	103	N
	3003	1.3	10.2	7.9	142	5.2	102	N
	3004	1.6	10.8	8.2	141	5.0	103	N
	3005	1.3	11.1	8.9	142	5.7	100	N
	3006	1.5	10.6	7.8	143	5.1	104	N
	3007	1.3	10.9	8.6	142	5.6	102	N
	3008	1.3	10.9	7.2	142	5.3	102	N
	3009	1.3	10.8	7.1	140	5.4	100	N
	3010	1.4	10.7	7.2	141	5.4	102	N
4M	4001	1.3	10.4	8.9	140	5.8	98	N
	4002	1.2	10.1	8.6	142	5.4	101	N
	4003	1.3	10.3	9.1	139	5.7	99	N
	4004	1.3	10.7	8.4	141	5.4	102	N
	4005	1.2	10.5	9.4	140	4.9	99	N
	4006	1.1	10.6	9.0	143	5.5	103	N
	4007	1.2	10.8	7.9	142	5.9	103	N
	4008	1.4	10.4	8.9	141	5.1	99	N
	4009	1.1	10.6	7.7	142	5.5	103	N
	4010	1.3	10.6	7.4	141	5.2	103	N

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	113	40	67	2VBRR	638	0.03	15
	1502	86	27	75	2VBRR	375	0.11	14
	1503	72	35	71	2VBRR	142	0.11	12
	1504	66	30	32	2VBRR	203	0.09	13
	1505	87	24	47	2VBRR	355	0.03	12
	1506	89	31	84	2VBRR	313	0.09	15
	1507	136	33	70	2VBRR	666	0.06	13
	1508	93	40	57	2VBRR	149	0.15	15
	1509	116	28	64	2VBRR	836	0.07	14
	1510	75	24	44	2VBRR	135	0.07	16
2F	2501	111	39	46	2VBRR	634	0.06	16
	2502	84	33	66	2VBRR	216	0.06	12
	2503	118	28	59	2VBRR	546	0.05	14
	2504	116	33	55	2VBRR	393	0.06	16
	2505	101	28	68	2VBRR	529	0.09	17
	2506	110	37	71	2VBRR	588	0.08	20
	2507	95	34	58	2VBRR	510	0.05	19
	2508	91	27	45	2VBRR	464	0.06	14
	2509	125	22	84	2VBRR	995	0.04	18
	2510	82	32	66	2VBRR	136	0.05	14

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	0.4	158	76	43	6.0	4.1	1.9
	1502	0.5	137	78	60	6.8	4.8	2.0
	1503	0.4	194	75	58	6.9	5.1	1.8
	1504	0.4	178	99	73	7.0	5.1	1.9
	1505	0.3	131	58	45	5.9	4.2	1.7
	1506	0.4	118	64	43	6.3	4.6	1.7
	1507	0.4	123	86	40	6.5	4.3	2.2
	1508	0.4	208	67	54	6.8	5.0	1.8
	1509	0.4	143	80	50	6.5	4.4	2.1
	1510	0.5	171	73	37	6.5	4.5	2.0
2F	2501	0.4	143	99	45	6.2	4.0	2.2
	2502	0.3	108	55	42	6.3	4.4	1.9
	2503	0.4	118	59	38	6.1	4.4	1.7
	2504	0.4	103	89	69	6.7	4.3	2.4
	2505	0.4	112	66	54	6.6	4.4	2.2
	2506	0.4	118	88	55	5.9	3.9	2.0
	2507	0.5	120	88	48	6.3	4.4	1.9
	2508	0.4	174	133	135	6.4	4.3	2.1
	2509	0.4	136	82	41	5.9	3.7	2.2
	2510	0.4	152	71	26	5.9	3.7	2.2

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	2.2	10.3	5.4	143	4.9	106	N
	1502	2.4	10.7	5.8	142	4.3	103	N
	1503	2.8	11.0	6.6	140	4.7	101	N
	1504	2.7	10.9	6.3	142	4.7	104	N
	1505	2.5	10.8	7.5	141	4.8	103	N
	1506	2.7	10.5	7.5	144	4.5	107	N
	1507	2.0	10.7	9.0	142	4.9	101	N
	1508	2.8	10.7	5.6	140	4.5	103	N
	1509	2.1	10.3	7.8	141	5.2	101	N
	1510	2.3	10.4	8.0	142	4.8	105	N
2F	2501	1.8	10.9	7.8	143	5.0	105	N
	2502	2.3	10.4	7.6	144	4.2	107	N
	2503	2.6	10.2	9.4	143	4.6	102	N
	2504	1.8	11.1	7.9	142	4.5	104	N
	2505	2.0	11.1	7.9	141	5.2	102	N
	2506	2.0	10.4	7.4	143	4.7	105	N
	2507	2.3	11.1	8.3	142	5.2	102	N
	2508	2.0	11.3	8.1	142	4.6	103	N
	2509	1.7	10.4	7.3	142	4.7	102	N
	2510	1.7	10.4	6.8	142	4.6	105	N

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	65	30	83	2VBRR	132	0.03	17
	3502	88	30	57	2VBRR	509	0.06	14
	3503	89	26	65	2VBRR	328	0.05	12
	3504	83	27	58	2VBRR	408	0.07	18
	3505	194	103	46	2VBRR	535	0.09	21
	3506	97	41	45	2VBRR	314	0.06	14
	3507	102	24	74	2VBRR	508	0.06	17
	3508	191	43	59	2VBRR	598	0.05	17
	3509	148	26	74	2VBRR	1398	0.06	14
	3510	119	46	60	2VBRR	262	0.09	13
4F	4501	160	34	71	2VBRR	1405	0.08	15
	4502	100	31	55	2VBRR	542	0.15	14
	4503	126	44	53	2VBRR	514	0.08	12
	4504	97	32	62	2VBRR	407	0.10	18
	4505	158	128	46	2VBRR	165	0.11	14
	4506	126	35	76	2VBRR	821	0.11	15
	4507	71	29	78	2VBRR	141	0.11	20
	4508	100	29	74	2VBRR	213	0.04	18
	4509	131	74	82	2VBRR	226	0.09	16
	4510	97	35	93	2VBRR	273	0.11	18

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	0.5	131	74	46	6.1	4.0	2.1
	3502	0.5	147	68	50	6.0	3.8	2.2
	3503	0.4	105	84	53	6.8	4.5	2.3
	3504	0.5	130	87	51	6.9	4.6	2.3
	3505	0.5	115	95	29	6.5	4.3	2.2
	3506	0.4	115	92	42	6.4	4.2	2.2
	3507	0.5	141	67	46	6.3	3.9	2.4
	3508	0.5	147	57	34	6.2	3.8	2.4
	3509	0.4	121	71	34	6.6	4.0	2.6
	3510	0.5	114	79	41	6.3	3.8	2.5
4F	4501	0.6	124	47	52	6.1	3.8	2.3
	4502	0.5	134	81	60	6.5	4.1	2.4
	4503	0.5	124	66	54	6.6	4.1	2.5
	4504	0.5	144	39	41	5.8	3.6	2.2
	4505	0.4	128	98	86	7.1	4.6	2.5
	4506	0.4	124	80	36	6.7	4.3	2.4
	4507	0.5	131	102	67	7.1	4.4	2.7
	4508	0.5	141	55	27	6.5	4.0	2.5
	4509	0.4	168	68	55	5.9	3.5	2.4
	4510	0.5	128	41	42	6.4	3.9	2.5

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Individual Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	1.9	10.7	6.9	140	4.8	104	N
	3502	1.7	10.8	6.1	143	4.5	105	N
	3503	2.0	11.1	8.3	145	4.7	106	N
	3504	2.0	11.0	8.0	142	4.8	104	N
	3505	2.0	10.8	7.7	142	4.7	102	N
	3506	1.9	10.7	7.4	142	4.5	106	N
	3507	1.6	10.5	6.8	142	4.9	102	N
	3508	1.6	10.4	6.7	142	4.6	104	N
	3509	1.5	10.4	8.3	143	5.2	102	N
	3510	1.5	10.5	8.4	140	5.0	102	N
4F	4501	1.7	10.4	5.2	142	4.8	102	N
	4502	1.7	10.5	5.8	141	4.6	101	N
	4503	1.6	10.9	7.5	142	5.1	103	N
	4504	1.6	10.4	7.4	141	4.8	104	N
	4505	1.8	11.8	8.7	142	4.8	103	N
	4506	1.8	10.9	9.2	142	4.8	103	N
	4507	1.6	11.1	7.8	142	5.0	102	N
	4508	1.6	10.4	6.3	144	4.2	106	N
	4509	1.5	10.6	8.0	143	4.6	103	N
	4510	1.6	10.6	7.2	142	5.3	104	N

Appendix 14

Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	81	53	130	2VBRR	218	0.08	14
	1012	131	60	152	2VBRR	1195	0.07	21
	1013	151	77	152	2VBRR	651	0.15	20
	1014	80	53	131	2VBRR	297	0.07	17
	1015	63	59	99	2VBRR	123	0.08	18
4M	4011	62	31	142	2VBRR	337	0.05	17
	4012	58	40	105	2VBRR	148	0.08	16
	4013	64	46	111	2VBRR	144	0.08	21
	4014	130	23	71	2VBRR	1289	0.10	13
	4015	71	42	122	2VBRR	216	0.10	15

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Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	195	97	101	6.0	4.0	2.0
	1012	0.4	213	65	203	5.9	3.8	2.1
	1013	0.4	201	71	123	6.0	3.3	2.7
	1014	0.3	288	84	227	5.8	3.7	2.1
	1015	0.3	237	75	62	5.6	3.8	1.8
4M	4011	0.3	241	84	97	5.9	3.6	2.3
	4012	0.4	209	88	109	5.8	4.0	1.8
	4013	0.3	176	66	88	5.9	3.9	2.0
	4014	0.3	173	58	67	6.4	4.0	2.4
	4015	0.3	159	65	80	5.9	3.9	2.0

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Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	2.0	10.7	6.3	141	5.3	103	N
	1012	1.8	10.6	7.7	140	6.1	100	L+
	1013	1.2	10.8	7.1	139	5.3	101	N
	1014	1.8	11.0	7.7	138	5.1	99	N
	1015	2.1	10.5	7.8	139	5.4	101	N
4M	4011	1.6	10.3	8.0	139	5.4	101	N
	4012	2.2	10.8	7.4	140	4.8	103	N
	4013	2.0	11.3	6.7	140	5.1	101	N
	4014	1.7	11.2	8.4	140	5.6	100	N
	4015	2.0	11.0	7.3	141	5.1	102	N

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Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	149	46	38	2VBRR	954	0.10	18
	1512	106	55	66	2VBRR	832	0.04	17
	1513	147	40	43	2VBRR	1208	0.08	14
	1514	116	36	53	2VBRR	577	0.05	12
	1515	116	33	44	2VBRR	748	0.07	18
4F	4511	77	29	40	2VBRR	249	0.05	14
	4512	70	41	61	2VBRR	190	0.06	15
	4513	75	29	67	2VBRR	166	0.03	13
	4514	89	46	74	2VBRR	146	0.10	16
	4515	137	52	44	2VBRR	235	0.07	16

Appendix 14

Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	151	79	149	6.8	5.0	1.8
	1512	0.4	167	59	43	6.0	4.2	1.8
	1513	0.4	150	89	75	6.6	4.9	1.7
	1514	0.4	111	75	51	6.3	4.3	2.0
	1515	0.4	110	69	49	6.3	4.5	1.8
4F	4511	0.4	127	80	51	5.8	4.0	1.8
	4512	0.4	172	109	54	6.8	4.9	1.9
	4513	0.4	156	75	43	6.3	4.4	1.9
	4514	0.5	134	58	44	6.6	4.6	2.0
	4515	0.3	135	66	64	6.0	4.0	2.0

Appendix 14

Individual Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	11.3	4.5	139	4.8	101	N
	1512	2.3	10.9	6.0	141	4.8	103	N
	1513	2.9	11.2	6.7	139	4.8	100	N
	1514	2.2	11.0	6.4	139	4.6	103	N
	1515	2.5	10.7	6.7	140	4.5	101	N
4F	4511	2.2	10.5	6.1	140	4.5	101	N
	4512	2.6	11.3	6.3	140	4.4	101	N
	4513	2.3	10.4	5.7	140	4.8	106	N
	4514	2.3	10.8	7.3	140	4.6	102	N
	4515	2.0	11.3	7.5	139	5.0	103	N

Appendix 15

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.

Note:

For α1-acid Glycoprotein

Lower Limit of Quantification (LLOQ) = 12.50 ng/mL, <12.50 was assigned as 12.50/2 (6.25 ng/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)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	1001	82.79	17.80
	1002	59.86	26.39
	1003	59.97	19.47
	1004	70.68	18.11
	1005	85.86	13.54
	1006	80.98	18.24
	1007	78.53	17.88
	1008	62.35	27.15
	1009	62.22	22.96
	1010	39.27	17.46

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
2	2001	213.56	27.77
	2002	145.50	26.22
	2003	110.92	15.01
	2004	154.54	28.33
	2005	159.00	26.63
	2006	240.76	32.77
	2007	126.43	18.00
	2008	143.42	29.83
	2009	186.56	72.25
	2010	186.05	9.88

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
3	3001	222.77	75.17
	3002	239.63	59.87
	3003	298.46	122.47
	3004	322.69	124.06
	3005	317.12	455.91
	3006	285.91	311.74
	3007	340.18	167.68
	3008	239.46	31.75
	3009	407.35	86.74
	3010	272.53	150.96

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
4	4001	455.73	697.71
	4002	526.71	1294.84
	4003	457.33	1635.44
	4004	462.10	970.90
	4005	431.52	1884.14
	4006	566.37	1841.50
	4007	446.41	643.96
	4008	508.00	410.55
	4009	398.94	1421.71
	4010	422.96	1008.33

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	1501	50.57	17.59
	1502	48.60	21.66
	1503	<12.50	15.75
	1504	<12.50	22.99
	1505	72.74	26.27
	1506	53.17	25.54
	1507	60.63	22.42
	1508	<12.50	36.99
	1509	41.99	17.85
	1510	43.91	29.73

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
2	2501	93.71	9.41
	2502	107.13	30.38
	2503	135.83	47.97
	2504	129.54	77.09
	2505	181.20	54.35
	2506	88.62	19.45
	2507	96.28	18.88
	2508	175.03	37.19
	2509	150.48	21.73
	2510	143.14	13.49

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
3	3501	205.86	37.71
	3502	222.79	61.94
	3503	210.58	89.38
	3504	220.88	92.47
	3505	284.59	17.17
	3506	234.96	29.80
	3507	183.68	44.96
	3508	256.17	44.21
	3509	362.26	58.85
	3510	336.36	50.32

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
4	4501	424.90	256.46
	4502	281.59	364.66
	4503	401.27	156.60
	4504	468.62	638.23
	4505	343.45	129.64
	4506	449.31	231.02
	4507	492.44	245.89
	4508	476.83	147.58
	4509	592.07	101.92
	4510	563.33	339.84

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 57
Males

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	1011	91.34	17.01
	1012	106.30	23.06
	1013	387.60	31.78
	1014	95.20	14.57
	1015	43.40	18.40
4	4011	76.86	47.97
	4012	107.88	9.33
	4013	70.23	41.19
	4014	117.37	35.12
	4015	70.51	47.29

Appendix 15

Individual α1-acid Glycoprotein and α2-macroglobulin Values

Day 57
Females

Group 1 - Reference Item Group 4 - mRNA-1443 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	1511	52.87	61.31
	1512	41.90	14.13
	1513	48.44	19.65
	1514	58.19	23.02
	1515	52.24	19.66
4	4511	61.88	21.02
	4512	48.82	42.49
	4513	60.30	69.27
	4514	63.72	25.60
	4515	59.58	26.40

Appendix 16

Individual Cytokines 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	b	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-1α

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)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 16

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	118.99	<11.70	339.91
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	90.57	<11.70	345.25
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	74.42	<11.70	321.02
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	94.08	<11.70	<141.00
		57	<11.70	<352.00	<2.93	54.11	<11.70	<141.00
	1012	1 - 6 h Post Dose	373.33	<352.00	<2.93	203.22	<11.70	<141.00
		15 - 6 h Post Dose	42.92	<352.00	<2.93	110.39	<11.70	<141.00
		29 - 6 h Post Dose	52.89	<352.00	<2.93	116.52	<11.70	302.80
		43 - 6 h Post Dose	48.07	<352.00	<2.93	74.02	<11.70	<141.00
		57	42.20	<352.00	<2.93	68.19	<11.70	<141.00
	1013	1 - 6 h Post Dose	<11.70	<352.00	<2.93	319.79	<11.70	481.45
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	210.00	<11.70	305.49
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	162.07	<11.70	576.30
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	454.12	<11.70	386.09
		57	<11.70	<352.00	<2.93	736.65	<11.70	<141.00

Appendix 16

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	<11.70	<352.00	<2.93	115.16	<11.70	294.91
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	138.43	<11.70	403.76
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	75.74	<11.70	521.48
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	110.75	<11.70	469.74
		57	<11.70	<352.00	<2.93	75.15	<11.70	343.06
	1015	1 - 6 h Post Dose	332.68	<352.00	<2.93	252.03	<11.70	331.30
		15 - 6 h Post Dose	184.22	<352.00	6.57	183.64	<11.70	354.33
		29 - 6 h Post Dose	34.56	<352.00	6.57	125.26	<11.70	478.17
		43 - 6 h Post Dose	29.24	<352.00	5.98	105.66	<11.70	406.39
		57	43.04	<352.00	6.27	111.51	<11.70	319.41

Appendix 16

Individual Cytokine Values

Males

Group 4 - mRNA-1443 96 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	<11.70	<352.00	<2.93	145.79	<11.70	343.16
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	101.29	<11.70	324.02
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	142.11	<11.70	421.85
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	505.29	<11.70	389.83
		57	<11.70	<352.00	<2.93	76.34	<11.70	<141.00
	4012	1 - 6 h Post Dose	<11.70	<352.00	<2.93	128.93	<11.70	367.80
		15 - 6 h Post Dose	310.85	<352.00	<2.93	378.00	<11.70	<141.00
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	395.12	<11.70	319.08
		43 - 6 h Post Dose	31.99	<352.00	<2.93	655.51	<11.70	297.27
		57	304.73	<352.00	<2.93	135.16	<11.70	<141.00
	4013	1 - 6 h Post Dose	<11.70	<352.00	<2.93	190.88	<11.70	521.48
		15 - 6 h Post Dose	140.34	<352.00	<2.93	200.06	<11.70	381.01
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	152.64	<11.70	589.28
		43 - 6 h Post Dose	<11.70	775.66	6.07	401.74	<11.70	535.55
		57	135.95	<352.00	<2.93	111.92	<11.70	<141.00

Appendix 16

Individual Cytokine Values

Males

Group 4 - mRNA-1443 96 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	<11.70	<352.00	<2.93	234.42	<11.70	563.78
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	180.90	<11.70	441.75
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	239.72	<11.70	528.55
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	276.81	<11.70	525.13
		57	<11.70	<352.00	<2.93	87.70	<11.70	<141.00
	4015	1 - 6 h Post Dose	<11.70	<352.00	7.67	151.29	<11.70	533.75
		15 - 6 h Post Dose	<11.70	<352.00	7.67	253.85	<11.70	423.99
		29 - 6 h Post Dose	<11.70	<352.00	9.38	612.87	<11.70	478.21
		43 - 6 h Post Dose	<11.70	919.49	8.66	581.21	<11.70	505.05
		57	<11.70	<352.00	<2.93	90.16	<11.70	<141.00

Appendix 16

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	<11.70	<352.00	<2.93	137.57	<11.70	<141.00
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	129.74	<11.70	391.57
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	117.83	<11.70	<141.00
		43 - 6 h Post Dose	<11.70 b	<352.00 b	<2.93 b	97.81 b	<11.70 b	<141.00
		57	<11.70	<352.00	<2.93	92.24	<11.70	<141.00
	1512	1 - 6 h Post Dose	SNC	SNC	SNC	SNC	SNC	SNC
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	82.27	<11.70	290.50
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	60.33	<11.70	361.51
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	80.94	<11.70	283.54
		57	<11.70	<352.00	<2.93	71.84	<11.70	<141.00
	1513	1 - 6 h Post Dose	<11.70	<352.00	<2.93	96.19	<11.70	<141.00
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	76.11	<11.70	<141.00
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	57.59	<11.70	310.43
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	69.10	<11.70	<141.00
		57	<11.70	<352.00	<2.93	73.49	<11.70	<141.00

Appendix 16

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	1514	1 - 6 h Post Dose	<11.70	<352.00	<2.93	95.18	<11.70	<141.00
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	108.26	<11.70	357.16
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	79.41	<11.70	323.91
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	62.74	<11.70	299.91
		57	<11.70	<352.00	<2.93	76.36	<11.70	358.52
	1515	1 - 6 h Post Dose	114.70	<352.00	<2.93	105.69	<11.70	<141.00
		15 - 6 h Post Dose	51.83	<352.00	<2.93	102.27	<11.70	<141.00
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	104.85	<11.70	566.67
		43 - 6 h Post Dose	60.09	<352.00	<2.93	103.83	<11.70	<141.00
		57	61.38	<352.00	<2.93	87.49	<11.70	<141.00

Appendix 16

Individual Cytokine Values

Females

Group 4 - mRNA-1443 96 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	126.97	<11.70	343.19
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	494.92	<11.70	430.21
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	954.28	<11.70	562.70
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	1382.09	24.33	506.13
		57	<11.70	<352.00	<2.93	58.24	<11.70	<141.00
	4512	1 - 6 h Post Dose	<11.70	<352.00	<2.93	146.30	<11.70	349.22
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	197.62	<11.70	317.25
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	616.18	<11.70 b	435.24
		43 - 6 h Post Dose	<11.70	883.36	<2.93	553.58	<11.70	430.49
		57	<11.70	<352.00	<2.93	102.39	<11.70	<141.00
	4513	1 - 6 h Post Dose	<11.70	<352.00	<2.93	122.24	<11.70	446.67
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	108.51	<11.70	449.38
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	740.58	<11.70	650.91
		43 - 6 h Post Dose	<11.70	<352.00	7.45	471.06	<11.70	463.41
		57	<11.70	<352.00	<2.93	59.12	<11.70	<141.00

Appendix 16

Individual Cytokine Values

Females

Group 4 - mRNA-1443 96 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	88.17	<11.70	503.12
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	78.31	<11.70	510.88
		29 - 6 h Post Dose	<11.70	<352.00	<2.93	161.92	<11.70	470.31
		43 - 6 h Post Dose	<11.70	<352.00	<2.93	98.82	<11.70	333.88
		57	<11.70	<352.00	<2.93	66.57	<11.70	<141.00
	4515	1 - 6 h Post Dose	39.61	<352.00	<2.93	130.21	<11.70	953.07
		15 - 6 h Post Dose	<11.70	<352.00	<2.93	104.40	<11.70	494.92
		29 - 6 h Post Dose	26.41	<352.00	<2.93	141.97	<11.70	602.45
		43 - 6 h Post Dose	<11.70	<352.00	7.42	328.18	<11.70	461.59
		57	167.85	<352.00	<2.93	149.22	<11.70	<141.00

Appendix 17

FINAL REPORT

Study Phase: Ophthalmology Evaluation

Test Facility Study No. 5002158

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)

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Appendix 17

LIST OF APPENDICES

Appendix 17

1. INTRODUCTION

This report presents the ophthalmology evaluations for the study entitled *A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 in Sprague-Dawley Rats followed by a 2-Week Recovery Period* (Study No. 5002158).

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 (µg/dose)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1443	10 / 9.6	200	0.05 / 0.048	10	10	-	-
3	mRNA-1443	30 / 29	200	0.15 / 0.145	10	10	-	-
4	mRNA-1443	100 / 96	200	0.5 / 0.48	10	10	5	5

- : Not applicable
[a] Values based on SoA issued on 16 Mars 2017 / Values based on SoA issued on 30 May 2017

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 17

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-1443 by Intramuscular Injection to Sprague Dawley Rats for 6 Weeks at doses of 10 / 9.6, 30 / 29, and 100 / 96 µg/dose did not result in any test item-related ophthalmic changes.

Appendix 17

5. REPORT APPROVAL

(b) (6) _____ Date: 11 SEP 2017

Appendix 17

Appendix 1
Individual Ophthalmic Findings

Appendix 17

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 17

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)[a]
1	Reference Item	0
2	mRNA-1443	10 / 9.6
3	mRNA-1443	30 / 29
4	mRNA-1443	100 / 96

[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 30 May 2017.

Appendix 17
Appendix 1

Individual Ophthalmic Findings

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-8	-7	41	42
1	m	1001	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		1003	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		1004	Lens Op, Cortex, Ant, Multi	Left	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		1007	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		1008	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		1010	Cornea, Op, Multi, Pinpoint	Left	.	.	.	1
			Lens,Op ,Nucleus	Left	.	1	.	1
		1011	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
			Retina, Fold	Right	.	X	.	X
			Retina, Fold	Left	.	X	.	X
		1012	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
		1013	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		1015	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 17
Appendix 1

Individual Ophthalmic Findings

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-8	-7	41	42
2	m	2002	Lens Op, Cortex, Ant, Focal	Left Temporal	.	.	.	1
		2003	Lens Op, Cortex, Ant, Multi	Left Superior	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		2005	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		2006	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		2007	Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		2008	Cornea, Op, Multi, Pinpoint	Right	.	1	.	.
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 17
Appendix 1

Individual Ophthalmic Findings

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-8	-7	41	42
3	m	3001	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		3002	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		3006	Lens,Op ,Nucleus	Right	.	1	.	1
			Lens,Op ,Nucleus	Left	.	1	.	1
		3007	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		3008	Lens,Op ,Nucleus	Right	.	1	.	1
		3010	Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
			Lens,Op ,Nucleus	Right	.	1	.	1

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 17
Appendix 1

Individual Ophthalmic Findings

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-8	-7	41	42
4	m	4001	Lens Op, Cortex, Ant, Focal	Right Inferior	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
		4002	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4004	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		4005	Vitreous, Hemorrhage	Right	.	1	.	.
			Lens,Op ,Nucleus	Left	.	1	.	1
		4006	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		4007	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	.
		4009	Cornea, Opacity, Focal	Left	.	1	.	1
			Iris, Pers Pup Membrane	Right	.	X	.	X
			Lens Op, Cortex, Ant, Focal	Right Supero-Nasal	.	.	.	1
		4013	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
			Lens,Op ,Nucleus	Right	.	1	.	2
		4014	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4015	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 17
Appendix 1

Individual Ophthalmic Findings

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-8	-7	41	42
1	f	1501	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		1504	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1505	Lens Op, Cortex, Ant, Focal	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		1507	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1508	Cornea, Loss of Luster	Left	.	.	X	.
		1510	Lens Op, Cortex, Ant, Focal	Right Inferior	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		1512	Cornea, Op, Multi, Pinpoint	Right	1	.	.	.
			Cornea, Op, Multi, Pinpoint	Left	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	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

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Appendix 1

Individual Ophthalmic Findings

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-8	-7	41	42
2	f	2501	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	1	.
		2502	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
			Lens,Op ,Nucleus	Left	1	.	1	.
		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	.
		2505	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		2508	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		2509	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
			Lens,Op ,Nucleus	Left	1	.	1	.
		2510	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 17
Appendix 1

Individual Ophthalmic Findings

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-8	-7	41	42
3	f	3502	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3503	Cornea, Loss of Luster	Right	.	.	X	.
			Cornea, Loss of Luster	Left	.	.	X	.
		3504	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
		3505	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
			Lens,Op ,Nucleus	Left	1	.	1	.
		3506	Lens,Op ,Nucleus	Right	.	.	1	.
		3508	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3509	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		3510	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 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 17
Appendix 1

Individual Ophthalmic Findings

5002158

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-8	-7	41	42
4	f	4501	Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
			Lens Nucleus Prominent	Right	X	.	X	.
			Lens Nucleus Prominent	Left	X	.	X	.
		4502	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		4504	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4505	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4506	Lens Op, Cortex, Ant, Focal	Left Superior	.	.	1	.
		4507	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
			Lens,Op ,Nucleus	Right	.	.	2	.
		4510	Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
		4511	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4512	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		4514	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
			Lens,Op ,Nucleus	Right	1	.	1	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight

Group 1 - 0 ug/dose Group 2 - 9.6 ug/dose Group 3 - 29 ug/dose Group 4 - 96 ug/dose

Appendix 18

Final Report

To

Valera, A Moderna Venture

on

Immunogenic Response of Rat T Cells following mRNA-1443 Vaccination

August 24, 2017

Appendix 18

Final Report

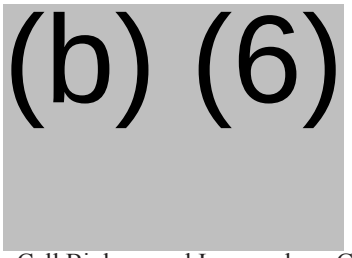
Immunogenic Response of Rat T Cells following mRNA-1443 Vaccination

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



Cell Biology and Immunology Group

Project: 15119.01.01.38
Submitted: August 24, 2017

Appendix 18

TABLE OF CONTENTS

Appendix 18

INTRODUCTION

The objective of the present study was to evaluate the T cell responses of rats vaccinated with mRNA-1443. Rat blood cells were stimulated with overlapping peptide library for pp65 and interferon gamma (INFγ) producing T cells 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. 5002158). In total, 80 blood samples were received from CRLM over the course of two days, 03-May-2017 (male rat samples) and 04-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.

(b) (4)

Appendix 18

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 18

RESULTS and **CONCLUSIONS**

The objective of this study was to evaluate the T cell responses of rats vaccinated with mRNA-1443 by assessment of Interferon gamma (INFγ) producing T cells by intracellular cytokine staining and flow cytometric analysis. There was minimal noted antigen-specific response to the pp-65 peptide library seen in this study.

A detailed table of individual animal responses is presented in the Appendix (p.7-14). A summary of INFγ production responses are presented in the table below.

Summary of Results - pp65 Specific INFγ Response

	Group	Test material	N	Dose level (μg)	pp65 specific CD4+ T cells Range (%)*;	Mean (%);	SD	pp65 specific CD8+ T cells Range (%)*;	Mean (%);	SD
Males	1	Reference	10	0	0.00 - 0.18;	0.00;	0.13	0.00 - 0.00;	0.00;	0.07
	2	mRNA-1443	10	9.6	0.00 - 0.27;	0.00;	0.12	0.00 - 1.07;	0.12;	0.34
	3	mRNA-1443	10	29	0.00 - 0.22;	0.00;	0.20	0.00 - 0.57;	0.00;	0.45
	4	mRNA-1443	9	96	0.00 - 0.10;	0.00;	0.11	0.00 - 0.41;	0.00;	0.37
Females	1	Reference	10	0	0.00 - 0.48;	0.00;	0.25	0.00 - 0.18;	0.01;	0.09
	2	mRNA-1443	10	9.6	0.00 - 0.62;	0.00;	0.56	0.00 - 0.22;	0.01;	0.11
	3	mRNA-1443	10	29	0.00 - 0.48;	0.00;	0.34	0.00 - 0.17;	0.01;	0.10
	4	mRNA-1443	10	96	0.00 - 0.68;	0.09;	0.38	0.00 - 0.55;	0.00;	0.43

*For purpose of Range and Mean calculation, values < 0.00 following Unstimulated Control subtraction were set to 0.00 for reporting.

Conclusions

The mRNA-1443 elicited minimal CD4 and CD8 T cell responses to pp65. The animals that received all dose levels of mRNA-1443 showed minimal and varying T cell responses for pp65 peptide library. In male rats immunized with 96 μg of mRNA-1443, the range of pp65-specific CD4 and CD8 T cells secreting IFNγ were 0-0.10% and 0-0.41%, respectively. In female rats that received 96 μg of mRNA-1443, the range of pp65-specific CD4 and CD8 T cells were 0-0.68% and 0-0.55%, respectively.

Male rats immunized with 29 μg of mRNA-1443, the range of pp65-specific CD4 and CD8 T cells secreting IFNγ were 0-0.22% and 0-0.57%, respectively. In female rats that received 29 μg of mRNA-1443, the range of pp65-specific CD4 and CD8 T cells were 0-0.48% and 0-0.17%, respectively.

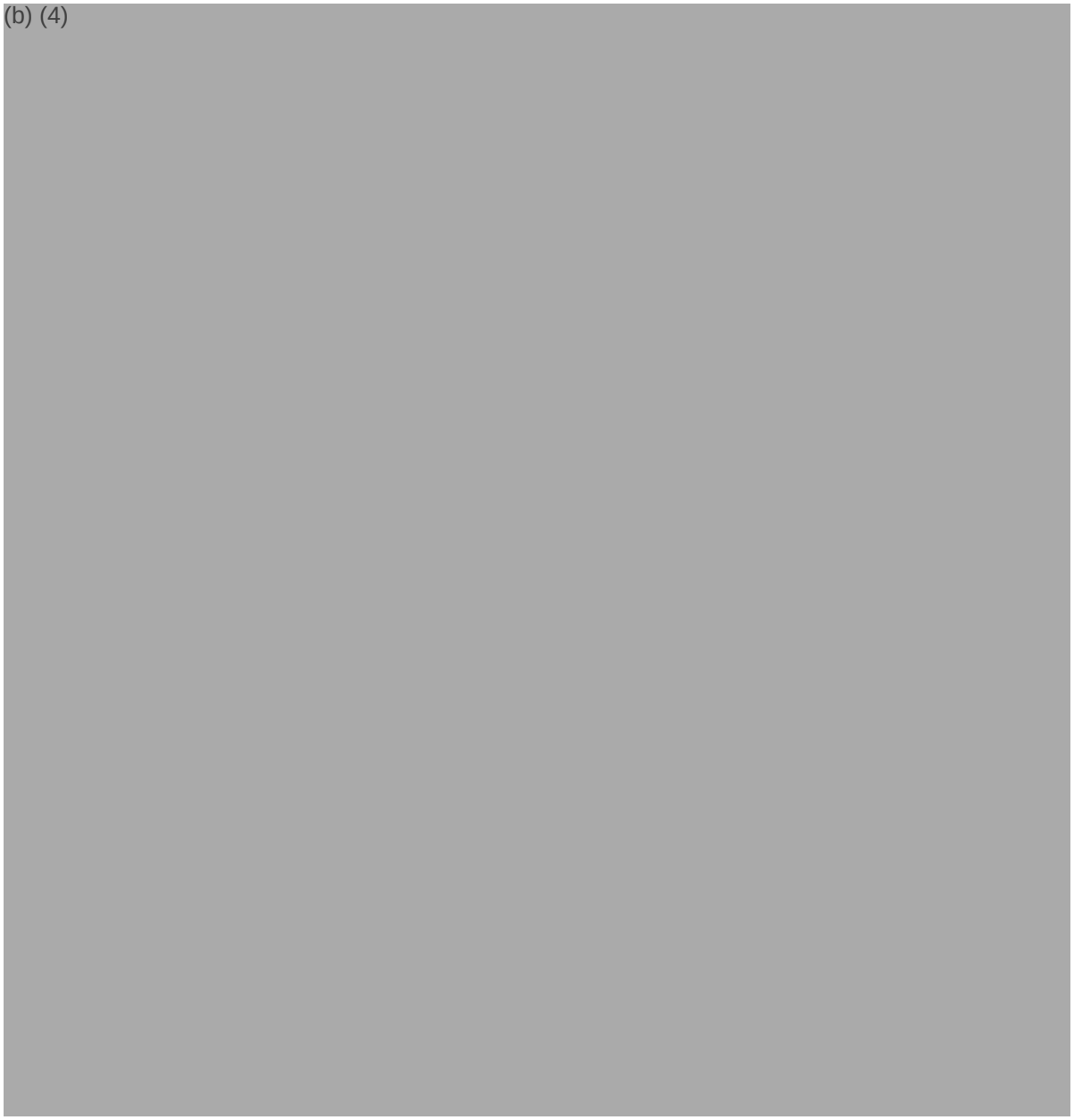
Male rats immunized with 9.6 μg of mRNA-1443, the range of pp65-specific CD4 and CD8 T cells secreting IFNγ were 0-0.27% and 0-1.07%, respectively. In female rats that received 9.6 μg of mRNA-1443, the range of pp65-specific CD4 and CD8 T cells were 0-0.62% and 0-0.22%, respectively.

Appendix 18

Appendix

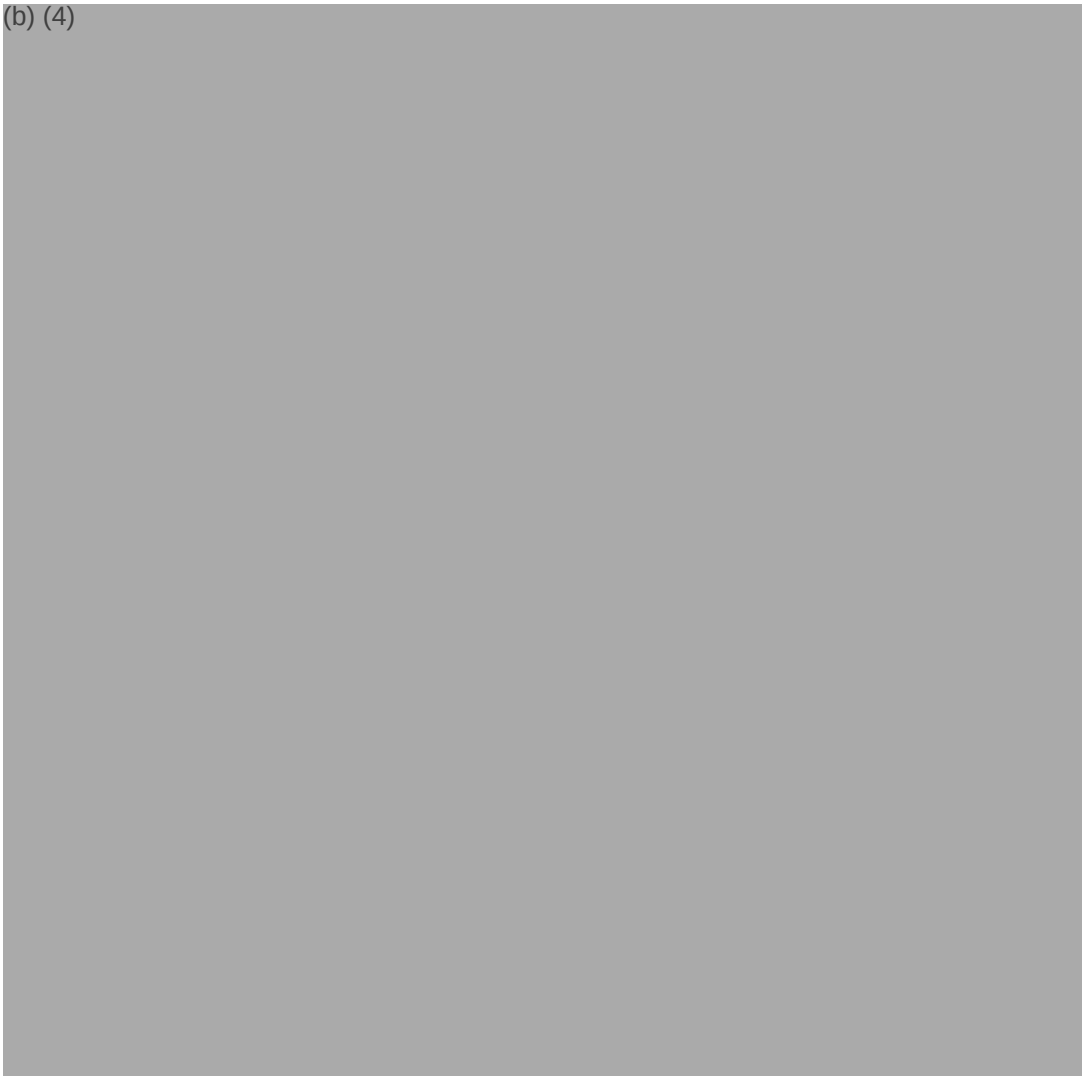
Appendix 18

(b) (4)



Appendix 18

(b) (4)



Appendix 18

mRNA-1443 - Intracellular IFNγ Production following Antigen Stimulation
Group 1 - Males

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated 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	0.14	0.21		
	Stimulated	9.41	24.44	9.27	24.23
	pp65	0.22	0.00	0.08	-0.21
1002	Unstimulated	0.07	0.00		
	Stimulated	1.85	5.06	1.78	5.06
	pp65	0.00	0.00	-0.07	0.00
1003	Unstimulated	0.10	0.00		
	Stimulated	2.29	7.99	2.19	7.99
	pp65	0.00	0.00	-0.10	0.00
1004	Unstimulated	0.00	0.00		
	Stimulated	3.48	7.14	3.48	7.14
	pp65	0.00	0.00	0.00	0.00
1005	Unstimulated	0.30	0.00		
	Stimulated	10.60	44.44	10.29	44.44
	pp65	0.00	0.00	-0.30	0.00
1006	Unstimulated	0.00	0.00		
	Stimulated	3.53	8.34	3.53	8.34
	pp65	0.10	0.00	0.10	0.00
1007	Unstimulated	0.06	0.00		
	Stimulated	5.76	17.32	5.71	17.32
	pp65	0.04	0.00	-0.02	0.00
1008	Unstimulated	0.04	0.00		
	Stimulated	14.83	38.54	14.79	38.54
	pp65	0.05	0.00	0.01	0.00
1009	Unstimulated	0.00	0.00		
	Stimulated	1.14	2.21	1.14	2.21
	pp65	0.18	0.00	0.18	0.00
1010	Unstimulated	0.00	0.00		
	Stimulated	8.71	40.81	8.71	40.81
	pp65	0.00	0.00	0.00	0.00

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
Group 1 Mean	Unstimulated	0.07	0.02		
	Stimulated	6.16	19.63	6.09	19.61
	pp65	0.06	0.00	-0.01	-0.02
Group 1 StDev	Unstimulated	0.09	0.07		
	Stimulated	4.53	16.28	4.50	16.27
	pp65	0.08	0.00	0.13	0.07

Appendix 18

mRNA-1443 - Intracellular IFNγ Production following Antigen Stimulation
Group 2 – Males

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated 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	0.00	0.00		
	Stimulated	10.30	24.89	10.30	24.89
	pp65	0.00	0.11	0.00	0.11
2002	Unstimulated	0.00	0.00		
	Stimulated	11.57	45.32	11.57	45.32
	pp65	0.00	0.00	0.00	0.00
2003	Unstimulated	0.00	0.00		
	Stimulated	7.49	20.96	7.49	20.96
	pp65	0.00	0.00	0.00	0.00
2004	Unstimulated	0.09	0.00		
	Stimulated	3.27	8.18	3.18	8.18
	pp65	0.09	0.00	0.00	0.00
2005	Unstimulated	0.09	0.00		
	Stimulated	4.73	8.36	4.65	8.36
	pp65	0.00	0.00	-0.09	0.00
2006	Unstimulated	0.00	0.00		
	Stimulated	4.53	13.69	4.53	13.69
	pp65	0.27	1.07	0.27	1.07
2007	Unstimulated	0.22	0.00		
	Stimulated	4.59	11.66	4.37	11.66
	pp65	0.00	0.00	-0.22	0.00
2008	Unstimulated	0.14	0.00		
	Stimulated	2.80	9.23	2.66	9.23
	pp65	0.17	0.00	0.03	0.00
2009	Unstimulated	0.08	0.00		
	Stimulated	3.56	10.47	3.48	10.47
	pp65	0.00	0.00	-0.08	0.00
2010	Unstimulated	0.00	0.00		
	Stimulated	2.91	7.29	2.91	7.29
	pp65	0.00	0.00	0.00	0.00

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
Group 2 Mean	Unstimulated	0.06	0.00		
	Stimulated	5.57	16.01	5.51	16.01
	pp65	0.05	0.12	-0.01	0.12
Group 2 StDev	Unstimulated	0.08	0.00		
	Stimulated	3.14	11.83	3.18	11.83
	pp65	0.09	0.34	0.12	0.34

Appendix 18

mRNA-1443 - Intracellular IFNγ Production following Antigen Stimulation
Group 3 – Males

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated 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	0.47	0.21		
	Stimulated	1.13	0.50	0.66	0.30
	pp65	0.05	0.00	-0.42	-0.21
3002	Unstimulated	0.00	0.68		
	Stimulated	3.86	17.41	3.86	16.73
	pp65	0.22	1.25	0.22	0.57
3003	Unstimulated	0.36	1.18		
	Stimulated	3.42	9.93	3.06	8.75
	pp65	0.05	0.00	-0.31	-1.18
3004	Unstimulated	0.00	0.00		
	Stimulated	3.16	16.72	3.16	16.72
	pp65	0.00	0.00	0.00	0.00
3005	Unstimulated	0.00	0.16		
	Stimulated	5.48	9.79	5.48	9.64
	pp65	0.09	0.05	0.09	-0.10
3006	Unstimulated	0.00	0.00		
	Stimulated	0.95	2.69	0.95	2.69
	pp65	0.00	0.00	0.00	0.00
3007	Unstimulated	0.00	0.00		
	Stimulated	2.04	4.53	2.04	4.53
	pp65	0.19	0.28	0.19	0.28
3008	Unstimulated	0.04	0.00		
	Stimulated	0.87	5.52	0.83	5.52
	pp65	0.05	0.08	0.01	0.08
3009	Unstimulated	0.04	0.09		
	Stimulated	0.83	1.20	0.79	1.11
	pp65	0.11	0.00	0.07	-0.09
3010	Unstimulated	0.06	0.00		
	Stimulated	2.26	7.82	2.21	7.82
	pp65	0.00	0.00	-0.06	0.00

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated Subtracted: Percent of T_c
		$IFN\gamma^+$ $(CD3^+/4^+/IFN^+)$	$IFN\gamma^+$ $(CD3^+/8^+/IFN^+)$	$IFN\gamma^+$ $(CD3^+/4^+/IFN^+)$	$IFN\gamma^+$ $(CD3^+/8^+/IFN^+)$
Group 3 Mean	Unstimulated	0.10	0.23		
	Stimulated	2.40	7.61	2.30	7.38
	pp65	0.08	0.17	-0.02	-0.06
Group 3 StDev	Unstimulated	0.17	0.39		
	Stimulated	1.56	5.95	1.60	5.82
	pp65	0.08	0.39	0.20	0.45

Appendix 18

mRNA-1443 - Intracellular IFNγ Production following Antigen Stimulation
Group 4 – Males

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated 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	9.34	19.59	9.34	19.59
	pp65	0.00	0.00	0.00	0.00
4002	Unstimulated	0.00	0.00		
	Stimulated	1.75	2.51	1.75	2.51
	pp65	0.07	0.00	0.07	0.00
4003	Unstimulated	0.14	0.06		
	Stimulated	2.62	8.18	2.48	8.11
	pp65	0.00	0.00	-0.14	-0.06
4004	Unstimulated	0.00	0.00		
	Stimulated	2.25	21.41	2.25	21.41
	pp65	0.00	0.41	0.00	0.41
4005	Unstimulated	0.08	0.17		
	Stimulated	2.85	16.80	2.77	16.62
	pp65	0.14	0.00	0.06	-0.17
4006	Unstimulated	0.49	0.00		
	Stimulated	3.13	11.84	2.63	11.84
	pp65	0.24	0.00	-0.26	0.00
4007	Unstimulated	0.00	0.00		
	Stimulated	4.67	7.25	4.67	7.25
	pp65	0.00	0.00	0.00	0.00
4008	Unstimulated	*	*		
	Stimulated	6.81	26.72	*	*
	pp65	0.00	0.00	*	*
4009	Unstimulated	0.12	0.99		
	Stimulated	4.73	22.06	4.61	21.07
	pp65	0.22	0.00	0.10	-0.99
4010	Unstimulated	0.00	0.00		
	Stimulated	5.72	19.40	5.72	19.40
	pp65	0.00	0.00	0.00	0.00

*Sample clotted, no data

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
Group 4 Mean	Unstimulated	0.09	0.14		
	Stimulated	4.39	15.58	4.02	14.20
	pp65	0.07	0.04	-0.02	-0.09
Group 4 StDev	Unstimulated	0.16	0.32		
	Stimulated	2.38	7.75	2.40	6.97
	pp65	0.10	0.13	0.11	0.37

Appendix 18

mRNA-1443 - Intracellular IFNγ Production following Antigen Stimulation
Group 1 – Females

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated 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	0.08	0.00		
	Stimulated	3.90	14.14	3.82	14.14
	pp65	0.56	0.00	0.48	0.00
1502	Unstimulated	0.37	0.00		
	Stimulated	5.08	14.88	4.72	14.88
	pp65	0.08	0.00	-0.28	0.00
1503	Unstimulated	0.25	0.00		
	Stimulated	4.18	23.46	3.93	23.46
	pp65	0.38	0.00	0.13	0.00
1504	Unstimulated	0.56	0.00		
	Stimulated	10.00	20.74	9.44	20.74
	pp65	0.33	0.00	-0.24	0.00
1505	Unstimulated	0.28	0.00		
	Stimulated	6.38	17.72	6.10	17.72
	pp65	0.27	0.18	0.00	0.18
1506	Unstimulated	0.30	0.00		
	Stimulated	3.47	4.95	3.17	4.95
	pp65	0.23	0.10	-0.07	0.10
1507	Unstimulated	0.49	0.00		
	Stimulated	9.03	39.33	8.54	39.33
	pp65	0.23	0.00	-0.27	0.00
1508	Unstimulated	0.14	0.26		
	Stimulated	7.57	15.19	7.43	14.93
	pp65	0.23	0.07	0.09	-0.19
1509	Unstimulated	0.46	0.00		
	Stimulated	4.42	8.21	3.96	8.21
	pp65	0.10	0.00	-0.36	0.00
1510	Unstimulated	0.27	0.00		
	Stimulated	3.21	8.87	2.94	8.87
	pp65	0.27	0.00	0.00	0.00

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
Group 1 Mean	Unstimulated	0.32	0.03		
	Stimulated	5.73	16.75	5.40	16.72
	pp65	0.27	0.03	-0.05	0.01
Group 1 StDev	Unstimulated	0.15	0.08		
	Stimulated	2.41	9.77	2.33	9.77
	pp65	0.14	0.06	0.25	0.09

Appendix 18

mRNA-1443 - Intracellular IFNγ Production following Antigen Stimulation
Group 2 – Females

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated 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	0.16	0.00		
	Stimulated	5.92	31.06	5.76	31.06
	pp65	0.16	0.00	0.00	0.00
2502	Unstimulated	0.45	0.18		
	Stimulated	8.80	12.60	8.35	12.42
	pp65	0.54	0.07	0.09	-0.11
2503	Unstimulated	0.19	0.00		
	Stimulated	5.36	9.74	5.17	9.74
	pp65	0.00	0.00	-0.19	0.00
2504	Unstimulated	0.15	0.00		
	Stimulated	5.44	27.21	5.29	27.21
	pp65	0.21	0.00	0.06	0.00
2505	Unstimulated	0.09	0.00		
	Stimulated	8.64	43.83	8.55	43.83
	pp65	0.09	0.16	0.00	0.16
2506	Unstimulated	0.16	0.18		
	Stimulated	1.80	4.64	1.64	4.46
	pp65	0.29	0.00	0.13	-0.18
2507	Unstimulated	0.35	0.00		
	Stimulated	3.36	12.20	3.01	12.20
	pp65	0.00	0.00	-0.35	0.00
2508	Unstimulated	1.84	0.00		
	Stimulated	3.98	23.61	2.14	23.61
	pp65	0.28	0.00	-1.56	0.00
2509	Unstimulated	0.17	0.00		
	Stimulated	2.20	10.11	2.02	10.11
	pp65	0.19	0.22	0.02	0.22
2510	Unstimulated	0.17	0.00		
	Stimulated	2.94	12.93	2.77	12.93
	pp65	0.79	0.00	0.62	0.00

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
Group 2 Mean	Unstimulated	0.37	0.04		
	Stimulated	4.84	18.79	4.47	18.76
	pp65	0.25	0.05	-0.12	0.01
Group 2 StDev	Unstimulated	0.53	0.08		
	Stimulated	2.46	12.23	2.56	12.26
	pp65	0.25	0.08	0.56	0.11

Appendix 18

mRNA-1443 - Intracellular IFNγ Production following Antigen Stimulation
Group 3 – Females

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated 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	0.66	0.00		
	Stimulated	4.22	20.85	3.56	20.85
	pp65	0.19	0.00	-0.47	0.00
3502	Unstimulated	0.00	0.00		
	Stimulated	4.51	18.86	4.51	18.86
	pp65	0.48	0.00	0.48	0.00
3503	Unstimulated	0.50	0.26		
	Stimulated	1.91	10.08	1.41	9.82
	pp65	0.98	0.27	0.48	0.01
3504	Unstimulated	0.40	0.00		
	Stimulated	4.70	23.72	4.30	23.72
	pp65	0.42	0.00	0.01	0.00
3505	Unstimulated	0.51	0.00		
	Stimulated	7.49	32.32	6.97	32.32
	pp65	0.45	0.17	-0.06	0.17
3506	Unstimulated	0.34	0.00		
	Stimulated	3.61	13.76	3.26	13.76
	pp65	0.09	0.16	-0.26	0.16
3507	Unstimulated	0.25	0.00		
	Stimulated	5.83	20.72	5.58	20.72
	pp65	0.14	0.00	-0.11	0.00
3508	Unstimulated	0.77	0.00		
	Stimulated	3.74	15.22	2.97	15.22
	pp65	0.42	0.00	-0.35	0.00
3509	Unstimulated	0.24	0.22		
	Stimulated	0.93	3.07	0.69	2.85
	pp65	0.00	0.00	-0.24	-0.22
3510	Unstimulated	0.00	0.00		
	Stimulated	3.05	16.28	3.05	16.28
	pp65	0.31	0.00	0.31	0.00

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
Group 3 Mean	Unstimulated	0.37	0.05		
	Stimulated	4.00	17.49	3.63	17.44
	pp65	0.35	0.06	-0.02	0.01
Group 3 StDev	Unstimulated	0.26	0.10		
	Stimulated	1.86	7.93	1.84	8.00
	pp65	0.28	0.10	0.34	0.10

Appendix 18

mRNA-1443 - Intracellular IFNγ Production following Antigen Stimulation
Group 4 – Females

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated 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	25.15	21.95	25.15	21.95
	pp65	0.68	0.00	0.68	0.00
4502	Unstimulated	0.16	0.77		
	Stimulated	8.37	19.05	8.21	18.28
	pp65	0.47	0.00	0.31	-0.77
4503	Unstimulated	0.00	0.00		
	Stimulated	8.99	32.26	8.99	32.26
	pp65	0.37	0.40	0.37	0.40
4504	Unstimulated	0.41	0.54		
	Stimulated	8.06	31.13	7.65	30.59
	pp65	0.28	0.00	-0.13	-0.54
4505	Unstimulated	0.14	0.38		
	Stimulated	2.73	20.66	2.59	20.28
	pp65	0.14	0.00	0.00	-0.38
4506	Unstimulated	0.31	0.51		
	Stimulated	3.61	5.42	3.30	4.90
	pp65	0.21	0.00	-0.10	-0.51
4507	Unstimulated	0.35	0.43		
	Stimulated	9.33	18.06	8.98	17.63
	pp65	0.00	0.00	-0.35	-0.43
4508	Unstimulated	0.21	0.00		
	Stimulated	3.28	28.57	3.07	28.57
	pp65	0.24	0.00	0.04	0.00
4509	Unstimulated	0.90	0.00		
	Stimulated	7.51	18.13	6.60	18.13
	pp65	0.41	0.55	-0.50	0.55
4510	Unstimulated	0.00	0.00		
	Stimulated	5.83	42.68	5.83	42.68
	pp65	0.56	0.00	0.56	0.00

Animal ID	Assay Condition	Percent of T_h	Percent of T_c	Unstimulated Subtracted: Percent of T_h	Unstimulated Subtracted: Percent of T_c
		$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/4^+/IFN^+$)	$IFN\gamma^+$ ($CD3^+/8^+/IFN^+$)
Group 4 Mean	Unstimulated	0.25	0.26		
	Stimulated	8.29	23.79	8.04	23.53
	pp65	0.34	0.09	0.09	-0.17
Group 4 StDev	Unstimulated	0.27	0.29		
	Stimulated	6.42	10.24	6.48	10.38
	pp65	0.20	0.20	0.38	0.43

Appendix 19

FINAL REPORT

Study Phase: Molecular Biology – Purity Analysis

Test Facility Study No. 5002158

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)

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Appendix 19

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Appendix 19

LIST OF TABLES

LIST OF APPENDICES

Appendix 19

1. SUMMARY

The bulk test item was analyzed using the (b) (4) System for the determination of mRNA-1443 purity.

The bulk test item was collected at the end of the dosing period of Study No. 5002158 entitled "A 6-Week (4 Doses) Intramuscular Injection Toxicity Study of mRNA-1443 in Sprague-Dawley Rats followed by a 2-Week Recovery Period."

The end of use bulk test item analysis demonstrated purity results of (b) (4)

2. INTRODUCTION

This report describes the analytical evaluation of mRNA-1443 purity in the bulk test item from Study No. 5002158.

For the work detailed in this report, the analytical experimental phase start date was 10 May 2017 and the end date was 12 Jun 2017.

3. EXPERIMENTAL DESIGN

3.1. Bulk Test Item End of Use Analysis

Analysis of the bulk test item was carried out with regards to the purity analysis.

At the end of the study dosing phase, one vial of test item was received for purity analysis.

4. MATERIALS AND METHODS

4.1. Materials

4.1.1. Reference Standard

Identification:	CX-000479 mRNA
Physical Description:	Clear, colorless solution, no visible particulates
Batch/Lot No.:	MTDS16032
Concentration:	2.19 mg/mL
Retest Date:	Nov 2017
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

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4.1.2. Bulk Test Item

Identification:	mRNA-1443 (in lipid nanoparticles)
Physical Description:	0.5 mL per vial, white to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP17017
Concentration:	2.6 /2.5* mg/mL
Retest Date:	23 Feb 2018
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

* Concentration based on SoA released on 16 March 2017 /Concentration based on SoA released on 22 Jun 2017.

4.1.3. Characterization of Reference Standard and Bulk Test Item Sample

The Sponsor provided the documentation for the identity, strength, purity, and composition of the reference standard and bulk test item sample. Copies of the supplied Certificates of Analysis (CofA) or equivalent documentation are presented in Appendix 3.

4.1.4. Inventory and Disposition of Reference Standard and Bulk Test Item Sample

Records of the receipt, distribution, and storage of the reference standard and bulk test item sample were maintained. All unused Sponsor-supplied reference standard and bulk test item sample will be discarded before issue of the final report.

4.2. Methods

(b) (4)

4.3. Computerized Systems

Critical computerized systems used in this study phase are listed below (see Text Table 1).

Appendix 19

Text Table 1
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
(b) (4)	1.1.0.11	Data acquisition
Empower 3 (Waters Corporation)	Build 3471 SR1	Data regression analysis and measurement of purity
Excel	2007	Data analysis and tabulation
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	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. DEVIATIONS

Deviations from the analytical procedure occurred during this phase of the study. These deviations were documented in the raw data and study records. They were minor in nature and had no impact upon the integrity of the data for its intended purpose.

No study plan deviation occurred during this phase of the study.

6. RESULTS AND CONCLUSION

(b) (4)

The end of use bulk test item analysis demonstrate a purity of (b) (4) which is similar to the original results provided by the Sponsor on the Certificate of Analysis. As per Certificate of Analysis, the purity specification is expected to be (b) (4)

Appendix 19

7. REPORT APPROVAL

(b) (6)

_____ Date: 11 Sep 2017

(b) (6)

Appendix 19

Table 1 End of Dosing Period Sample Purity Results

Peak ID	Replicate ID	Replicate ID	Measured Purity Results (%)			Original Purity Results in SoA (%)
			Results	Mean Results	Global Mean	
Main Peak	1	1	(b) (4)			
		2				
	2	1				
		2				
	3	1				
		2				
Pre Peak	1	1				
		2				
	2	1				
		2				
	3	1				
		2				
Post Peak	1	1				
		2				
	2	1				
		2				
	3	1				
		2				

Appendix 19

Appendix 1

(b) (4)

Appendix 19

charles river

ANALYTICAL PROCEDURE

TITLE: (b) (4)	AP No: AP.5002158.RNA.01	Effective Date: Signature of AP
	Page 1 of 2 pages	Supersedes Date: N/Ap
Prepared by: (b) (6) (b) (6)		Date: 09 May 2017
Reviewed by: (b) (6) (b) (6)		Date: 09 May 2017
Approved by: (b) (6) (b) (6)		Date: 09 May 2017

(b) (4)

3.0 RESPONSIBILITY

All personnel performing this procedure are responsible for compliance with this AP.

(b) (4)

5.0 MATERIALS

(b) (4)

Appendix 19

AP No: AP.5002158.RNA.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 2 of 2 pages

5.3 (b) (4)

6.0 **GENERAL GUIDELINES**

(b) (4)

7.0

8.0 **REVISION HISTORY**

Version	Date	Reason for revision
01	Signature of AP	New AP

Appendix 19

(b) (4)

Study/Reference No: 5002158 Assay I.D.: Pro-xx

Page: 1 of 3

Table 1: Reagents / Materials

Name	Batch / Lot #	Inventory #	Expiry date	Analyst / Date
(b) (4)				

Table 2: Instruments

Name	ID	Analyst / Date
(b) (4)		

Comments:

Appendix #1 (AP.5002158.RNA.01)

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(b) (4)

Study/Reference No: 5002158 Assay I.D.: Pro-xx

Page: 2 of 3

Table 3: Samples

Assay Sample #	(b) (4)			Volume of sample added (✓)	Volume of PBS to add for total volume to equal 500 µL	Volume of PBS added (✓)	Analyst / Date
1				( )		( )	
2				( )		( )	
3				( )		( )	
4				( )		( )	
5				( )		( )	
6				( )		( )	
7				( )		( )	
8				( )		( )	
9				( )		( )	
10				( )		( )	
11				( )		( )	
12				( )		( )	
13				( )		( )	
14				( )		( )	
15				( )		( )	
16				( )		( )	
17				( )		( )	
18				( )		( )	
19				( )		( )	
20				( )		( )	
21				( )		( )	
22				( )		( )	

Comments: _____

Appendix #1 (AP.5002158.RNA.01)

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(b) (4)

Study/Reference No: 5002158 Assay I.D.: Pro-xx

Page: 3 of 3

Table 4: (b) (4)

Steps	Performed (✓)	Analyst / Date
(b) (4)	( )	
	( )	
	( )	
	( )	
	( )	
	( ) or N/Ap □	
	( )	
	( )	
	( )	
	( ) or N/Ap □	
	( )	
	( )	
(b) (4)		

Comments: _____

All pages reviewed by / Date: _____

Appendix #1 (AP.5002158.RNA.01)

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Appendix 2

(b) (4)

Appendix 19

charles river

ANALYTICAL PROCEDURE

TITLE: (b) (4)	AP No: AP.5002158.RQF.01	Effective Date: Signature of AP
	Page 1 of 4 pages	Supersedes Date: N/Ap
Prepared by: (b) (6) (b) (6)		Date: 09 May 2017
Reviewed by: (b) (6) (b) (6)		Date: 09 May 2017
Approved by: (b) (6) (b) (6)		Date: 09 May 2017

1.0 (b) (4)

2.0

3.0 **RESPONSIBILITY**

All Laboratory Sciences staff are responsible for compliance with this AP.

4.0 (b) (4)

5.0 **MATERIALS**

(b) (4)

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AP No: AP.5002158.RQF.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 2 of 4 pages

5.2 (b) (4)

5.3

5.4 **Reagents**

(b) (4)

6.0 **PREPARATION OF REAGENTS**

(b) (4)

Appendix 19

AP No: AP.5002158.RQF.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 3 of 4 pages

6.1 (b) (4)

6.2

6.3

6.4

7.0 (b) (4)

8.0 ACCEPTANCE CRITERIA

(b) (4)

Appendix 19

AP No: AP.5002158.RQF.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 4 of 4 pages

8.2 (b) (4)

8.3

8.4 (b) (4)

9.0 **REVISION HISTORY**

Version	Date	Reason for revision
01	Signature Date of AP	New AP

Appendix 19

(b) (4)

Study/Reference No: 5002158 Assay I.D.: Pro-xx

Page: 1 of 6

REAGENTS / WORKING SOLUTIONS

Name	*Batch / Lot #*	*Inventory #*	*Expiry Date*	*Entered by (Init. / Date)*
(b) (4)				

INSTRUMENTS

Name	*ID*	*Entered by (Init. / Date)*
(b) (4)		

Comments:

Appendix #1 (AP.5002158.RQF.01)

Appendix 19

(b) (4)

Study/Reference No: 5002158 Assay I.D.: Pro-xx

Page: 2 of 6

Preparation of: (b) (4)

Batch / Lot #

Reagent	Batch / Lot #	Inventory #	Expiry Date	Volume	Performed (✓)
(b) (4)				(b) (4)	( )
					( )

Performed by / Date:

Preparation of (b) (4)

Batch / Lot #

Reagent	Batch / Lot #	Inventory #	Expiry Date	Volume (mL)	Performed (✓)
(b) (4)				(b) (4)	( )
					( )

Performed by / Date:

Preparation of: (b) (4)

Batch / Lot #

Reagent	Batch / Lot #	Inventory #	Expiry Date	Volume (mL)	Performed (✓)
(b) (4)				(b) (4)	( )
					( )

Performed by / Date:

Comments: _____

Appendix #1 (AP.5002158.RQF.01)

Appendix 19

(b) (4)

Study/Reference No: 5002158 Assay I.D.: Pro-xx

Page: 3 of 6

(b) (4)

Steps	Performed (√)	Performed by (Init./Date)
(b) (4)		
	( )	
	( )	
	( )	
	( )	
	( )	
	( )	
	( )	
	( )	
	( ) or N/Ap □	
	( ) or N/Ap □	

Comments: _____

Appendix #1 (AP.5002158.RQF.01),

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(b) (4)

Study/Reference No: 5002158 Assay I.D.: Pro-xx

Page: 4 of 6

(b) (4)

Steps	Performed (√)	Performed by (Init./Date)
(b) (4)	( ) or N/Ap □	
	( ) or N/Ap □	
	( ) or N/Ap □	
	( )	
	( ) or N/Ap □	
	( )	
	( )	
	( )	

Comments: _____

Appendix #1 (AP.5002158.RQF.01)

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(b) (4)

Study/Reference No: 5002158 Assay I.D.: Pro-xx

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(b) (4)

Steps	Performed (√)	Performed by (Init./Date)
(b) (4)	( )	
	( )	
	( )	
	( )	
	( )	
	( )	

Clarifications to Prosize, if any: _____

Comments: _____

Appendix #1 (AP.5002158.RQF.01)

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(b) (4)

Study/Reference No: 5002158 Assay I.D.: Pro-xx

Page: 6 of 6

DATA REVIEW

Performed by: _____ Date: _____

Controls:

(b) (4) /

Reference Standard (RS):

(b) (4) Yes or No

Samples

(b) (4) Yes or No
/3

/3

Yes or No

SCIENTIFIC REVIEW

Performed by: _____ Date: _____

Controls met all acceptance criteria:	Yes / No
Reference Standard met all acceptance criteria:	Yes / No
Study samples met all acceptance criteria:	Yes / No
Study samples to be repeated are flagged:	Yes / N/Ap
Assay is acceptable:	Yes or No

All pages reviewed by / Date: _____

Appendix #1 (AP.5002158.RQF.01)

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(b) (4)

96-WELL PLATE LAYOUT* Assay ID: _____

	1	2	3	4	5	6	7	8	9	10	11	12	
A	RS-1	Empty	Empty	Empty	Empty	Empty	S 1-1	Empty	Empty	Empty	Empty	Empty	A
B	RS-2	Empty	Empty	Empty	Empty	Empty	S 1-2	Empty	Empty	Empty	Empty	Empty	B
C	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	C
D	Empty	Empty	Empty	Empty	Empty	Empty	S 2-1	Empty	Empty	Empty	Empty	Empty	D
E	Empty	Empty	Empty	Empty	Empty	Empty	S 2-2	Empty	Empty	Empty	Empty	Empty	E
F	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty	F
G	Empty	Empty	Empty	Empty	Empty	Empty	S 3-1	Empty	Empty	Empty	Empty	Empty	G
H	Empty	Empty	Empty	Empty	Empty	Empty	S 3-2	Empty	Empty	Empty	Empty	Ladder	H
	1	2	3	4	5	6	7	8	9	10	11	12	

Approved by / Date: _____

Comments: RS = reference standard ; S = sample _____

*Plate sequence to be updated as required.

Reviewed by/Date: _____

Appendix #2: (AP.5002158.RQF.01) Page 01 of 01

Appendix 19

Appendix 3
Certificates of Analysis

Appendix 19

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phone 617-714-6500 • fax 617-583-1998

Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	15 Jun 2017
Revision	004
Product name	**mRNA-1443 Test Article**
Product description	mRNA-1443 LNP in 100mM Tris, 60mM NaCl, 7% PG
Lot No.	**MTDP 17017**
Drug Substance (API)	CX000479 Lot MTDS16032
Date of Manufacture	23-Feb-2017
Re-test Date	23-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	Sanger Sequencing	Outsourced	Sequence matches standard	Conforms
mRNA Content	(b) (4)	2017_03_12-003	(b) (4)	(b) (4)
mRNA Purity	(b) (4)	2017_03_16-006	(b) (4)	(b) (4)
% 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	(b) (4)
Lipid	UPLC-CAD	2017_03_12-002	Lipid / Target Concentration (mg/mL): SM102, Cholesterol, DSPC, PEG-DMG (b) (4); Total Impurity (% Area): Report	Lipid / Concentration (mg/mL): SM102, Cholesterol, DSPC, PEG-DMG, Total Impurity (% Area) (b) (4)

Doc: DPAD-SOA-0001.4 *Page 1 of 2*

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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	Size	*Number of Particles/mL
			(b) (4)			
Bioburden	USP <61>	Study Number 949975-S01	TAMC TYMC	(b) (4)	TAMC TYMC	(b) (4)

*Reported value is a pooled result with MTDP17015. The analytical lab provider assumed these lots were to be combined for this test.

Data Approved: (b) (6) (b) (6) **Date:** 22Jun2017

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Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	30 May 2017
Revision	003
Product\Test Article	mRNA-1443 (CMV 7) in 100 mM TRIS 60 mM NaCl 7% (w/v PG) 2.4 mg/mL , 0.5mL Fill volume
Lot No.	MTDP17017
Moderna Protocol	DPAD-PRO-0002
Drug Substance (API)	CX000479 Lot MTDS16032
Date of Manufacture	23 Feb 2017
Stability Initiation Date	13 Mar 2017
Stability Time Point	T=0, Release

Test	Method	Testing Reference	Target Attributes	Results
mRNA Content	(b) (4)	2017_03_12-003	(b) (4)	
Endotoxin	USP <85>	0317-022 (ACCI)		
Bioburden	USP <61>	949975-S01 (Nelson Labs)		

*Original reported results was (b) (4) results changes with the updated Drug Substance SOA v 3.

Author: (b) (6) (b) (6) Date: 31 May 2017

Data reviewed: (b) (6) Date: 31-MAY-2017

Revision	Date	Description
1	17 Mar 2017	Original
2	03Apr2017	Concentration updated to reflect Drug Substance SoA v 3 (that was used for reference standard)
3	30May2017	Concentration updated to reflect Drug Substance SoA v 4 (that was used for reference standard)

Data generated in accordance with standard Moderna Therapeutics laboratory Practices and have been verified for accuracy

Doc: DPAD-SOA-0001 *Page 1 of 1*

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Summary of Analysis

Document number	DPAD-SOA-0001
Date of Document Generation	16 Mar 2017
Revision	001
Product\Test Article	mRNA-1443 (CMV 7) in 100 mM TRIS 60 mM NaCl 7% (w/v PG) 2.6 mg/mL , 0.5mL Fill volume
Lot No.	MTDP17017
Moderna Protocol	DPAD-PRO-0002
Drug Substance (API)	CX005282 Lot MTDS16032
Date of Manufacture	21 Feb 2017
Stability Initiation Date	13 Mar 2017
Stability Time Point	T=0, Release

Test	Method	Testing Reference	Target Attributes	Results
mRNA Content	(b) (4)	2017_03_12-003	(b) (4)	
Endotoxin	USP <85>	0317-022 (ACCI)		
Bioburden	USP <61>	949975-S01 (Nelson Labs)		

Author: (b) (6) (b) (6) 8 Mar 2017

Data reviewed: (b) (6) 6 Mar 2017

Data generated in accordance with standard Moderna Therapeutics laboratory Practices and have been verified for accuracy

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SUMMARY OF ANALYSIS

Sample Description:	**CX-000479 mRNA** (GLP tox enabling batch)
mRNA length:	(b) (4)
SCC:	33.86 µg/mL
Plasmid ID:	PL-012371
Lot or Batch No:	**MTDS16032**
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	November 2016
Date of Analysis:	November 2016
Storage:	Shipping Temperature: ≤ -15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	November 2017

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Appearance	SOP-0045, v1.0	Clear, colorless solution, no visible particulates	Clear, colorless solution, no visible particulates	2016_12_14-048-(b) (6)
Identity	RT/Sanger Sequencing TSOP134.03	Sequence matches 100% description of the coding region	Sequence matches 100% description of the coding region	209-TSOP134-144.00
Total RNA content	DSAD-TM-0019*	(b) (4)		2017_02_22-019-(b) (6)
Purity	DSAD-TM-0010			2016_12_14-048-(b) (6)
Product related impurities	DSAD-TM-0010	Report % Pre-main peak % Post-main areas	(b) (4)	2016_12_14-048-(b) (6)
pH	SOP-0046, v1.0	(b) (4)		2016_12_14-048-(b) (6)
Residual DNA template	qPCR TSOP344.01			209-TSOP344-137.00 (MTDS 16032)

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Residual total protein	SOP-0182, v0.1	(b) (4)	2016_11_28-033-(b) (6)
Residual solvents TEA	SOP-0185, v0.1	Report results	2016_11_28-004-(b) (6)
IPA	SOP-0183, v0.1		2016_11_28-004-(b) (6)
Ethanol	SOP-0183, v0.1		2016_11_28-004-(b) (6)
Hexylene glycol	SOP-0184, v0.1		2016_12_06-019-(b) (6)
% Poly A tailed RNA (% Tailless RNA)	DSAD-TM-0013	Report % main peak area	2016_12_14-048-(b) (6)
% 5' Capped	DSAD-TM-0021		2016_11_30-006-(b) (6)
Bacterial Endotoxins	USP<85>		Result provided by PD
Bioburden	USP<61>		16-12798

(b) (4)
(b) (4) Reference: 2017_02_22-019-(b) (6)

Signatures:

(b) (6)
Generated by: (b) (6) 12 Apr 17 Date:

(b) (6)
Reviewed by: (b) (6) 12 APR 2017 Date:

Appendix 20

NON-GLP FINAL REPORT

Study Phase: Immunology - Alpha-1-acid Glycoprotein, alpha-2-macroglobulin and Cytokines

Test Facility Study No. 5002158

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB)

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Appendix 20

TABLE OF CONTENTS

Appendix 20

LIST OF APPENDICES

Appendix 20

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. 5002158 titled "*A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 in Sprague-Dawley Rats followed by a 2-Week Recovery Period*".

For the work detailed in this report, the phase experimental start date was 19 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.5002158.AGP.02
Alpha-2-macroglobulin (A2M)	AP.5002158.A2M.01
IL-1β, IL-6, IP-10, MCP-1, MIP-1α and TNF-α	AP.5002158.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 20

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 7 AGP assays were performed and one assay was out of the method's acceptance criteria. All results were reported from the assays that met the 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 8 A2M assays were performed and two assays were out of the method's 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).

Appendix 20

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 3 assays were out of the method's acceptance criteria due to technical oversight during the standard curve preparation. 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 Appendix 16.

IL-1β

The quantifiable IL-1β concentration range in the reference item group was 29.24 pg/mL to 373.33 pg/mL. All IL-1β concentrations observed amongst the dosed group were lower or within the control group range. No statistically significant changes were observed.

IL-6

Quantifiable results were observed in only 3 animals on Day 43, 6 hours post dose: males 4013 and 4015 and female 4512.

For all other animals, males and females, at all time points, the IL-6 concentrations observed were below the LLOQ. No statistically significant changes were observed.

Appendix 20

TNF-α

Punctual TNF-α concentrations similar to the concentrations observed in the control group were detected in males. TNF-α concentrations detected in females were all below the LLOQ except for 2 dosed females on Day 43 6 hours post dose. No statistically significant changes were observed.

IP-10

Higher concentrations of IP-10, when compared to the reference item group, were observed in the high dosed group of mRNA-1443 with the highest concentrations being generally observed on Days 29 and 43, 6 hours post dose in both genders. On Days 29 and Day 43, a 2.8 to 2.9-fold increase in males and a 6.2 to 6.8-fold increase in females were observed when compared to the mean IP-10 concentration detected in the control group.

The changes were statistically significant on days 29 and 43 6 hours post dose for males and on day 29 6 hours post dose in females.

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. MIP-1α concentration close to the LLOQ was detected in one female. No statistically significant changes were observed.

MCP-1

In males, MCP-1 concentrations were similar between dosed and control animals. In females, a 7.4-fold increase was observed on Day 1, a 1.9-fold increase on day 15, a 1.7-fold increase on day 29 and a 2.8-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, 29 and 43 6 hours post dose for females.

On day 57, the concentration of MCP-1 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.

Appendix 20

3. CONCLUSION

Statistically significant increases of IP-10 concentrations were observed in both genders dosed with mRNA-1443 at 96 μg/dose. Higher concentrations were generally observed on Day 43. IP-10 concentrations were back to control level on Day 57.

In dosed females, MCP-1 concentrations were increased on Days 1, 15, 29 and 43 6 hours post dose when compared to the control group, and the increases were statistically significant. MCP-1 concentrations were back to normal 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 20

4. REPORT APPROVAL

(b) (6)

(b) (6)

Date: 27 Sep 2017

Appendix 20

Appendix 1
Deviations

Appendix 20

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 20

Appendix 2
AP.5002158.AGP.02

Appendix 20

ANALYTICAL PROCEDURE

charles river | every step of the way.

Title: ELISA METHOD FOR THE QUANTITATIVE DETECTION OF ALPHA 1 ACID GLYCOPROTEIN IN RAT SERUM	AP Number: AP.5002158.AGP.02	Effective Date: Signature of AP
	Page 1 of 6 pages	Supersedes: 08 Mar 2017
Prepared and approved by: (b) (6) (b) (6)		Date: 18 May 2017
Authorized by: (b) (6) (b) (6)		Date: 18/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.

Appendix 20

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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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(b) (4)

11. ACCEPTANCE CRITERIA

(b) (4)

Appendix 20

No: AP.5002158.AGP.02	Date effective: Signature of AP	Supersedes: 08 Mar 2017	Page 6 of 6 pages

(b) (4)

12. VERSION HISTORY

Version	Date	Reason for revision
02	Date of AP signature	LLOQ and LQC re-adjusted Appendices updated accordingly
01	08 Mar 2017	New AP

Appendix 20

Assay Information Sheet

Study/reference number: 5002158 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.5002158.AGP.02) 1 of 1

Appendix 20

AGP standards and QC's Preparation Sheet

Study/reference number: 5002158 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)	( )	(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)	(b) (4)		( )		
MQC		HQC				( )		
LQC		MQC				( )		

Pipette ID(s): _____

Performed by/date: _____ Reviewed by/date: _____

Appendix #2 (AP.5002158.AGP.02) 1 of 1

Appendix 20

Study Samples Dilution Prepation Sheet

Study/reference number: 5002158 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.5002158.AGP.02) 1 of 1

Appendix 20

Study/reference number: 5002158 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 (v)
(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.5002158.AGP.02) 1 of 1

Appendix 20

Rat AGP Assay Sheets

Study/reference number: 5002158 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.5002158.AGP.02) 1 of 4

Appendix 20

Rat AGP Assay Sheets

Study/reference number: 5002158

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 #5 (AP.5002158.AGP.02)

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Appendix 20

Rat AGP Assay Sheets

Study/reference number: 5002158

Steps	Assay ID:	Assay ID:	Assay ID:	Assay ID:	Performed by/date
	Time / Performed (√)	Time / Performed (√)	Time / Performed (√)	Time / Performed (√)	
(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.5002158.AGP.02)

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Appendix 20

Rat AGP Assay Sheets

Study/reference number: 5002158

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.5002158.AGP.02)

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Appendix 20

Appendix 3
AP.5002158.A2M.01

Appendix 20

ANALYTICAL PROCEDURE

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Title: ELISA METHOD FOR THE QUANTITATIVE DETECTION OF ALPHA 2-MACROGLOBULIN IN RAT SERUM	AP Number: AP.5002158.A2M.01	Effective Date: Signature of AP
	Page 1 of 5 pages	Supersedes: N/A
Approved by: (b) (6) (b) (6)		Date: 18 May 2017
Authorized by: (b) (6) (b) (6)		Date: 18/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 sample dilutions 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.5002158.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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(b) (4)

7. **ASSAY PROCEDURE**

(b) (4)

8. **EXPORTING DATA TO WATSON LIMS**

(b) (4)

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No: AP.5002158.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)

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No: AP.5002158.A2M.01	Date effective: Signature of AP	Supersedes: N/A	Page 5 of 5 pages

(b) (4)

11. **VERSION HISTORY**

Version	Date	Reason for revision
01	Date of AP signature	N/A

Appendix 20

Assay information sheet

Study/reference number: 5002158 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.5002158.A2M.01) 1 of 1

Appendix 20

Standards and QC's preparation sheet

Study/reference number: 5002158 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)	STD stock	(b) (4)		(b) (4)	( )	(b) (4)	
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.5002158.A2M.01) 1 of 1

Appendix 20

Study sample dilutions sheet

Study/reference number: 5002158

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) [redacted]	[redacted]	[redacted]	[redacted]	( )	(b) (4) [redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	( )	[redacted]

Pipette ID(s): ______________________________

Performed by/date: ____________________ Reviewed by/date: ____________________

Appendix #3 (AP.5002158.A2M.01) 1 of 1

Appendix 20

Study/reference number: 5002158 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: _____

Appendix #4 (AP.5002158.A2M.01) 1 of 1

Appendix 20

Rat A2M Assay sheet

Study/reference number: 5002158 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.5002158.A2M.01) 1 of 4

Appendix 20

Rat A2M Assay sheet

Study/reference number: 5002158

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: ____________________

Appendix #5 (AP.5002158.A2M.01)

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Appendix 20

Rat A2M Assay sheet

Study/reference number: 5002158

Steps	Assay ID:	Assay ID:	Assay ID:	Assay ID:	Performed by/date
	Time / Performed (√)	Time / Performed (√)	Time / Performed (√)	Time / Performed (√)	
(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.5002158.A2M.01)

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Appendix 20

Rat A2M Assay sheet

Study/reference number: 5002158

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 4
AP.5002158.Cyt.01

Appendix 20

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.5002158.Cyt.01	Effective Date: Date of AP signature
	Page 1 of 7 pages	Supersedes: N/A
Approved by: (b) (6) (b) (6)		Date: 23 May 2017
Authorized by: (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 20

Assay information sheet

Study/reference number: 5002158 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-1ß	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
ULOQ	(b) (4)					
LLOQ						

2.3 Standard concentration:

Standards ID	Concentration (pg/mL) IL-1ß	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-1ß	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-1ß	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 20

Standards and QCs cytokine preparation sheet

Study/reference number: 5002158 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 (√)	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 20

Study samples dilution sheet

Study/reference number: 5002158 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)		(b) (4)		( )	(b) (4)
					( )	
					( )	
					( )	
					( )	
					( )	
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					( )	
					( )	

Pipette ID(s): ________________________________

Performed by/date: ____________________ Reviewed by/date: ________________

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Study/reference number: 5002158 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 20

Rat cytokines assay sheet

Study/reference number: 5002158

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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Rat cytokines assay sheet

Study/reference number: 5002158

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.5002158.Cyt.01)

Appendix 20

Rat cytokines assay sheet

Study/reference number: 5002158

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 20

Rat cytokines assay sheet

Study/reference number: 5002158

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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Appendix 20

Rat cytokines assay sheet

Study/reference number: 5002158

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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Appendix 21

FINAL REPORT

Study Phase: Pathology

Test Site Reference No. 20122333

Test Facility Study No. 5002158

TEST SITE:
Charles River Laboratories, Inc.
15 Worman's Mill Court, Suite I
Frederick, MD 21701
United States

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

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Appendix 21

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Appendix 21

LIST OF TABLES

LIST OF APPENDICES

Appendix 21

QUALITY ASSURANCE STATEMENT

Study Number: 5002158

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
10-Aug-2017 - 11-Aug-2017 13-Aug-2017 - 14-Aug-2017	Draft Phase Report - Pathology	15-Aug-2017	15-Aug-2017	15-Aug-2017	15-Aug-2017
15-Sep-2017	Final Phase Report - Pathology	15-Sep-2017	15-Sep-2017	15-Sep-2017	15-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.

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

15 Sep 2017
Date

Appendix 21

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)
(b) (6) _____ Date: 15-SEP-2017

Appendix 21

1. SUMMARY

The objective of this study was to determine the potential toxicity of mRNA-1443, 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.

Ten rats/sex/group were assigned to the Main Study and were distributed as follows: Group 1 received the Reference article, Groups 2, 3, and 4 received mRNA-1443 at doses of 10/9.6, 30/29, and 100/96 µg/dose, respectively, given into the lateral compartment of the thigh via intramuscular injection on days 1, 15, 29, and 43. Five rats/sex/group were assigned to the Recovery Study in either Group 1 or 4.

A complete gross pathological examination was performed on Main and Recovery rats and organ weights were recorded. A detailed microscopic evaluation was performed on Main animals from Groups 1 and 4 and Recovery animals (Groups 1 and 4). A microscopic evaluation limited to gross lesions and target organs was performed on Main animals from Groups 2 and 3. There were no early deaths during the Main Study or Recovery period.

At the end of the Main Study 6-week dosing period , test article-related gross changes were noted at the injection sites to include abnormal (firm) consistency, swelling, and dark or pale foci. At the end of the Recovery period, no test article-related gross pathology or organ weight changes were noted.

Test article-related increases in splenic weights were noted in males and females and were statistically significant at dosages ≥ 10/9.6 µg in males and 100/9.6 µg in females. There was no histologic correlate to the weight change.

Test article-related related gross findings at the injection site (firm consistency, swelling, and pale and/or dark foci) had histologic correlates of regionally extensive mixed cellular inflammation (neutrophils, macrophages, and lymphocytes) with edema, variably accompanied by hemorrhage. This stereotypic acute inflammatory response occurred predominantly within dermal, subcuticular, and intermuscular fascial planes, reflecting extension along non-specific, regionally extensive paths of least resistance that continued to lateral and deep margins of injection site sections. Perineurial mixed-cell inflammation was observed associated with the sciatic nerve and is considered an extension of regionally extensive acute inflammation occurring at the test article injection site. Of note, the sciatic nerve contained no changes within the nerve fibers, inflammation did not broach the epineurium, and inflammation/edema was generally of a lesser severity than the injection site proper.

The regionally extensive acute inflammatory response observed at the injection site in all Main Study male and females ≥10/9.6 µg/dose demonstrated marked improvement in the Recovery Group. Recovery group males and females (100/96 µg/dose) had resolution of edema and mixed cellular inflammation at the injection site that was replaced by minimal mononuclear interstitial inflammation variably comprising lymphocytes, macrophages, and infrequent plasma cells. These changes reflect resolution of the acute inflammatory response in recovery 100 µg/dose males and females following a two-week recovery period.

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Locoregional relevant lymph nodes (popliteal and inguinal) in both sexes displayed dose-dependent, minimal to moderate lymphoid hyperplasia, and minimal to mild medullary plasmacytosis. These lymph node changes reflect a non-specific, secondary reactive immunologic response to local acute inflammation at the injection site. Inguinal and popliteal lymph nodes occasionally had locally extensive, minimal to mild peripheral (interstitial) inflammation and edema. The peripheral interstitial edema and inflammation are presumed to be secondary to extension of the local inflammatory response centered at the injection site; additionally, the relatively dependent location of these lymph nodes likely contributed to accumulation of locally extensive interstitial inflammation and edema.

Test article-related decreased cellularity of the splenic periarteriolar lymphoid sheath occurred at low incidence in males and females at ≥ 10/9.6 µg/dose, with females having slightly increased incidence vs. males. Although males did not display any evident dose-dependent trend, increased incidence in females at 100/96 µg/dose may indicate a dose-dependent effect.

In the bone marrow, test article-related increased myeloid hematopoiesis occurred in males ≥ 10/9.6 µg/dose and females at ≥ 30/29 µg/dose. Incidence in males and females generally trended upward with increasing dose, suggesting a dose-dependent effect. Microscopically, this change had a consistent appearance comprising distinctive islands of early myeloid precursors with no appreciable atypia.

Liver sections displayed a periportal to midzonal microvesicular vacuolar change with minimal to moderate magnitude. While present in all groups including controls, this change demonstrated a slight dose-dependent increase in incidence and magnitude consistent with a test article exacerbation of a background lesion. This change was also observed within recovery animals, but with decreased magnitude and incidence (partial resolution).

All other histological changes observed in the study 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-1443.

2. RESPONSIBLE PERSONNEL

Principal Investigator, Pathology	(b) (6) Charles River Laboratories, Inc. Frederick, Maryland
Test Site Management	(b) (6) Charles River Laboratories, Inc. Frederick, Maryland

3. INTRODUCTION

This report presents the pathology findings in rats assigned to Study No. 5002158. The objective of this study were to determine the potential toxicity of mRNA-1443, when given by

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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)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1443	10 / 9.6	200	0.05 / 0.048	10	10	-	-
3	mRNA-1443	30 / 29	200	0.15 / 0.145	10	10	-	-
4	mRNA-1443	100 / 96	200	0.5 / 0.48	10	10	5	5

- : Not applicable
[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 30 May 2017.

All animals were submitted for necropsy on Day 44 (Terminal Euthanasia) or Day 57 (Recovery Euthanasia). Necropsies were performed and organ weights were collected by Test Facility personnel. Statistical analysis of organ weight data was performed by the Test Facility. Tissues required for microscopic evaluation were trimmed, processed routinely, embedded in paraffin, and stained with hematoxylin and eosin at the Test Facility. Microscopic evaluation was conducted by the Principal Investigator, a board-certified veterinary pathologist on protocol-specified tissues from all animals in Groups 1 and 4, all Recovery euthanasia animals, and all gross lesions from all animals. Additionally, potential target tissues (liver, injection site, bone marrow, spleen, sciatic nerve, popliteal lymph node, and inguinal lymph node) were evaluated in all Group 2 and 3 animals.

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

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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 sent to the Test Facility for archiving. Study materials will be retained for a period of 1 year following issue of the audited Draft Report. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study. 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

No unscheduled deaths occurred during the course of this study.

5.2. Gross Pathology

5.2.1. Terminal Euthanasia Animals (Day 44)

(Table 1 and Appendix 8).

Test article-related gross pathology findings are summarized in Text Table 3.

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**	**10/9.6**	**30/29**	**100/96**	**0**	**10/9.6**	**30/29**	**100/96**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Injection Site (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency; firm	0	2	9	10	0	2	10	10
Swelling	0	1	4	7	0	0	1	2
Focus; dark	0	0	3	1	0	0	1	1
Focus; pale	0	0	0	1	0	0	0	0
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	2	2	2	0	0	0	1
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	3	5	0	1	2	4

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-1443.

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5.2.2. Recovery Euthanasia Animals (Day 57)

(Table 2 and Appendix 8)

At the end of the recovery period, no test article-related gross findings were noted. The 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-1443.

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)

Test article-related organ weight changes are summarized in Text Table 4.

Text Table 4
Summary of Organ Weight Data – Terminal Euthanasia (Day 44)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**10/9.6**	**30/29**	**100/96**	**10/9.6**	**30/29**	**100/96**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Spleen (No. Weighed)[a]	(10)	(10)	(10)	(10)	(10)	(10)
% diff Group 1	**16.5343**	15.7402	**22.8217**	14.0207	13.9037	20.0535
% of body weight	**21.13059**	**20.11467**	**31.40503**	9.34063	13.78629	**20.28219**
% of brain weight	14.89285	**18.35570**	**24.47485**	15.32076	13.87448	**20.57586**

[a] All values expressed as percent difference of control group means.
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – $P \leq 0.05$; refer to data tables for actual significance levels and tests used.

Test article-related organ weight changes

Statistically significant increased splenic weights were noted in males at ≥10/9.6 µg/dose and females at 100/96 µg/dose. There were no gross or microscopic changes that correlated to the above weight changes.

No other test article-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-1443.

5.3.2. Recovery Euthanasia Animals (Day 57)

(Table 6, Table 7, Table 8, Appendix 5, Appendix 6, and Appendix 7)

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Test article-related organ weight changes noted at the terminal euthanasia were not observed at the end of the recovery period (Day 57). There were 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, the organ weight differences observed were considered incidental and/or related to difference of sexual maturity and unrelated to administration of mRNA-1443.

5.4. Histopathology

5.4.1. Terminal Euthanasia (Day 44)

(Table 9 and Appendix 8)

Test article-related microscopic findings are summarized in Text Table 5.

Text Table 5
Summary of Microscopic Findings – Terminal Euthanasia (Day 44)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10/9.6**	**30/29**	**100/96**	**0**	**10/9.6**	**30/29**	**100/96**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injection	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(3)[a]	(10)	(10)	(10)	(1)	(10)	(10)	(10)
Minimal	3	1	0	0	0	2	0	0
Mild	0	3	0	0	1	7	0	0
Moderate	0	6	4	0	0	1	7	0
Marked	0	0	6	10	0	0	3	10
Liver	10	10	10	10	10	10	10	10
Vacuolation, microvesicular, periportal to midzonal	(1)	(6)	(9)	(9)	(5)	(8)	(8)	(9)
Minimal	1	6	6	4	5	5	5	5
Mild	0	0	3	4	0	3	2	3
Moderate	0	0	0	1	0	0	1	1
Spleen	10	10	10	10	10	10	10	10
Decreased cellularity, lymphoid, periarteriolar sheath	(0)	(2)	(1)	(1)	(0)	(1)	(1)	(4)
Minimal	0	2	1	1	0	1	1	4
Lymph node, inguinal	10	10	10	10	10	9	9	10
Inflammation, mixed cell; perinodal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Mild	0	0	0	1	0	0	0	0
Plasmacytosis	(0)	(1)	(0)	(7)	(0)	(0)	(0)	(3)
Minimal	0	1	0	5	0	0	0	3
Mild	0	0	0	2	0	0	0	0
Hyperplasia; lymphoid	(1)	(6)	(4)	(5)	(0)	(5)	(7)	(4)
Minimal	1	2	2	3	0	3	2	3
Mild	0	3	1	2	0	1	5	1
Moderate	0	1	1	0	0	1	0	0
Lymph node, popliteal	9	10	10	10	10	10	10	10
Inflammation, mixed cell; perinodal	(0)	(9)	(10)	(6)	(0)	(9)	(9)	(7)

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	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10/9.6**	**30/29**	**100/96**	**0**	**10/9.6**	**30/29**	**100/96**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Minimal	0	3	6	1	0	5	3	2
Mild	0	6	2	4	0	4	5	4
Moderate	0	0	2	1	0	0	1	1
Plasmacytosis	(1)	(0)	(0)	(3)	(1)	(1)	(1)	(5)
Minimal	1	0	0	3	1	1	1	2
Mild	0	0	0	0	0	0	0	3
Hyperplasia; lymphoid	(0)	(9)	(8)	(5)	(0)	(8)	(9)	(8)
Minimal	0	6	5	3	0	3	6	5
Mild	0	3	3	2	0	5	3	3
Sciatic nerve	10	10	10	10	10	10	10	10
Inflammation, mixed cell; perineurial	(0)	(10)	(10)	(10)	(5)	(10)	(9)	(10)
Minimal	0	1	4	0	5	0	4	2
Mild	0	5	3	8	0	6	3	7
Moderate	0	3	3	2	0	3	2	1
Marked	0	1	0	0	0	1	0	0
Bone marrow	10	10	10	10	10	10	10	10
Increased hematopoiesis; myeloid	(0)	(2)	(2)	(5)	(1)	(0)	(4)	(4)
Minimal	0	2	2	4	1	0	4	4
Mild	0	0	0	1	0	0	0	0

[a] Numbers in parentheses represent the number of animals with the finding.

Injection Site

A dose-dependent, minimal to marked mixed cellular inflammation accompanied by edema was noted in males and females at dosages equal to or greater than 10/9.6 µg/dose. This change was characterized by a stereotypic acute inflammatory milieu comprising increased clear space expanding the interstitium (edema) accompanied by numerous neutrophils variably admixed with foamy macrophages, lymphocytes, and rare plasma cells and hemosiderophages, as well as variable quantities of extravasated erythrocytes (hemorrhage).

Sciatic Nerve

A dose-dependent, minimal to marked mixed cellular inflammation of the perineurial tissue was observed and was variably accompanied by edema. Of note, the sciatic nerve contained no changes within the nerve fibers, inflammation did not broach the epidneurium, and inflammation/edema was generally of a lesser severity than the injection site proper.

Inguinal and popliteal lymph nodes

Similar to the sciatic nerve, a minimal to moderate mixed cellular inflammation surrounded the inguinal and/or popliteal lymph node in males and females at ≥ 10/9.6 µg/dose, reflected as perinodal interstitial mixed cell inflammation variably accompanied by small amounts of edema. Inflammation did not extend into the lymph node capsule. The inguinal lymph node site generally had less incidence and severity of peripheral inflammation vs. the popliteal site.

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Intrinsic lymph node changes included lymphoid hyperplasia and medullary plasmacytosis; these changes were orderly and of a character and magnitude that would be expected of reactive lymph nodes that are a non-specific and appropriate secondary consequence of injection site inflammation. These non-specific reactive changes were observed in relevant locoregional injection site lymph nodes (inguinal, popliteal) at a higher rate and slightly higher magnitude than controls.

Spleen

Males and females at ≥ 10/9.6 µg/dose had slightly increased incidence of a minimally decreased cellularity of the periarteriolar lymphoid sheath. Although males did not display any evident dose-dependent trend, increased incidence in females at 100/96 µg/dose may indicate a dose-dependent effect. Microscopically, this change was characterized by subtle attrition of periarteriolar lymphocytes and variably accompanied by a slight increase in tingible body macrophages.

Bone Marrow

Males at ≥ 10/9.6 µg/dose and females at ≥ 30/29 µg/dose had increased incidence of minimal to mild increased myeloid hematopoiesis (myeloid hyperplasia) with a distinctive appearance. Incidence in males and females generally trends upward with increasing dose, suggesting a dose-dependent effect. Microscopically, this change was consistently characterized by multifocal aggregates of precursor cells predominantly composed of early myeloid lineage and typically found adjacent to the cortex and/or trabeculae.

Liver

Males and females in control and treated groups display microvescular hepatocellular vacuolation without nuclear displacement throughout periportal to midzonal regions. However, this change demonstrated a dose-dependent increase in incidence and magnitude at ≥ 10/9.6 µg/dose in both genders, consistent with a test-article exacerbation of a background lesion.

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-1443.

5.4.2. Recovery Euthanasia (Day 57)

(Table 10 and Appendix 8)

Microscopic findings noted at the terminal euthanasia were observed at the end of the recovery period (Day 57) and are summarized in Text Table 6.

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Text Table 6
Summary of Microscopic Findings – Recovery Euthanasia (Day 57)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10/9.6**	**30/29**	**100/96**	**0**	**10/9.6**	**30/29**	**100/96**
No. Animals Examined	**5**	**-**	**-**	**5**	**5**	**-**	**-**	**5**
Injection site	5	-	-	5	5	-	-	5
Infiltration, mononuclear cell	(1)[a]	-	-	(4)	(0)	-	-	(4)
Minimal	1	-	-	4	0	-	-	4
Liver	5	-	-	5	5	-	-	5
Vacuolation, microvesicular, periportal to midzonal	(0)	-	-	(1)	(2)	-	-	(4)
Minimal	0	-	-	0	2	-	-	1
Mild	0	-	-	1	0	-	-	3
Lymph node, inguinal	5	-	-	5	5	-	-	5
Plasmacytosis	(1)	-	-	(2)	(0)	-	-	(0)
Minimal	1	-	-	2	0	-	-	0
Hyperplasia; lymphoid	(2)	-	-	(3)	(1)	-	-	(1)
Minimal	2	-	-	2	1	-	-	1
Mild	0	-	-	1	0	-	-	0
Lymph node, popliteal	5	-	-	5	5	-	-	5
Infiltration, mononuclear cell; perinodal	(0)	-	-	(1)	(0)	-	-	(1)
Minimal	0	-	-	1	0	-	-	1
Plasmacytosis	(2)	-	-	(3)	(0)	-	-	(2)
Minimal	2	-	-	2	0	-	-	0
Mild	0	-	-	1	0	-	-	2
Hyperplasia; lymphoid	(1)	-	-	(3)	(0)	-	-	(5)
Minimal	0	-	-	3	0	-	-	5
Mild	1	-	-	0	0	-	-	0
Sciatic nerve	5	-	-	5	5	-	-	5
Infiltration, mononuclear cell; perineurial	(0)	-	-	(5)	(1)	-	-	(4)
Minimal	0	-	-	5	1	-	-	2
Mild	0	-	-	0	0	-	-	2

[a] Numbers in parentheses represent the number of animals with the finding.

Injection Site

In 100/96 µg dose recovery group males and females there is resolution of edema and acute mixed cellular inflammation when compared with Main Study (Day 44) 100/96 µg dose animals. When present, the interstitial to perivascular inflammatory population is minimal and comprises a mixture of lymphocytes and macrophages with rare plasma cells and is consistent with a healing process.

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Sciatic nerve

Minimal to mild infiltration of mononuclear cells was noted in both sexes, suggesting partial recovery from the mixed cellular inflammation observed by the end of the Recovery period.

Inguinal and popliteal lymph nodes

Perinodal mixed-cell inflammation is absent in 100/96 µg dose group males and females following recovery. As part of the resolving/resolved acute inflammation, a minimal mononuclear cell infiltration is occasionally present within the interstitium and/or perivascularly, albeit with much decreased frequency and incidence when compared with initial perinodal inflammation at Day 44.

Intrinsic lymph node changes including lymphoid hyperplasia and medullary plasmacytosis have decreased incidence and magnitude following recovery, consistent with a resolving/resolved inflammatory response.

Liver

Males and females in control and treated groups display microvescular hepatocelluar vacuolation throughout periportal to midzonal regions. This change occurred at decreased incidence and magnitude when compared with Main Study (Day 44) animals indicating improvement. Amongst recovery animals, this change was observed in (2) control females (minimal), (1) 100/96 µg dose male (mild), and (4) (1 minimal, 3 mild) 100/96 µg dose females. However, the higher incidence in 100/96 µg dose recovery animals suggests that this test-article effect has not fully resolved.

Microscopic findings noted in the bone marrow and spleen at terminal euthanasia were no longer observed at the end of the recovery period and therefore were considered completely recovered.

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-1443.

6. CONCLUSIONS

Intramuscular injection of mRNA-1443 for 6 weeks (4 doses) in rats for up to 44 days at doses of 0, 10/9.6, 30/29, or 100/96 µg/dose resulted in locally extensive interstitial inflammation and edema at the intramuscular injection site (correlating with abnormal firm consistency and swelling). This inflammation extended to the connective tissues surrounding the sciatic nerve and popliteal and inguinal lymph nodes (correlating with inguinal and popliteal lymph node enlargement), plasmacytosis and lymphoid hyperplasia in the politeal and inguinal lymph nodes, myeloid hyperplasia in the bone marrow, decreased cellularity in the periarteriolar sheath of the spleen, and microvesicular vacuolation in the periportal to midzonal area in the liver.

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After a 2 week recovery period, macroscopic and organ weights differences were completely recovered. The microscopic changes observed in the inguinal and popliteal lymph nodes were nearly or fully resolved, and changes in the spleen and the bone marrow were completely resolved. The mixed cellular inflammation observed at injection sites and in the connective tissues surrounding the sciatic nerve and inguinal and popliteal lymph node was replaced by an infiltrate of mononucluear cells and was considered as a healing process from the previous inflammation. There was a decrease in incidence and severity of the of the hepatocellular microvesicular vacuolation noted at the end of the Main phase, suggesting partial resolution.

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Table 1
Summary of Gross Pathology Findings (Day 44)

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5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 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, 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	9	10	10	10	.	.	.	.
Small	1	0	0	0	.	.	.	.
Abnormal consistency; soft	1	0	0	0	.	.	.	.
Focus; pale	1	0	0	0	.	.	.	.
Focus; raised	1	0	0	0	.	.	.	.
ESOPHAGUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	10	10	10	10	10	10
Discoloration; dark	0	1	0	0	0	0	0	0
Dilatation	0	1	0	0	0	0	0	0

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5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ESOPHAGUS (Continued...)								
Thick	0	1	0	0	0	0	0	0
EYE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	9	10
Focus; dark	0	0	0	0	0	0	1	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	9	10	10	10	10	8	10
Focus; dark	0	1	0	0	0	0	2	0
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	9	10	10	10	10	10
Focus; dark	0	0	1	0	0	0	0	0
GLAND, PROSTATE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	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	10	9	10	10	10	9	10	10
Enlargement	0	1	0	0	0	0	0	0
Small	0	0	0	0	0	1	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	8	10	9	10	9	10	10	10
Focus; depressed	1	0	1	0	1	0	0	0
Focus; pale	1	0	1	0	0	0	0	0
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	9	10	10	9	10	10	10
Focus; dark	0	1	0	0	0	0	0	0
Parasite	0	0	0	0	1	0	0	0
LARYNX								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LIVER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	3	4	5	5	3	6	5	6

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LIVER (Continued...)								
Focus; depressed	1	0	0	0	0	0	0	0
Focus; pale	7	6	5	5	6	4	5	4
Nodule	0	0	0	0	1	0	0	0
LUNG								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	7	8	5	8	10	8	9	8
Focus; dark	3	2	5	2	0	2	1	2
Focus; depressed	0	0	1	0	0	0	1	1
Discoloration; dark	0	0	1	0	0	0	0	0
Abnormal consistency	0	0	1	0	0	0	0	0
LYMPH NODE								
Submitted	0	0	0	0	0	0	1	1
Discoloration; dark	.	.	.	.	.	.	0	1
Enlargement	.	.	.	.	.	.	1	0
LYMPH NODE, INGUINAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	7	8	8	10	10	10	9
Focus; dark	0	1	0	1	0	0	0	0
Enlargement	0	2	2	2	0	0	0	1
LYMPH NODE, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	8	5	9	6	7	8	9
Focus; dark	1	2	4	1	4	3	2	1
Enlargement	0	0	1	0	0	0	0	1
LYMPH NODE, MESENTERIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	9	10	10	10	9	10	10
Focus; dark	1	0	0	0	0	0	0	0
Enlargement	0	1	0	0	0	1	0	0
LYMPH NODE, POPLITEAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	7	7	5	10	9	8	6

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, POPLITEAL (Continued...)								
Enlargement	0	3	3	5	0	1	2	4
MUSCLE, SKELETAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	9	10	9	10	10	10
Material accumulation; clot	0	0	1	0	1	0	0	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
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	7	0	0	10	8	0	0
Abnormal consistency; firm	0	2	9	10	0	2	10	10
Swelling	0	1	4	7	0	0	1	2
Focus; dark	0	0	3	1	0	0	1	1
Focus; pale	0	0	0	1	0	0	0	0
SKIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	10	10	10	10	10	10
Scab; dark	0	1	0	0	0	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

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	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
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	10	10	10	10	10	10	10
STOMACH								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	8	8	8	8	9	10	10
Focus; dark	0	2	2	2	1	1	0	0
Focus; pale	0	0	0	0	1	0	0	0
Thick	0	0	0	0	0	1	0	0
SUBCUTIS								
Submitted	0	0	0	0	0	1	0	0
Mass	.	.	.	.	.	1	.	.
TESTIS								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	9	10	10	10	.	.	.	.
Abnormal consistency; soft	1	0	0	0	.	.	.	.
Focus; pale	1	0	0	0	.	.	.	.

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
THYMUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	7	6	4	8	4	7	9	8
Focus; dark	3	3	6	2	5	3	1	2
Enlargement	0	1	0	0	0	0	0	0
Small	0	0	0	0	1	0	0	0
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 21

Table 2
Summary of Gross Pathology Findings (Day 57)

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
ARTERY, AORTA				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BODY CAVITY, NASAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE MARROW				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, FEMUR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, STERNUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BRAIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
CERVIX				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
EPIDIDYMIS				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
ESOPHAGUS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
EYE				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GALT				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, ADRENAL				
Submitted	5	5	5	5
No Visible Lesions	3	4	5	5
Focus; dark	0	1	0	0
Enlargement	2	0	0	0
GLAND, HARDERIAN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, MAMMARY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PARATHYROID				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PITUITARY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PROSTATE				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, SALIVARY, MANDIBULAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, SEMINAL VESICLE				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, THYROID				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	4
Enlargement	0	0	0	1
HEART				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
KIDNEY				
Submitted	5	5	5	5
No Visible Lesions	5	4	5	5
Focus; pale	0	1	0	0
LARGE INTESTINE, CECUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, COLON				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, RECTUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARYNX				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LIVER				
Submitted	5	5	5	5
No Visible Lesions	3	4	4	4
Focus; pale	2	1	1	1
LUNG				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	3
Focus; dark	0	0	0	1
Focus; pale	0	0	0	1
LYMPH NODE				
Submitted	1	2	0	1
Discoloration; dark	1	0	.	1
Enlargement	0	2	.	0
LYMPH NODE, INGUINAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, MANDIBULAR				
Submitted	5	5	5	5
No Visible Lesions	4	4	5	4
Focus; dark	1	1	0	1
LYMPH NODE, MESENTERIC				
Submitted	5	5	5	5
No Visible Lesions	5	4	5	5
Focus; dark	0	1	0	0
LYMPH NODE, POPLITEAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
MUSCLE, SKELETAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, OPTIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, SCIATIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
OVARY				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
PANCREAS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SITE, INJECTION				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SKIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
SMALL INTESTINE, DUODENUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, ILEUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, JEJUNUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, CERVICAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, LUMBAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, THORACIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPLEEN				
Submitted	5	5	5	5
No Visible Lesions	4	5	5	5
Focus; raised	1	0	0	0
Enlargement	1	0	0	0
Irregular surface	1	0	0	0
STOMACH				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
TESTIS				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
THYMUS				
Submitted	5	5	5	5
No Visible Lesions	4	4	4	5

Appendix 21

5002158 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
THYMUS (Continued...)				
Focus; dark	1	1	1	0
TONGUE				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
TRACHEA				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
URINARY BLADDER				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
UTERUS				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
VAGINA				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5

Appendix 21

Table 3
Summary of Organ Weight Values - Absolute (Day 44)

Appendix 21

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	535.2	2.2067	1.2117	0.06679	0.01420	1.3265	0.02269
	SD	37.1	0.0757	0.0766	0.00663	0.00159	0.1499	0.00375
	N	10	10	10	10	10	10	10
2M	Mean	512.8	2.2352	1.2222	0.06190	0.01388	1.2570	0.02465
	SD	29.9	0.0939	0.0499	0.00635	0.00137	0.1516	0.00857
	N	10	10	10	10	10	10	10
	%Diff G1	-4.2	1.2915	0.8666	-7.32146	-2.25352	-5.2394	8.63817
3M	Mean	515.6	2.1543	1.2125	0.06033	0.01426	1.2702	0.02129
	SD	55.1	0.1051	0.0981	0.00538	0.00131	0.1957	0.00361
	N	10	10	10	10	10	10	10
	%Diff G1	-3.7	-2.3746	0.0660	-9.67211	0.42254	-4.2443	-6.17012
4M	Mean	500.5	2.1699	1.1980	0.06660	0.01363	1.2531	0.02421
	SD	61.9	0.0878	0.0922	0.01157	0.00281	0.2092	0.00706
	N	10	10	10	10	10	10	10
	%Diff G1	-6.5	-1.6676	-1.1306	-0.28447	-4.01408	-5.5334	6.69899

Appendix 21

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	Mean	1.8440	3.1657	13.9654	1.7330	--	0.9193	3.7565
	SD	0.1243	0.1627	1.4328	0.0927	--	0.1193	0.2845
	N	10	10	10	10	--	10	10
2M	Mean	1.7483	3.1034	13.2985	1.6762	--	1.0713a	3.8918
	SD	0.2047	0.1990	1.6621	0.0949	--	0.1244	0.2920
	N	10	10	10	10	--	10	10
	%Diff G1	-5.1898	-1.9680	-4.7754	-3.2776	--	16.5343	3.6018
3M	Mean	1.7782	3.0021	13.9916	1.7354	--	1.0640	3.7632
	SD	0.2134	0.3887	2.0710	0.1877	--	0.1416	0.2613
	N	10	10	10	10	--	10	10
	%Diff G1	-3.5683	-5.1679	0.1876	0.1385	--	15.7402	0.1784
4M	Mean	1.8215	3.1022	14.3530	1.7471	--	1.1291a	3.7176
	SD	0.2566	0.3471	2.2755	0.2065	--	0.2192	0.3062
	N	10	10	10	10	--	10	10
	%Diff G1	-1.2202	-2.0059	2.7754	0.8136	--	22.8217	-1.0355

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

Appendix 21

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		THYMUS g	UTERUS g
1M	Mean	0.4577	--
	SD	0.0868	--
	N	10	--
2M	Mean	0.5113	--
	SD	0.1527	--
	N	10	--
	%Diff G1	11.7107	--
3M	Mean	0.4630	--
	SD	0.1383	--
	N	10	--
	%Diff G1	1.1580	--
4M	Mean	0.4391	--
	SD	0.0803	--
	N	10	--
	%Diff G1	-4.0638	--

Appendix 21

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	290.6	2.0622	--	0.07127	0.01748	--	0.01694
	SD	22.4	0.1023	--	0.01255	0.00283	--	0.00341
	N	10	10	--	10	10	--	10
2F	Mean	301.7	2.0303	--	0.06706	0.01613	--	0.01799
	SD	30.4	0.0961	--	0.00926	0.00241	--	0.00264
	N	10	10	--	10	10	--	10
	%Diff G1	3.8	-1.5469	--	-5.90711	-7.72311	--	6.19835
3F	Mean	289.9	2.0504	--	0.07014	0.01788	--	0.01919
	SD	24.9	0.0870	--	0.00861	0.00208	--	0.00313
	N	10	10	--	10	10	--	10
	%Diff G1	-0.2	-0.5722	--	-1.58552	2.28833	--	13.28217
4F	Mean	288.5	2.0424	--	0.07524	0.01497a	--	0.01679
	SD	31.0	0.0839	--	0.01289	0.00158	--	0.00400
	N	10	10	--	10	10	--	10
	%Diff G1	-0.7	-0.9601	--	5.57037	-14.35927	--	-0.88548

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

Appendix 21

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	Mean	1.2079	1.8739	7.5143	1.2510	0.0981	0.5984	--
	SD	0.0897	0.1468	0.7751	0.1187	0.0136	0.0843	--
	N	10	10	10	10	10	10	--
2F	Mean	1.2462	1.8545	7.8768	1.3472	0.1005	0.6823	--
	SD	0.1667	0.1536	0.9701	0.1346	0.0132	0.0766	--
	N	10	10	10	10	10	10	--
	%Diff G1	3.1708	-1.0353	4.8241	7.6898	2.4465	14.0207	--
3F	Mean	1.1396	1.8474	7.7964	1.3372	0.0950	0.6816	--
	SD	0.1033	0.1977	0.8574	0.1168	0.0111	0.1190	--
	N	10	10	10	10	10	10	--
	%Diff G1	-5.6544	-1.4142	3.7542	6.8905	-3.1600	13.9037	--
4F	Mean	1.1923	1.8855	8.1836	1.3746	0.0970	0.7184	--
	SD	0.1209	0.2802	0.8699	0.1176	0.0108	0.0976	--
	N	10	10	10	10	10	10	--
	%Diff G1	-1.2915	0.6190	8.9070	9.8801	-1.1213	20.0535	--

Appendix 21

Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		THYMUS g	UTERUS g
1F	Mean	0.4126	0.7479
	SD	0.0995	0.4380
	N	10	10
2F	Mean	0.4300	0.5694
	SD	0.0854	0.1394
	N	10	10
	%Diff G1	4.2172	-23.8668
3F	Mean	0.4358	0.7330
	SD	0.1209	0.3134
	N	10	10
	%Diff G1	5.6229	-1.9922
4F	Mean	0.4011	0.4999
	SD	0.1441	0.1432
	N	10	10
	%Diff G1	-2.7872	-33.1595

Appendix 21

Table 4
Summary of Organ Weight Values - Relative to Body Weight (Day 44)

Appendix 21

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.41395	0.22728	0.01252	0.00265	0.24916	0.00425	0.34531
	SD	0.02960	0.01977	0.00141	0.00018	0.03418	0.00069	0.02306
	N	10	10	10	10	10	10	10
2M	Mean	0.43682	0.23906	0.01210	0.00271	0.24570	0.00475	0.34061
	SD	0.02488	0.01683	0.00136	0.00025	0.03190	0.00130	0.02898
	N	10	10	10	10	10	10	10
	%Diff G1	5.52274	5.18267	-3.35223	2.27055	-1.39131	11.73459	-1.36304
3M	Mean	0.42045	0.23622	0.01179	0.00277	0.24912	0.00413	0.34537
	SD	0.02946	0.01735	0.00135	0.00016	0.05101	0.00055	0.02814
	N	10	10	10	10	10	10	10
	%Diff G1	1.56866	3.93192	-5.84295	4.64233	-0.01734	-2.82642	0.01489
4M	Mean	0.43922	0.24205	0.01331	0.00273	0.25067	0.00483	0.36433
	SD	0.05423	0.02962	0.00175	0.00045	0.02898	0.00124	0.02769
	N	10	10	10	10	10	10	10
	%Diff G1	6.10398	6.50069	6.29915	2.87219	0.60531	13.81208	5.50602

Appendix 21

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.59293	2.60493	0.32464	--	0.17228	0.70322	0.08602
	SD	0.03267	0.13048	0.01978	--	0.02440	0.04940	0.01807
	N	10	10	10	--	10	10	10
2M	Mean	0.60559	2.58696	0.32727	--	0.20868d	0.76093	0.09909
	SD	0.02923	0.21096	0.01670	--	0.01793	0.06617	0.02662
	N	10	10	10	--	10	10	10
	%Diff G1	2.13495	-0.68997	0.80893	--	21.13059	8.20606	15.18904
3M	Mean	0.58354	2.70419	0.33671	--	0.20693d	0.73467	0.08931
	SD	0.05616	0.14440	0.01082	--	0.02270	0.06519	0.02327
	N	10	10	10	--	10	10	10
	%Diff G1	-1.58353	3.81044	3.71928	--	20.11467	4.47102	3.82519
4M	Mean	0.62359	2.85704b	0.35014d	--	0.22638f	0.74946	0.08876
	SD	0.06184	0.13110	0.02598	--	0.03859	0.07872	0.01887
	N	10	10	10	--	10	10	10
	%Diff G1	5.16990	9.67841	7.85435	--	31.40503	6.57497	3.17722

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)

Appendix 21

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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 21

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	Mean	0.71263	--	0.02450	0.00603	--	0.00582	0.41608
	SD	0.05563	--	0.00359	0.00096	--	0.00100	0.01836
	N	10	--	10	10	--	10	10
2F	Mean	0.67708	--	0.02234	0.00536	--	0.00598	0.41372
	SD	0.05301	--	0.00325	0.00071	--	0.00085	0.04488
	N	10	--	10	10	--	10	10
	%Diff G1	-4.98938	--	-8.81592	-11.13204	--	2.89204	-0.56696
3F	Mean	0.71115	--	0.02446	0.00620	--	0.00666	0.39379
	SD	0.05628	--	0.00454	0.00081	--	0.00122	0.02582
	N	10	--	10	10	--	10	10
	%Diff G1	-0.20824	--	-0.17068	2.85150	--	14.55088	-5.35861
4F	Mean	0.71324	--	0.02619	0.00521	--	0.00578	0.41374
	SD	0.05959	--	0.00411	0.00048	--	0.00089	0.01319
	N	10	--	10	10	--	10	10
	%Diff G1	0.08467	--	6.89623	-13.56059	--	-0.68036	-0.56246

Appendix 21

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	Mean	0.64640	2.58520	0.43100	0.03375	0.20695	--	0.14149
	SD	0.04761	0.16805	0.03270	0.00387	0.03154	--	0.03097
	N	10	10	10	10	10	--	10
2F	Mean	0.61807	2.60732	0.44759	0.03339	0.22628	--	0.14247
	SD	0.06071	0.09331	0.03257	0.00336	0.01341	--	0.02431
	N	10	10	10	10	10	--	10
	%Diff G1	-4.38198	0.85542	3.84847	-1.08513	9.34063	--	0.68970
3F	Mean	0.63923	2.68726	0.46244	0.03288	0.23548	--	0.14812
	SD	0.06676	0.14223	0.03409	0.00380	0.03831	--	0.03129
	N	10	10	10	10	10	--	10
	%Diff G1	-1.10891	3.94776	7.29557	-2.57861	13.78629	--	4.67962
4F	Mean	0.65166	2.83925f	0.47823e	0.03380	0.24892b	--	0.13712
	SD	0.04114	0.13175	0.03180	0.00385	0.01902	--	0.03540
	N	10	10	10	10	10	--	10
	%Diff G1	0.81447	9.82692	10.95811	0.13707	20.28219	--	-3.09281

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)

Appendix 21

Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		UTERUS %
1F	Mean	0.26028
	SD	0.16332
	N	10
2F	Mean	0.19103
	SD	0.05464
	N	10
	%Diff G1	-26.60562
3F	Mean	0.25621
	SD	0.11945
	N	10
	%Diff G1	-1.56524
4F	Mean	0.17467
	SD	0.05055
	N	10
	%Diff G1	-32.89185

Appendix 21

Table 5
Summary of Organ Weight Values - Relative to Brain Weight (Day 44)

Appendix 21

Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	54.93717	3.03108	0.64327	60.15808	1.02749	83.55838	143.47688
	SD	3.48309	0.33136	0.06537	6.86507	0.16201	4.72739	5.92078
	N	10	10	10	10	10	10	10
2M	Mean	54.73563	2.77113	0.62075	56.31437	1.09769	78.20737	138.92236
	SD	2.49058	0.27618	0.05198	7.22140	0.35058	8.26107	8.29886
	N	10	10	10	10	10	10	10
	%Diff G1	-0.36684	-8.57629	-3.50193	-6.38935	6.83182	-6.40391	-3.17439
3M	Mean	56.27704	2.80373	0.66164	59.03661	0.98473	82.35892	139.15363
	SD	3.61638	0.25272	0.04717	9.54936	0.13743	6.98844	14.39955
	N	10	10	10	10	10	10	10
	%Diff G1	2.43891	-7.50073	2.85596	-1.86419	-4.16183	-1.43547	-3.01320
4M	Mean	55.17248	3.06408	0.62900	57.62472	1.10641	83.84139	143.10853
	SD	2.86687	0.48568	0.13059	8.46888	0.28069	10.24060	16.09562
	N	10	10	10	10	10	10	10
	%Diff G1	0.42833	1.08859	-2.21813	-4.21117	7.68070	0.33870	-0.25673

Appendix 21

Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	Mean	633.00544	78.54352	--	41.70881	170.44151	20.80716	--
	SD	63.13716	3.46149	--	5.68685	14.68585	4.30585	--
	N	10	10	--	10	10	10	--
2M	Mean	596.10692	74.99528	--	47.92044	174.52948	22.85998	--
	SD	80.09692	2.97386	--	5.02421	16.56021	6.73407	--
	N	10	10	--	10	10	10	--
	%Diff G1	-5.82910	-4.51755	--	14.89285	2.39846	9.86590	--
3M	Mean	647.71190	80.40267	--	49.36475a	174.81462	21.40861	--
	SD	75.55118	5.68640	--	5.78046	11.43287	6.00698	--
	N	10	10	--	10	10	10	--
	%Diff G1	2.32328	2.36703	--	18.35570	2.56576	2.89057	--
4M	Mean	660.77980	80.42331	--	51.91698b	171.21857	20.27134	--
	SD	96.51786	8.17777	--	9.17232	10.13922	3.81940	--
	N	10	10	--	10	10	10	--
	%Diff G1	4.38770	2.39330	--	24.47485	0.45591	-2.57518	--

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

Appendix 21

Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	Mean	--	3.45924	0.85030	--	0.81898	58.65868	91.10057
	SD	--	0.58769	0.14285	--	0.14706	4.62059	8.67104
	N	--	10	10	--	10	10	10
2F	Mean	--	3.30492	0.79340	--	0.88500	61.27286	91.32104
	SD	--	0.44358	0.10230	--	0.11667	6.61697	5.93772
	N	--	10	10	--	10	10	10
	%Diff G1	--	-4.46121	-6.69141	--	8.06088	4.45659	0.24201
3F	Mean	--	3.42103	0.87021	--	0.93608	55.59938	90.07688
	SD	--	0.40514	0.07307	--	0.15133	4.73560	8.64241
	N	--	10	10	--	10	10	10
	%Diff G1	--	-1.10463	2.34184	--	14.29739	-5.21542	-1.12369
4F	Mean	--	3.67776	0.73284a	--	0.81850	58.31052	92.10199
	SD	--	0.56069	0.06803	--	0.17050	4.40243	11.23555
	N	--	10	10	--	10	10	10
	%Diff G1	--	6.31681	-13.81423	--	-0.05940	-0.59353	1.09925

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

Appendix 21

Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	Mean	364.66789	60.75792	4.75098	29.12029	--	19.87811	36.22148
	SD	35.88516	5.97271	0.55768	4.56387	--	4.33259	20.80260
	N	10	10	10	10	--	10	10
2F	Mean	387.40300	66.25156a	4.94754	33.58174	--	21.19628	28.00724
	SD	36.16671	4.23311	0.55474	3.04888	--	4.30962	6.68881
	N	10	10	10	10	--	10	10
	%Diff G1	6.23447	9.04185	4.13735	15.32076	--	6.63122	-22.67781
3F	Mean	379.70201	65.17112	4.63039	33.16058	--	21.15181	35.76106
	SD	32.03540	4.19057	0.47171	4.98418	--	5.43296	15.15197
	N	10	10	10	10	--	10	10
	%Diff G1	4.12269	7.26358	-2.53807	13.87448	--	6.40750	-1.27114
4F	Mean	399.93400	67.23042b	4.74609	35.11205b	--	19.55053	24.51663
	SD	29.28902	3.87046	0.45027	3.96178	--	6.57462	7.02593
	N	10	10	10	10	--	10	10
	%Diff G1	9.67075	10.65292	-0.10297	20.57586	--	-1.64799	-32.31468

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

Appendix 21

Table 6
Summary of Organ Weight Values - Absolute (Day 57)

Appendix 21

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	596.2	2.2762	1.2726	0.07050	0.01302	1.1886	0.01750
	SD	50.4	0.0663	0.0573	0.01629	0.00093	0.1294	0.00268
	N	5	5	5	5	5	5	5
4M	Mean	564.8	2.2332	1.2758	0.06550	0.01448	1.1952	0.01766
	SD	35.1	0.0751	0.1171	0.01569	0.00142	0.1247	0.00221
	N	5	5	5	5	5	5	5
	%Diff G1	-5.3	-1.8891	0.2515	-7.09220	11.21352	0.5553	0.91429

Appendix 21

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	Mean	1.8772	3.3394	17.4524	1.7194	--	1.6062	4.0392
	SD	0.1633	0.1051	2.0214	0.1254	--	1.1432	0.2590
	N	5	5	5	5	--	5	5
4M	Mean	1.7756	3.2604	15.6342	1.7274	--	1.2300	3.9090
	SD	0.1878	0.3042	2.2301	0.0815	--	0.3826	0.1544
	N	5	5	5	5	--	5	5
	%Diff G1	-5.4123	-2.3657	-10.4181	0.4653	--	-23.4217	-3.2234

Appendix 21

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		THYMUS g	UTERUS g
1M	Mean	0.4126	--
	SD	0.1549	--
	N	5	--
4M	Mean	0.3834	--
	SD	0.0638	--
	N	5	--
	%Diff G1	-7.0771	--

Appendix 21

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	293.2	2.0318	--	0.06624	0.01600	--	0.01578
	SD	11.9	0.0831	--	0.00612	0.00276	--	0.00168
	N	5	5	--	5	5	--	5
4F	Mean	304.8	2.0132	--	0.06448	0.01612	--	0.01724
	SD	19.8	0.0776	--	0.00703	0.00268	--	0.00394
	N	5	5	--	5	5	--	5
	%Diff G1	4.0	-0.9154	--	-2.65700	0.75000	--	9.25222

Appendix 21

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	Mean	1.1324	1.7702	6.9912	1.2454	0.0922	0.5708	--
	SD	0.0483	0.1566	0.6043	0.0699	0.0144	0.0746	--
	N	5	5	5	5	5	5	--
4F	Mean	1.1428	1.8044	7.3594	1.2620	0.0894	0.5576	--
	SD	0.0761	0.1820	1.0422	0.1299	0.0192	0.0647	--
	N	5	5	5	5	5	5	--
	%Diff G1	0.9184	1.9320	5.2666	1.3329	-3.0369	-2.3125	--

Appendix 21

Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		THYMUS g	UTERUS g
1F	Mean	0.3000	0.5946
	SD	0.0448	0.2149
	N	5	5
4F	Mean	0.3420	0.6724
	SD	0.0661	0.3186
	N	5	5
	%Diff G1	14.0000	13.0844

Appendix 21

Table 7
Summary of Organ Weight Values - Relative to Body Weight (Day 57)

Appendix 21

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.38345	0.21469	0.01190	0.00220	0.19949	0.00294	0.31495
	SD	0.02561	0.02058	0.00298	0.00029	0.01542	0.00036	0.01014
	N	5	5	5	5	5	5	5
4M	Mean	0.39627	0.22596	0.01157	0.00257	0.21251	0.00312	0.31431
	SD	0.02054	0.01661	0.00254	0.00029	0.02794	0.00031	0.02723
	N	5	5	5	5	5	5	5
	%Diff G1	3.34399	5.25081	-2.77577	16.83904	6.52594	6.40112	-0.20521

Appendix 21

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.56339	2.93659	0.29011	--	0.27706	0.67927	0.06864
	SD	0.05275	0.36580	0.03219	--	0.20781	0.04012	0.02425
	N	5	5	5	--	5	5	5
4M	Mean	0.57825	2.75838	0.30623	--	0.21706	0.69368	0.06783
	SD	0.05385	0.26641	0.01189	--	0.06224	0.03958	0.01053
	N	5	5	5	--	5	5	5
	%Diff G1	2.63743	-6.06880	5.55900	--	-21.65758	2.12164	-1.18697

Appendix 21

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		UTERUS %
1M	Mean	--
	SD	--
	N	--
4M	Mean	--
	SD	--
	N	--
	%Diff G1	--

Appendix 21

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	Mean	0.69354	--	0.02257	0.00545	--	0.00538	0.38631
	SD	0.03075	--	0.00155	0.00088	--	0.00049	0.01042
	N	5	--	5	5	--	5	5
4F	Mean	0.66199	--	0.02114	0.00529	--	0.00568	0.37510
	SD	0.03593	--	0.00166	0.00080	--	0.00134	0.01422
	N	5	--	5	5	--	5	5
	%Diff G1	-4.54809	--	-6.34973	-3.07179	--	5.50160	-2.90138

Appendix 21

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	Mean	0.60288	2.38344	0.42520	0.03151	0.19546	--	0.10258
	SD	0.03140	0.16550	0.02762	0.00519	0.03086	--	0.01681
	N	5	5	5	5	5	--	5
4F	Mean	0.59193	2.40669	0.41386	0.02949	0.18294	--	0.11174
	SD	0.04351	0.20119	0.03146	0.00735	0.01820	--	0.01643
	N	5	5	5	5	5	--	5
	%Diff G1	-1.81614	0.97551	-2.66619	-6.40548	-6.40752	--	8.92443

Appendix 21

Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		UTERUS %
1F	Mean	0.20481
	SD	0.08141
	N	5
4F	Mean	0.22596
	SD	0.12113
	N	5
	%Diff G1	10.32798

Appendix 21

Table 8
Summary of Organ Weight Values - Relative to Brain Weight (Day 57)

Appendix 21

Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	55.91378	3.09860	0.57295	52.19783	0.76755	82.45474	146.85511
	SD	2.09624	0.71693	0.05216	5.12492	0.10284	6.58229	7.53151
	N	5	5	5	5	5	5	5
4M	Mean	57.11549	2.92585	0.64772a	53.69524	0.78937	79.51395	145.92334
	SD	4.63972	0.64371	0.04972	7.07231	0.07726	8.13575	11.20433
	N	5	5	5	5	5	5	5
	%Diff G1	2.14923	-5.57502	13.05031	2.86871	2.84308	-3.56655	-0.63449

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

Appendix 21

Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	Mean	766.82153	75.52191	--	70.99860	177.31737	18.10768	--
	SD	88.42117	4.74876	--	51.17850	6.63109	6.87505	--
	N	5	5	--	5	5	5	--
4M	Mean	699.21961	77.37512	--	54.79363	175.08561	17.20998	--
	SD	89.96999	3.37334	--	15.35030	5.59281	3.16165	--
	N	5	5	--	5	5	5	--
	%Diff G1	-8.81586	2.45386	--	-22.82435	-1.25862	-4.95758	--

Appendix 21

Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	Mean	--	3.25600	0.78593	--	0.77592	55.77040	87.09850
	SD	--	0.19028	0.12045	--	0.06640	2.42561	6.47542
	N	--	5	5	--	5	5	5
4F	Mean	--	3.19835	0.79866	--	0.85487	56.72896	89.56686
	SD	--	0.27521	0.11718	--	0.17923	2.16513	7.55405
	N	--	5	5	--	5	5	5
	%Diff G1	--	-1.77037	1.61930	--	10.17570	1.71876	2.83399

Appendix 21

Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	Mean	344.61141	61.38991	4.52787	28.15510	--	14.78664	29.37521
	SD	34.09595	4.49762	0.59530	4.08608	--	2.33849	10.98199
	N	5	5	5	5	--	5	5
4F	Mean	365.21742	62.56821	4.43361	27.65104	--	16.95872	33.73963
	SD	46.60747	4.38825	0.92147	2.56267	--	2.99739	16.65276
	N	5	5	5	5	--	5	5
	%Diff G1	5.97949	1.91937	-2.08164	-1.79029	--	14.68947	14.85750

Appendix 21

Table 9
Summary of Histopathology Findings (Day 44)

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 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	10	10	10	10	10	10	10
No Visible Lesions	10	8	8	5	9	10	6	6
Increased hematopoiesis; myeloid	0	2	2	5	1	0	4	4
.... minimal	0	2	2	4	1	0	4	4
.... mild	0	0	0	1	0	0	0	0
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	0	0	10	.	.	.	.
No Visible Lesions	9	.	.	10	.	.	.	.
Sperm granuloma	1	.	.	0	.	.	.	.
.... moderate	1	.	.	0	.	.	.	.
Infiltration, mononuclear cell	1	.	.	0	.	.	.	.
.... minimal	1	.	.	0	.	.	.	.
Cribriform change	1	.	.	0	.	.	.	.
.... mild	1	.	.	0	.	.	.	.
Hypospermia	1	.	.	0	.	.	.	.
.... moderate	1	.	.	0	.	.	.	.
ESOPHAGUS								
Examined	10	1	0	10	10	0	0	10
No Visible Lesions	10	0	.	10	10	.	.	10

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ESOPHAGUS (Continued...)								
Hyperplasia; epithelial, lumen	0	1	.	0	0	.	.	0
.... mild	0	1	.	0	0	.	.	0
Hypertrophy; mural, myofiber	0	1	.	0	0	.	.	0
.... moderate	0	1	.	0	0	.	.	0
Dilatation	0	1	.	0	0	.	.	0
.... mild	0	1	.	0	0	.	.	0
EYE								
Examined	10	0	0	10	10	0	1	10
No Visible Lesions	10	.	.	10	10	.	1	10
GALT								
Examined	10	0	0	10	10	0	0	9
No Visible Lesions	10	.	.	10	10	.	.	9
Not Examined: Not Present In Section.	0	0	0	0	0	0	0	1
GLAND, ADRENAL								
Examined	10	1	0	10	10	0	2	10
No Visible Lesions	10	0	.	10	9	.	0	10
Congestion	0	1	.	0	0	.	2	0
.... mild	0	1	.	0	0	.	2	0
Infiltration, lymphocytic	0	0	.	0	1	.	0	0
.... minimal	0	0	.	0	1	.	0	0
GLAND, HARDERIAN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	9	8	.	.	8
Infiltration, mononuclear cell	1	.	.	1	2	.	.	2
.... minimal	1	.	.	1	2	.	.	2
GLAND, MAMMARY								
Examined	8	0	0	9	10	0	0	10
No Visible Lesions	8	.	.	9	10	.	.	10
Not Examined: Not Present In Section.	2	0	0	1	0	0	0	0
GLAND, PARATHYROID								
Examined	8	0	0	10	10	0	0	10
No Visible Lesions	7	.	.	9	9	.	.	8
Not Examined: Not Present In Section.	2	0	0	0	0	0	0	0
Fibrosis; interstitial	0	.	.	0	1	.	.	2

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, PARATHYROID (Continued...)								
.... minimal	0	.	.	0	1	.	.	1
.... mild	0	.	.	0	0	.	.	1
Infiltration, mononuclear cell	1	.	.	1	0	.	.	0
.... minimal	1	.	.	0	0	.	.	0
.... mild	0	.	.	1	0	.	.	0
GLAND, PITUITARY								
Examined	10	0	1	10	10	0	0	10
No Visible Lesions	10	.	0	10	10	.	.	10
Congestion	0	.	1	0	0	.	.	0
.... mild	0	.	1	0	0	.	.	0
GLAND, PROSTATE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, SEMINAL VESICLE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
GLAND, THYROID								
Examined	10	1	0	10	10	1	0	10
No Visible Lesions	4	0	.	5	5	1	.	4
Hyperplasia; follicle	0	1	.	0	0	0	.	0
.... mild	0	1	.	0	0	0	.	0
Thyroglossal duct remnant, squamous epithelium	6	1	.	5	5	0	.	6
.... minimal	6	1	.	5	5	0	.	5
.... mild	0	0	.	0	0	0	.	1
Fibrosis; interstitial	0	0	.	0	0	0	.	1
.... mild	0	0	.	0	0	0	.	1
HEART								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	1	.	.	4	4	.	.	5

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
HEART (Continued...)								
Murine progressive cardiomyopathy	9	.	.	6	6	.	.	5
.... minimal	9	.	.	6	6	.	.	5
KIDNEY								
Examined	10	0	1	10	10	0	0	10
No Visible Lesions	1	.	0	2	2	.	.	3
Cast; hyaline	3	.	1	1	2	.	.	0
.... minimal	3	.	1	1	2	.	.	0
Degeneration; hyaline droplets	1	.	0	0	0	.	.	0
.... moderate	1	.	0	0	0	.	.	0
Infiltration, mononuclear cell	5	.	0	2	5	.	.	5
.... minimal	5	.	0	2	5	.	.	5
Cyst; tubular	0	.	1	0	0	.	.	0
.... mild	0	.	1	0	0	.	.	0
Chronic progressive nephropathy	4	.	1	6	3	.	.	2
.... minimal	4	.	0	6	3	.	.	2
.... mild	0	.	1	0	0	.	.	0
LARGE INTESTINE, CECUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	9	.	.	10
Dilatation; crypt	0	.	.	0	1	.	.	0
.... minimal	0	.	.	0	1	.	.	0
LARGE INTESTINE, COLON								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	9	10	.	.	10
Parasitism; nematode	1	.	.	1	0	.	.	0
LARGE INTESTINE, RECTUM								
Examined	10	1	0	10	10	0	0	10
No Visible Lesions	10	0	.	10	8	.	.	9
Hemorrhage	0	1	.	0	1	.	.	0
.... minimal	0	0	.	0	1	.	.	0
.... mild	0	1	.	0	0	.	.	0
Dilatation; crypt	0	0	.	0	1	.	.	0
.... minimal	0	0	.	0	1	.	.	0
Parasitism; nematode	0	0	.	0	0	.	.	1

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LIVER								
Examined	10	10	10	10	10	10	10	10
Necrosis	0	2	0	2	0	1	1	2
.... minimal	0	1	0	2	0	1	1	2
.... mild	0	1	0	0	0	0	0	0
Hepatodiaphragmatic nodule	0	0	0	0	0	0	1	0
Tension lipidosis	2	4	3	3	5	2	4	3
.... minimal	2	4	3	3	5	2	4	3
Granuloma	0	0	0	0	1	0	0	0
.... mild	0	0	0	0	1	0	0	0
Fibrosis	0	0	0	1	0	0	0	0
.... minimal	0	0	0	1	0	0	0	0
Vacuolation, microvesicular, periportal to midzonal	1	6	9	9	5	8	8	9
.... minimal	1	6	6	4	5	5	5	5
.... mild	0	0	3	4	0	3	2	3
.... moderate	0	0	0	1	0	0	1	1
Infiltration, mixed cell	10	10	10	10	10	10	10	10
.... minimal	9	10	10	9	10	10	10	10
.... mild	1	0	0	1	0	0	0	0
LUNG								
Examined	10	2	5	10	10	2	1	10
No Visible Lesions	7	0	0	5	5	1	0	2
Atelectasis	0	1	5	0	0	0	0	2
.... minimal	0	0	3	0	0	0	0	0
.... mild	0	1	2	0	0	0	0	2
Hyperplasia; pneumocyte, type 2	1	0	0	0	0	0	0	0
.... minimal	1	0	0	0	0	0	0	0
Hemorrhage	0	1	2	0	0	0	0	0
.... minimal	0	1	1	0	0	0	0	0
.... marked	0	0	1	0	0	0	0	0
Crystal	2	1	0	3	0	1	1	0
.... minimal	2	1	0	3	0	1	1	0
Infiltration, mononuclear cell; perivascular	0	0	0	1	0	0	0	1

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LUNG (Continued...)								
.... minimal	0	0	0	1	0	0	0	1
Infiltration, mononuclear cell	0	0	0	0	0	0	0	1
.... minimal	0	0	0	0	0	0	0	1
Infiltration, mixed cell; perivascular	0	0	0	0	0	0	0	1
.... minimal	0	0	0	0	0	0	0	1
Infiltration, mixed cell	3	1	3	5	5	1	1	5
.... minimal	3	1	3	5	5	1	1	5
LYMPH NODE								
Examined	0	0	0	0	0	0	1	0
Infiltration, mononuclear cell; interstitial	.	.	.	.	.	.	1	.
.... minimal	.	.	.	.	.	.	1	.
Hyperplasia; lymphoid	.	.	.	.	.	.	1	.
.... minimal	.	.	.	.	.	.	1	.
LYMPH NODE, INGUINAL								
Examined	10	10	10	10	10	9	9	10
No Visible Lesions	9	4	6	1	10	4	2	4
Not Examined: Not Present In Section.	0	0	0	0	0	1	1	0
Hyperplasia; lymphoid	1	6	4	5	0	5	7	4
.... minimal	1	2	2	3	0	3	2	3
.... mild	0	3	1	2	0	1	5	1
.... moderate	0	1	1	0	0	1	0	0
Plasmacytosis	0	1	0	7	0	0	0	3
.... minimal	0	1	0	5	0	0	0	3
.... mild	0	0	0	2	0	0	0	0
Inflammation, mixed cell; perinodal	0	0	0	1	0	0	0	0
.... mild	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
Hemorrhage	0	1	0	0	0	0	0	0
.... minimal	0	1	0	0	0	0	0	0
LYMPH NODE, MANDIBULAR								
Examined	10	2	5	10	10	3	2	10
No Visible Lesions	9	0	0	9	6	0	0	9
Hemorrhage	1	2	3	0	3	0	0	1

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, MANDIBULAR (Continued...)								
.... minimal	1	2	1	0	3	0	0	1
.... mild	0	0	2	0	0	0	0	0
Hyperplasia; lymphoid	0	0	1	0	0	0	0	1
.... mild	0	0	1	0	0	0	0	0
.... moderate	0	0	0	0	0	0	0	1
Congestion	0	0	1	1	1	3	2	0
.... minimal	0	0	1	1	1	3	1	0
.... mild	0	0	0	0	0	0	1	0
LYMPH NODE, MEDIASTINAL								
Examined	0	0	0	0	0	0	0	1
Hemorrhage	.	.	.	.	.	.	.	1
.... mild	.	.	.	.	.	.	.	1
LYMPH NODE, MESENTERIC								
Examined	10	1	0	10	10	1	0	10
No Visible Lesions	10	0	.	10	10	0	.	10
Hyperplasia; lymphoid	0	1	.	0	0	1	.	0
.... mild	0	0	.	0	0	1	.	0
.... moderate	0	1	.	0	0	0	.	0
LYMPH NODE, POPLITEAL								
Examined	9	10	10	10	10	10	10	10
No Visible Lesions	8	0	0	1	9	0	0	1
Not Examined: Not Present In Section.	1	0	0	0	0	0	0	0
Plasmacytosis	1	0	0	3	1	1	1	5
.... minimal	1	0	0	3	1	1	1	2
.... mild	0	0	0	0	0	0	0	3
Hyperplasia; lymphoid	0	9	8	5	0	8	9	8
.... minimal	0	6	5	3	0	3	6	5
.... mild	0	3	3	2	0	5	3	3
Inflammation, mixed cell; perinodal	0	9	10	6	0	9	9	7
.... minimal	0	3	6	1	0	5	3	2
.... mild	0	6	2	4	0	4	5	4
.... moderate	0	0	2	1	0	0	1	1

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
MUSCLE, SKELETAL								
Examined	10	0	1	10	10	0	0	10
No Visible Lesions	10	.	0	10	10	.	.	10
Hemorrhage; acute	0	.	1	0	0	.	.	0
.... marked	0	.	1	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	5	0	1	0
Inflammation, mixed cell; perineurial	0	10	10	10	5	10	9	10
.... minimal	0	1	4	0	5	0	4	2
.... mild	0	5	3	8	0	6	3	7
.... moderate	0	3	3	2	0	3	2	1
.... marked	0	1	0	0	0	1	0	0
OVARY								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
PANCREAS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	8	10	.	.	10
Infiltration, mononuclear cell	0	.	.	2	0	.	.	0
.... minimal	0	.	.	2	0	.	.	0
SITE, INJECTION								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	4	0	0	0	1	0	0	0
Inflammation, mixed cell	3	10	10	10	1	10	10	10
.... minimal	3	1	0	0	0	2	0	0
.... mild	0	3	0	0	1	7	0	0
.... moderate	0	6	4	0	0	1	7	0
.... marked	0	0	6	10	0	0	3	10
Degeneration/necrosis; myofiber	6	9	10	9	8	10	8	7
.... minimal	6	6	6	8	8	10	8	7
.... mild	0	3	4	1	0	0	0	0

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SKIN								
Examined	9	1	0	10	10	0	0	10
No Visible Lesions	9	0	.	10	10	.	.	9
Not Examined: Not Present In Section.	1	0	0	0	0	0	0	0
Hyperkeratosis	0	1	.	0	0	.	.	0
.... moderate	0	1	.	0	0	.	.	0
Infiltration, mixed cell	0	0	.	0	0	.	.	1
.... minimal	0	0	.	0	0	.	.	1
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, CERVICAL								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPINAL CORD, LUMBAR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	9
Infiltration, mononuclear cell; perivascular	1	.	.	0	0	.	.	0
.... minimal	1	.	.	0	0	.	.	0
Cyst; epithelial, subdural space	0	.	.	0	0	.	.	1
.... mild	0	.	.	0	0	.	.	1
SPINAL CORD, THORACIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPLEEN								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	8	9	9	10	9	9	6
Increased hematopoiesis	0	0	0	1	0	0	0	0

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SPLEEN (Continued...)								
.... minimal	0	0	0	1	0	0	0	0
Decreased cellularity; periarteriolar lymphoid sheath	0	2	1	1	0	1	1	4
.... minimal	0	2	1	1	0	1	1	4
STOMACH								
Examined	10	2	2	10	10	1	0	10
No Visible Lesions	8	2	0	8	7	0	.	9
Hemorrhage	0	0	2	0	0	0	.	0
.... minimal	0	0	2	0	0	0	.	0
Congestion	0	0	0	2	1	0	.	0
.... minimal	0	0	0	2	1	0	.	0
Inflammation, eosinophilic	0	0	0	0	0	1	.	0
.... mild	0	0	0	0	0	1	.	0
Infiltration, mixed cell	2	0	0	0	2	0	.	1
.... minimal	2	0	0	0	2	0	.	1
SUBCUTIS								
Examined	0	0	0	0	0	1	0	0
Abscess; chronic active	.	.	.	.	.	1	.	.
.... mild	.	.	.	.	.	1	.	.
TESTIS								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	8	.	.	10	.	.	.	.
Vacuolation; sertoli cell	1	.	.	0	.	.	.	.
.... mild	1	.	.	0	.	.	.	.
Atrophy; seminiferous tubule	2	.	.	0	.	.	.	.
.... mild	1	.	.	0	.	.	.	.
.... marked	1	.	.	0	.	.	.	.
THYMUS								
Examined	10	4	6	10	10	3	1	10
No Visible Lesions	6	0	0	5	2	0	0	5
Hemorrhage	3	3	5	5	5	2	1	4
.... minimal	3	3	2	5	5	2	1	3
.... mild	0	0	3	0	0	0	0	1
Cyst; epithelial	0	0	0	0	0	0	0	1

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
THYMUS (Continued...)								
.... minimal	0	0	0	0	0	0	0	1
Congestion	1	0	2	0	3	1	0	0
.... minimal	1	0	0	0	3	1	0	0
.... mild	0	0	2	0	0	0	0	0
Hyperplasia; lymphoid	0	1	0	0	0	0	0	0
.... mild	0	1	0	0	0	0	0	0
Ectopia	0	0	0	0	1	0	0	0
.... minimal	0	0	0	0	1	0	0	0
Infiltration, mixed cell; perivascular	0	0	0	0	0	0	0	1
.... minimal	0	0	0	0	0	0	0	1
TONGUE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	9	10	.	.	10
Infiltration, mononuclear cell	1	.	.	1	0	.	.	0
.... minimal	1	.	.	1	0	.	.	0
TRACHEA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	6	.	.	7	8	.	.	7
Infiltration, mononuclear cell	4	.	.	2	1	.	.	0
.... minimal	4	.	.	2	1	.	.	0
Dilatation; submucosal, glandular	0	.	.	1	1	.	.	3
.... minimal	0	.	.	0	1	.	.	2
.... mild	0	.	.	1	0	.	.	1
URINARY BLADDER								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	8	.	.	10	9	.	.	10
Infiltration, mononuclear cell	2	.	.	0	1	.	.	0
.... minimal	2	.	.	0	1	.	.	0
UTERUS								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	9
Dilatation	.	.	.	.	0	.	.	1
.... moderate	.	.	.	.	0	.	.	1

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	9.6 ug/dose Group 2	29 ug/dose Group 3	96 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
VAGINA								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10

Appendix 21

Table 10
Summary of Histopathology Findings (Day 57)

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
ARTERY, AORTA				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BONE MARROW				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, FEMUR				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, STERNUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BRAIN				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
CERVIX				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
EPIDIDYMIS				
Examined	5	5	.	.
No Visible Lesions	5	5	.	.
ESOPHAGUS				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
EYE				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
GALT				
Examined	5	4	5	5
No Visible Lesions	5	4	5	5
Not Examined: Not Present In Section.	0	1	0	0
GLAND, ADRENAL				
Examined	5	5	5	5
No Visible Lesions	5	4	5	5
Congestion	0	1	0	0

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, ADRENAL (Continued...)				
.... mild	0	1	0	0
GLAND, HARDERIAN				
Examined	5	5	5	5
No Visible Lesions	4	5	4	4
Infiltration, mononuclear cell	1	0	1	1
.... minimal	1	0	1	1
GLAND, MAMMARY				
Examined	5	5	5	5
No Visible Lesions	4	5	5	4
Vacuolation; epithelial	0	0	0	1
.... moderate	0	0	0	1
Immaturity; alveolus/duct	1	0	0	0
.... marked	1	0	0	0
GLAND, PARATHYROID				
Examined	5	5	5	5
No Visible Lesions	5	4	5	5
Fibrosis; interstitial	0	1	0	0
.... minimal	0	1	0	0
GLAND, PITUITARY				
Examined	5	5	5	5
No Visible Lesions	5	5	4	5
Cyst	0	0	1	0
GLAND, PROSTATE				
Examined	5	5	.	.
No Visible Lesions	5	3	.	.
Infiltration, mononuclear cell	0	2	.	.
.... marked	0	1	.	.
.... moderate	0	1	.	.
GLAND, SALIVARY, MANDIBULAR				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, SEMINAL VESICLE				
Examined	5	5	.	.
No Visible Lesions	5	5	.	.

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, THYROID				
Examined	5	5	5	5
No Visible Lesions	3	3	2	0
Hyperplasia; follicle	0	0	0	1
.... mild	0	0	0	1
Thyroglossal duct remnant, squamous epithelium	2	2	3	4
.... minimal	2	2	2	3
.... mild	0	0	1	1
HEART				
Examined	5	5	5	5
No Visible Lesions	4	3	5	4
Murine progressive cardiomyopathy	1	2	0	1
.... minimal	1	2	0	1
KIDNEY				
Examined	5	5	5	5
No Visible Lesions	0	0	2	5
Cast; hyaline	2	0	0	0
.... minimal	2	0	0	0
Infiltration, mononuclear cell	1	2	2	0
.... minimal	1	2	2	0
Chronic progressive nephropathy	4	3	1	0
.... minimal	4	3	1	0
LARGE INTESTINE, CECUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, COLON				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, RECTUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	4
Parasitism; nematode	0	0	0	1
LIVER				
Examined	5	5	5	5

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LIVER (Continued...)				
Necrosis	1	0	0	0
.... minimal	1	0	0	0
Tension lipidosis	0	1	1	0
.... minimal	0	1	1	0
Vacuolation, microvesicular, periportal to midzonal	0	1	2	4
.... minimal	0	0	2	1
.... mild	0	1	0	3
Infiltration, mixed cell	5	5	5	5
.... minimal	4	5	5	5
.... mild	1	0	0	0
LUNG				
Examined	5	5	5	5
No Visible Lesions	3	4	3	3
Hyperplasia; pneumocyte, type 2	1	0	0	0
.... minimal	1	0	0	0
Infiltration, mononuclear cell	0	0	1	0
.... minimal	0	0	1	0
Infiltration, mixed cell	2	1	1	2
.... minimal	2	1	1	2
Metaplasia; osseous	1	0	0	0
.... minimal	1	0	0	0
LYMPH NODE, AXILLARY, LEFT				
Examined	0	1	0	0
Sinus histiocytosis	.	1	.	.
.... minimal	.	1	.	.
Hyperplasia; lymphoid	.	1	.	.
.... mild	.	1	.	.
LYMPH NODE, ILIAC, RIGHT				
Examined	0	1	0	0
Hemorrhage; interstitial	.	1	.	.
.... moderate	.	1	.	.
LYMPH NODE, INGUINAL				
Examined	5	5	5	5

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, INGUINAL (Continued...)				
No Visible Lesions	2	2	4	4
Hyperplasia; lymphoid	2	3	1	1
.... minimal	2	2	1	1
.... mild	0	1	0	0
Plasmacytosis	1	2	0	0
.... minimal	1	2	0	0
LYMPH NODE, MANDIBULAR				
Examined	5	5	5	5
No Visible Lesions	4	4	5	4
Hemorrhage	1	1	0	0
.... minimal	1	1	0	0
Congestion	0	0	0	1
.... minimal	0	0	0	1
LYMPH NODE, MEDIASTINAL				
Examined	1	0	0	0
Hemorrhage	1	.	.	.
.... mild	1	.	.	.
LYMPH NODE, MESENTERIC				
Examined	5	5	5	5
No Visible Lesions	5	4	5	5
Hemorrhage	0	1	0	0
.... moderate	0	1	0	0
LYMPH NODE, POPLITEAL				
Examined	5	5	5	5
No Visible Lesions	2	1	5	0
Plasmacytosis	2	3	0	2
.... minimal	2	2	0	0
.... mild	0	1	0	2
Hyperplasia; lymphoid	1	3	0	5
.... minimal	0	3	0	5
.... mild	1	0	0	0
Infiltration, mononuclear cell; perinodal	0	1	0	1
.... minimal	0	1	0	1

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
MUSCLE, SKELETAL				
Examined	5	5	5	5
No Visible Lesions	5	4	4	3
Infiltration, mononuclear cell	0	1	1	2
.... minimal	0	1	1	2
NERVE, OPTIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, SCIATIC				
Examined	5	5	5	5
No Visible Lesions	5	0	4	1
Infiltration, mononuclear cell; perineurial	0	5	1	4
.... minimal	0	5	1	2
.... mild	0	0	0	2
OVARY				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
PANCREAS				
Examined	5	5	5	5
No Visible Lesions	2	2	2	3
Fibrosis	0	0	1	0
.... minimal	0	0	1	0
Infiltration, mononuclear cell	1	3	2	2
.... minimal	1	3	2	1
.... mild	0	0	0	1
Infiltration, mixed cell	2	0	0	0
.... minimal	1	0	0	0
.... mild	1	0	0	0
SITE, INJECTION				
Examined	5	5	5	5
No Visible Lesions	1	0	3	0
Degeneration/necrosis; myofiber	4	4	2	3
.... minimal	4	4	2	3
Infiltration, mononuclear cell	1	4	0	4

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
SITE, INJECTION (Continued...)				
.... minimal	1	4	0	4
SKIN				
Examined	5	5	5	5
No Visible Lesions	5	4	5	5
Crust; serocellular	0	1	0	0
.... mild	0	1	0	0
SMALL INTESTINE, DUODENUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, ILEUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, JEJUNUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, CERVICAL				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, LUMBAR				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, THORACIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPLEEN				
Examined	5	5	5	5
No Visible Lesions	3	5	5	5
Congestion	1	0	0	0
.... moderate	1	0	0	0
Hyperplasia; lymphoid	2	0	0	0
.... minimal	1	0	0	0
.... mild	1	0	0	0
Hyperplasia; stromal	1	0	0	0
.... moderate	1	0	0	0

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
STOMACH				
Examined	5	5	5	5
No Visible Lesions	4	5	5	5
Cyst; epithelial	1	0	0	0
TESTIS				
Examined	5	5	.	.
No Visible Lesions	4	5	.	.
Atrophy; seminiferous tubule	1	0	.	.
.... minimal	1	0	.	.
THYMUS				
Examined	5	5	5	5
No Visible Lesions	1	3	3	4
Hemorrhage	4	1	1	1
.... minimal	4	1	1	1
Cyst; epithelial	0	0	1	0
.... minimal	0	0	1	0
Congestion	0	1	0	0
.... mild	0	1	0	0
TONGUE				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
TRACHEA				
Examined	5	5	5	5
No Visible Lesions	5	5	4	5
Infiltration, mononuclear cell	0	0	1	0
.... minimal	0	0	1	0
URINARY BLADDER				
Examined	5	5	5	5
No Visible Lesions	4	4	3	3
Accumulation; granular, transitional epithelium	0	0	1	1
.... minimal	0	0	1	1
Infiltration, mononuclear cell	1	1	1	1
.... minimal	1	1	1	1

Appendix 21 5002158 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
UTERUS				
Examined	.	.	5	5
No Visible Lesions	.	.	5	4
Infiltration, mononuclear cell	.	.	0	1
.... minimal	.	.	0	1
VAGINA				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5

Appendix 21

Appendix 1
Deviations

Appendix 21

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.

- Tissues that were supposed to be microscopically evaluated per protocol but were not available on the slide (and therefore not evaluated) are listed in the Individual Animal Data of the Pathology report as not present.

Appendix 21

Appendix 2
Individual Organ Weight Values -Absolute (Day 44)

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	555	2.184	1.300	0.0738	0.0147	1.123	0.0166
	1002	522	2.200	1.209	0.0728	0.0143	1.397	0.0217
	1003	485	2.228	1.189	0.0721	0.0127	1.342	0.0220
	1004	577	2.306	1.248	0.0627	0.0147	1.129	0.0236
	1005	545	2.121	1.245	0.0690	0.0137	1.261	0.0195
	1006	573	2.354	1.264	0.0690	0.0176	1.446	0.0263
	1007	577	2.107	1.104	0.0709	0.0158	1.364	0.0243
	1008	533	2.212	1.090MPI	0.0529	0.0131	1.631	0.0280
	1009	475	2.177	1.157	0.0605	0.0126	1.304	0.0184
	1010	510	2.178	1.311	0.0642	0.0128	1.268	0.0265
2M	2001	507	2.038	1.159	0.0598	0.0122	1.403	0.0187
	2002	516	2.200	1.192	0.0593	0.0149	1.060	0.0228
	2003	521	2.227	1.257	0.0580	0.0135	1.050	0.0253
	2004	506	2.327	1.167	0.0644	0.0133	1.366	0.0211
	2005	508	2.336	1.272	0.0577	0.0138	1.346	0.0207
	2006	581	2.350	1.196	0.0740	0.0166	1.342	0.0473MPI
	2007	476	2.223	1.226	0.0674	0.0135	1.036	0.0184
	2008	480	2.161	1.189	0.0670	0.0142	1.336	0.0198
	2009	536	2.217	1.252	0.0516	0.0119	1.229	0.0288
	2010	497	2.273	1.312	0.0598	0.0149	1.402	0.0236

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	1001	1.906	3.212	14.426	1.777	--	0.936	4.296
	1002	1.978	3.099	14.372	1.716	--	0.792	4.009
	1003	1.723	3.122	12.317	1.674	--	0.793	3.498
	1004	2.059	3.192	15.596	1.814	--	0.932	3.840
	1005	1.784	2.999	15.056	1.636	--	0.907	4.044
	1006	1.893	3.556	15.358	1.916	--	0.948	3.717
	1007	1.719	3.287	14.553	1.786	--	0.922	3.653
	1008	1.829	3.094	13.778	1.601	--	0.895	3.561MPI
	1009	1.663	3.022	11.039	1.720	--	0.850	3.416
	1010	1.886	3.074	13.159	1.690	--	1.218	3.531
2M	2001	1.697	2.897	14.673	1.542	--	1.016	3.939
	2002	1.956	3.359	14.319	1.740	--	1.216	3.715
	2003	1.599	3.259	14.568	1.771	--	1.086	4.327
	2004	1.757	3.006	12.666	1.741	--	1.135	3.585
	2005	1.773	3.297	12.304	1.676	--	1.112	4.032
	2006	2.211	3.333	16.340	1.817	--	1.299	3.596
	2007	1.518	2.872	11.437	1.662	--	0.895	3.886
	2008	1.689	2.964	11.635	1.525	--	1.033	3.795
	2009	1.555	3.163	13.580	1.624	--	0.974	4.409
	2010	1.728	2.884	11.463	1.664	--	0.947	3.634

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1M	1001	0.352	--
	1002	0.349	--
	1003	0.422	--
	1004	0.455	--
	1005	0.413	--
	1006	0.396	--
	1007	0.604	--
	1008	0.528	--
	1009	0.554	--
	1010	0.504	--
2M	2001	0.434	--
	2002	0.831MPI	--
	2003	0.499	--
	2004	0.413	--
	2005	0.431	--
	2006	0.711	--
	2007	0.474	--
	2008	0.303	--
	2009	0.526	--
	2010	0.491	--

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	455	2.121	1.242	0.0619	0.0121	1.587	0.0207
	3002	601	2.267	1.352	0.0668	0.0158	1.236	0.0221
	3003	586	2.278	1.236	0.0555	0.0153	1.288	0.0214
	3004	473	2.045	1.067	0.0641	0.0139	1.546	0.0205
	3005	514	2.054	1.298	0.0631	0.0139	1.226	0.0194
	3006	468	2.135	1.082	0.0571	0.0123	1.255	0.0187
	3007	531	2.225	1.254	0.0585	0.0151	1.137	0.0228
	3008	545	2.214	1.246	0.0559	0.0152	1.182	0.0254
	3009	441	1.972	1.089	0.0519	0.0136	0.904	0.0144
	3010	542	2.232	1.259	0.0685	0.0154	1.341	0.0275
4M	4001	565	2.251	1.238	0.0764	0.0128	1.440	0.0291
	4002	375	2.095	1.129	0.0458	0.0106	1.002	0.0181
	4003	503	2.275	1.206	0.0574	0.0109	1.156	0.0365
	4004	487	2.094	1.179	0.0724	0.0171	1.310	0.0211
	4005	524	2.036	1.105	0.0564	0.0124	0.977	0.0152
	4006	450	2.150	1.224	0.0572	0.0113	1.048	0.0200
	4007	523	2.104	1.058	0.0676	0.0150	1.399	0.0210
	4008	602	2.273	1.395	0.0781	0.0182	1.608	0.0322
	4009	498	2.167	1.203	0.0770	0.0164	1.211	0.0193
	4010	478	2.254	1.243	0.0777	0.0116	1.380	0.0296

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
3M	3001	1.787	3.072	11.766	1.602	--	0.862	3.700
	3002	2.029	3.886	17.116	2.030MPI	--	1.033	3.748
	3003	1.941	3.161	16.484	1.969	--	1.198	4.045
	3004	1.705	2.484	11.726	1.582	--	1.007	3.279
	3005	1.580	3.033	15.143	1.721	--	1.019	4.095
	3006	1.468	2.907	12.079	1.566	--	0.922	3.739
	3007	2.062	2.972	13.944	1.743	--	1.011	3.712
	3008	1.883	2.681	14.986	1.734	--	1.214	4.103
	3009	1.488	2.639	11.647	1.476	--	1.046	3.511
	3010	1.839	3.186	15.025	1.931	--	1.328	3.700
4M	4001	2.112	3.572	17.766	1.926	--	1.257	3.910
	4002	1.410	2.622	10.027	1.313	--	0.886	3.508
	4003	1.572	2.559	14.342	1.781	--	1.025	4.067
	4004	1.676	3.276	13.212	1.657	--	0.970	3.575
	4005	1.749	2.926	15.042	1.539	--	0.910	3.636
	4006	1.744	3.112	12.530	1.708	--	1.314	3.454
	4007	1.848	3.335	15.419	1.966	--	1.315	3.550
	4008	2.300	3.472	17.379	1.982	--	1.479	4.363
	4009	1.876	3.279	14.379	1.819	--	0.875	3.402
	4010	1.928	2.869	13.434	1.780	--	1.260	3.711

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
3M	3001	0.296	--
	3002	0.492	--
	3003	0.463	--
	3004	0.261	--
	3005	0.484	--
	3006	0.418	--
	3007	0.568	--
	3008	0.760	--
	3009	0.433	--
	3010	0.455	--
4M	4001	0.530	--
	4002	0.424	--
	4003	0.412	--
	4004	0.401	--
	4005	0.428	--
	4006	0.548	--
	4007	0.533	--
	4008	0.457	--
	4009	0.297	--
	4010	0.361	--

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	258	2.054	--	0.0651	0.0149	--	0.0119
	1502	308	2.137	--	0.0909	0.0193	--	0.0226
	1503	284	2.036	--	0.0668	0.0201	--	0.0153
	1504	314	2.057	--	0.0856	0.0191	--	0.0213
	1505	293	2.186	--	0.0513	0.0107	--	0.0174
	1506	273	2.029	--	0.0723	0.0178	--	0.0163
	1507	280	1.807	--	0.0610	0.0165	--	0.0124
	1508	267	2.106	--	0.0624	0.0188	--	0.0184
	1509	329	2.123	--	0.0725	0.0191	--	0.0158
	1510	300	2.087	--	0.0848	0.0185	--	0.0180
2F	2501	300	1.882	--	0.0615	0.0166	--	0.0197
	2502	279	2.019	--	0.0686	0.0140	--	0.0212
	2503	284	1.917	--	0.0735	0.0146	--	0.0143
	2504	273	2.004	--	0.0596	0.0155	--	0.0162MPI
	2505	353	2.149	--	0.0703	0.0171	--	0.0201
	2506	289	2.027	--	0.0498	0.0118	--	0.0159
	2507	309	1.964	--	0.0719	0.0152	--	0.0143
	2508	357	2.178	--	0.0694	0.0201	--	0.0210
	2509	274	2.050	--	0.0622	0.0180	--	0.0181
	2510	299	2.113	--	0.0838	0.0184	--	0.0191

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	1501	1.055	1.730	6.640	1.169	0.081	0.609	--
	1502	1.299	1.928	8.063MPI	1.236	0.121	0.663	--
	1503	1.179	1.946	7.981	1.395	0.097	0.588	--
	1504	1.212	2.095	8.738	1.383	0.114	0.776	--
	1505	1.199	1.664	6.880	1.138	0.108	0.496	--
	1506	1.101	1.701	6.561	1.182	0.086	0.546	--
	1507	1.203	1.853	6.786	1.135	0.084	0.611	--
	1508	1.219	1.865	7.469	1.119	0.104	0.652	--
	1509	1.373	1.879	8.391	1.346	0.099	0.522	--
	1510	1.239	2.078	7.634	1.407	0.087	0.521	--
2F	2501	1.214	1.621	7.622	1.196	0.096	0.674	--
	2502	1.146	1.920	7.300	1.279	0.106	0.616	--
	2503	1.034	1.918	7.205	1.291	0.092	0.623	--
	2504	1.205	1.727	7.130	1.190	0.094	0.654	--
	2505	1.481	1.949	9.142	1.574	0.135	0.851	--
	2506	1.482	1.608	7.870	1.436	0.091	0.599	--
	2507	1.065	1.846	7.809	1.241	0.100	0.706	--
	2508	1.449	2.055	10.046	1.528	0.095	0.736	--
	2509	1.162	1.902	7.061	1.327	0.092	0.631	--
	2510	1.224	1.999	7.583	1.410	0.104	0.733	--

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1F	1501	0.283	0.394
	1502	0.491	0.560
	1503	0.443	0.628
	1504	0.417	1.183
	1505	0.442	0.371
	1506	0.406	0.936
	1507	0.208MPI	0.458
	1508	0.430	1.771
	1509	0.449	0.633
	1510	0.557	0.545
2F	2501	0.567	0.366
	2502	0.349	0.886
	2503	0.448	0.535
	2504	0.338	0.637
	2505	0.485	0.651
	2506	0.397	0.590
	2507	0.308	0.450
	2508	0.525	0.542
	2509	0.401	0.531
	2510	0.482	0.506

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 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	315	1.967	--	0.0629	0.0148	--	0.0165
	3502	314	2.202	--	0.0789	0.0213	--	0.0204
	3503	311	2.152	--	0.0676	0.0193	--	0.0230
	3504	300	1.959	--	0.0593	0.0168	--	0.0235
	3505	307	2.156	--	0.0733	0.0201	--	0.0202
	3506	289	2.039	--	0.0632	0.0188	--	0.0156
	3507	277	2.024	--	0.0674	0.0171	--	0.0160
	3508	241	1.988	--	0.0850	0.0187	--	0.0195
	3509	286	2.018	--	0.0797	0.0162	--	0.0153
	3510	259	1.999	--	0.0641	0.0157	--	0.0219
4F	4501	244	2.008	--	0.0718	0.0144	--	0.0132
	4502	345	2.115	--	0.0676	0.0152	--	0.0227
	4503	282	2.010	--	0.0674	0.0138	--	0.0117
	4504	275	1.980	--	0.0629	0.0143	--	0.0143
	4505	334	2.161	--	0.0957	0.0187	--	0.0244
	4506	285	1.921	--	0.0692	0.0157	--	0.0157
	4507	295	2.160	--	0.0749	0.0158	--	0.0176
	4508	260	1.949	--	0.0680	0.0147	--	0.0159
	4509	294	2.063	--	0.1017	0.0143	--	0.0150
	4510	271	2.057	--	0.0732	0.0128	--	0.0174

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
3F	3501	1.236	1.914	8.038	1.344	0.087	0.685	--
	3502	1.256	2.113	8.826	1.529	0.112	0.822	--
	3503	1.272	1.921	8.756	1.348	0.102	0.653	--
	3504	1.160	1.967	7.946	1.314	0.098	0.600	--
	3505	1.068	2.037	8.913	1.513	0.097	0.896	--
	3506	1.238	1.797	7.395	1.201	0.084	0.579	--
	3507	1.050	1.604	7.437	1.375	0.078	0.769	--
	3508	1.047	1.744	6.792	1.167	0.088	0.676	--
	3509	1.064	1.467	7.435	1.267	0.110	0.640	--
	3510	1.005	1.910	6.426	1.314	0.094	0.496	--
4F	4501	1.060	1.570	7.237	1.228	0.099	0.643	--
	4502	1.392	2.292	9.316	1.547	0.113	0.919	--
	4503	1.126	1.792	8.052	1.443	0.097	0.617	--
	4504	1.100	1.603	7.719	1.279	0.103	0.651	--
	4505	1.415	2.286	9.433	1.468	0.112	0.785	--
	4506	1.178	1.855	7.812	1.254	0.081	0.725	--
	4507	1.233	1.977	9.079	1.456	0.090	0.747	--
	4508	1.111	1.623	6.841	1.221	0.088	0.588	--
	4509	1.167	2.164	8.391	1.405	0.086	0.755	--
	4510	1.141	1.693	7.956	1.445	0.101	0.754	--

Appendix 21

Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
3F	3501	0.538	0.637
	3502	0.564	0.611
	3503	0.559	1.260
	3504	0.429	0.523
	3505	0.539	0.427
	3506	0.473	0.842
	3507	0.403	0.493
	3508	0.237	1.169
	3509	0.354	0.984
	3510	0.262	0.384
4F	4501	0.303	0.407
	4502	0.782	0.439
	4503	0.411	0.462
	4504	0.249	0.477
	4505	0.437	0.466
	4506	0.348	0.450
	4507	0.377	0.425
	4508	0.373	0.546
	4509	0.343	0.893
	4510	0.388	0.434

Appendix 21

Appendix 3
Individual Organ Weight Values - Relative to Body Weight (Day 44)

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1001	0.3935	0.2342	0.01330	0.00265	0.2023	0.00299	0.3434
	1002	0.4215	0.2316	0.01395	0.00274	0.2676	0.00416	0.3789
	1003	0.4594	0.2452	0.01487	0.00262	0.2767	0.00454	0.3553
	1004	0.3997	0.2163	0.01087	0.00255	0.1957	0.00409	0.3568
	1005	0.3892	0.2284	0.01266	0.00251	0.2314	0.00358	0.3273
	1006	0.4108	0.2206	0.01204	0.00307	0.2524	0.00459	0.3304
	1007	0.3652	0.1913	0.01229	0.00274	0.2364	0.00421	0.2979
	1008	0.4150	0.2045MPI	0.00992	0.00246	0.3060	0.00525	0.3432
	1009	0.4583	0.2436	0.01274	0.00265	0.2745	0.00387	0.3501
	1010	0.4271	0.2571	0.01259	0.00251	0.2486	0.00520	0.3698
2M	2001	0.4020	0.2286	0.01179	0.00241	0.2767	0.00369	0.3347
	2002	0.4264	0.2310	0.01149	0.00289	0.2054	0.00442	0.3791
	2003	0.4274	0.2413	0.01113	0.00259	0.2015	0.00486	0.3069
	2004	0.4599	0.2306	0.01273	0.00263	0.2700	0.00417	0.3472
	2005	0.4598	0.2504	0.01136	0.00272	0.2650	0.00407	0.3490
	2006	0.4045	0.2059	0.01274	0.00286	0.2310	0.00814MPI	0.3806
	2007	0.4670	0.2576	0.01416	0.00284	0.2176	0.00387	0.3189
	2008	0.4502	0.2477	0.01396	0.00296	0.2783	0.00413	0.3519
	2009	0.4136	0.2336	0.00963	0.00222	0.2293	0.00537	0.2901
	2010	0.4573	0.2640	0.01203	0.00300	0.2821	0.00475	0.3477

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	1001	0.5787	2.5993	0.3202	--	0.1686	0.7741	0.0634
	1002	0.5937	2.7533	0.3287	--	0.1517	0.7680	0.0669
	1003	0.6437	2.5396	0.3452	--	0.1635	0.7212	0.0870
	1004	0.5532	2.7029	0.3144	--	0.1615	0.6655	0.0789
	1005	0.5503	2.7626	0.3002	--	0.1664	0.7420	0.0758
	1006	0.6206	2.6803	0.3344	--	0.1654	0.6487	0.0691
	1007	0.5697	2.5222	0.3095	--	0.1598	0.6331	0.1047
	1008	0.5805	2.5850	0.3004	--	0.1679	0.6681MPI	0.0991
	1009	0.6362	2.3240	0.3621	--	0.1789	0.7192	0.1166
	1010	0.6027	2.5802	0.3314	--	0.2388	0.6924	0.0988
2M	2001	0.5714	2.8941	0.3041	--	0.2004	0.7769	0.0856
	2002	0.6510	2.7750	0.3372	--	0.2357	0.7200	0.1610MPI
	2003	0.6255	2.7962	0.3399	--	0.2084	0.8305	0.0958
	2004	0.5941	2.5032	0.3441	--	0.2243	0.7085	0.0816
	2005	0.6490	2.4220	0.3299	--	0.2189	0.7937	0.0848
	2006	0.5737	2.8124	0.3127	--	0.2236	0.6189	0.1224
	2007	0.6034	2.4027	0.3492	--	0.1880	0.8164	0.0996
	2008	0.6175	2.4240	0.3177	--	0.2152	0.7906	0.0631
	2009	0.5901	2.5336	0.3030	--	0.1817	0.8226	0.0981
	2010	0.5803	2.3064	0.3348	--	0.1905	0.7312	0.0988

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	UTERUS %
1M	1001	--
	1002	--
	1003	--
	1004	--
	1005	--
	1006	--
	1007	--
	1008	--
	1009	--
	1010	--
2M	2001	--
	2002	--
	2003	--
	2004	--
	2005	--
	2006	--
	2007	--
	2008	--
	2009	--
	2010	--

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
3M	3001	0.4662	0.2730	0.01360	0.00266	0.3488	0.00455	0.3927
	3002	0.3772	0.2250	0.01111	0.00263	0.2057	0.00368	0.3376
	3003	0.3887	0.2109	0.00947	0.00261	0.2198	0.00365	0.3312
	3004	0.4323	0.2256	0.01355	0.00294	0.3268	0.00433	0.3605
	3005	0.3996	0.2525	0.01228	0.00270	0.2385	0.00377	0.3074
	3006	0.4562	0.2312	0.01220	0.00263	0.2682	0.00400	0.3137
	3007	0.4190	0.2362	0.01102	0.00284	0.2141	0.00429	0.3883
	3008	0.4062	0.2286	0.01026	0.00279	0.2169	0.00466	0.3455
	3009	0.4472	0.2469	0.01177	0.00308	0.2050	0.00327	0.3374
	3010	0.4118	0.2323	0.01264	0.00284	0.2474	0.00507	0.3393
4M	4001	0.3984	0.2191	0.01352	0.00227	0.2549	0.00515	0.3738
	4002	0.5587	0.3011	0.01221	0.00283	0.2672	0.00483	0.3760
	4003	0.4523	0.2398	0.01141	0.00217	0.2298	0.00726	0.3125
	4004	0.4300	0.2421	0.01487	0.00351	0.2690	0.00433	0.3441
	4005	0.3885	0.2109	0.01076	0.00237	0.1865	0.00290	0.3338
	4006	0.4778	0.2720	0.01271	0.00251	0.2329	0.00444	0.3876
	4007	0.4023	0.2023	0.01293	0.00287	0.2675	0.00402	0.3533
	4008	0.3776	0.2317	0.01297	0.00302	0.2671	0.00535	0.3821
	4009	0.4351	0.2416	0.01546	0.00329	0.2432	0.00388	0.3767
	4010	0.4715	0.2600	0.01626	0.00243	0.2887	0.00619	0.4033

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
3M	3001	0.6752	2.5859	0.3521	--	0.1895	0.8132	0.0651
	3002	0.6466	2.8479	0.3378MPI	--	0.1719	0.6236	0.0819
	3003	0.5394	2.8130	0.3360	--	0.2044	0.6903	0.0790
	3004	0.5252	2.4791	0.3345	--	0.2129	0.6932	0.0552
	3005	0.5901	2.9461	0.3348	--	0.1982	0.7967	0.0942
	3006	0.6212	2.5810	0.3346	--	0.1970	0.7989	0.0893
	3007	0.5597	2.6260	0.3282	--	0.1904	0.6991	0.1070
	3008	0.4919	2.7497	0.3182	--	0.2228	0.7528	0.1394
	3009	0.5984	2.6410	0.3347	--	0.2372	0.7961	0.0982
	3010	0.5878	2.7721	0.3563	--	0.2450	0.6827	0.0839
4M	4001	0.6322	3.1444	0.3409	--	0.2225	0.6920	0.0938
	4002	0.6992	2.6739	0.3501	--	0.2363	0.9355	0.1131
	4003	0.5087	2.8513	0.3541	--	0.2038	0.8085	0.0819
	4004	0.6727	2.7129	0.3402	--	0.1992	0.7341	0.0823
	4005	0.5584	2.8706	0.2937	--	0.1737	0.6939	0.0817
	4006	0.6916	2.7844	0.3796	--	0.2920	0.7676	0.1218
	4007	0.6377	2.9482	0.3759	--	0.2514	0.6788	0.1019
	4008	0.5767	2.8869	0.3292	--	0.2457	0.7248	0.0759
	4009	0.6584	2.8873	0.3653	--	0.1757	0.6831	0.0596
	4010	0.6002	2.8105	0.3724	--	0.2636	0.7764	0.0755

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	UTERUS %
3M	3001	--
	3002	--
	3003	--
	3004	--
	3005	--
	3006	--
	3007	--
	3008	--
	3009	--
	3010	--
4M	4001	--
	4002	--
	4003	--
	4004	--
	4005	--
	4006	--
	4007	--
	4008	--
	4009	--
	4010	--

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	1501	0.7961	--	0.02523	0.00578	--	0.00461	0.4089
	1502	0.6938	--	0.02951	0.00627	--	0.00734	0.4218
	1503	0.7169	--	0.02352	0.00708	--	0.00539	0.4151
	1504	0.6551	--	0.02726	0.00608	--	0.00678	0.3860
	1505	0.7461	--	0.01751	0.00365	--	0.00594	0.4092
	1506	0.7432	--	0.02648	0.00652	--	0.00597	0.4033
	1507	0.6454	--	0.02179	0.00589	--	0.00443	0.4296
	1508	0.7888	--	0.02337	0.00704	--	0.00689	0.4566
	1509	0.6453	--	0.02204	0.00581	--	0.00480	0.4173
	1510	0.6957	--	0.02827	0.00617	--	0.00600	0.4130
2F	2501	0.6273	--	0.02050	0.00553	--	0.00657	0.4047
	2502	0.7237	--	0.02459	0.00502	--	0.00760	0.4108
	2503	0.6750	--	0.02588	0.00514	--	0.00504	0.3641
	2504	0.7341	--	0.02183	0.00568	--	0.00593MPI	0.4414
	2505	0.6088	--	0.01992	0.00484	--	0.00569	0.4195
	2506	0.7014	--	0.01723	0.00408	--	0.00550	0.5128
	2507	0.6356	--	0.02327	0.00492	--	0.00463	0.3447
	2508	0.6101	--	0.01944	0.00563	--	0.00588	0.4059
	2509	0.7482	--	0.02270	0.00657	--	0.00661	0.4241
	2510	0.7067	--	0.02803	0.00615	--	0.00639	0.4094

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	1501	0.6705	2.5736	0.4531	0.0314	0.2360	--	0.1097
	1502	0.6260	2.6179MPI	0.4013	0.0393	0.2153	--	0.1594
	1503	0.6852	2.8102	0.4912	0.0342	0.2070	--	0.1560
	1504	0.6672	2.7828	0.4404	0.0363	0.2471	--	0.1328
	1505	0.5679	2.3481	0.3884	0.0369	0.1693	--	0.1509
	1506	0.6231	2.4033	0.4330	0.0315	0.2000	--	0.1487
	1507	0.6618	2.4236	0.4054	0.0300	0.2182	--	0.0743MPI
	1508	0.6985	2.7974	0.4191	0.0390	0.2442	--	0.1610
	1509	0.5711	2.5505	0.4091	0.0301	0.1587	--	0.1365
	1510	0.6927	2.5447	0.4690	0.0290	0.1737	--	0.1857
2F	2501	0.5403	2.5407	0.3987	0.0320	0.2247	--	0.1890
	2502	0.6882	2.6165	0.4584	0.0380	0.2208	--	0.1251
	2503	0.6754	2.5370	0.4546	0.0324	0.2194	--	0.1577
	2504	0.6326	2.6117	0.4359	0.0344	0.2396	--	0.1238
	2505	0.5521	2.5898	0.4459	0.0382	0.2411	--	0.1374
	2506	0.5564	2.7232	0.4969	0.0315	0.2073	--	0.1374
	2507	0.5974	2.5272	0.4016	0.0324	0.2285	--	0.0997
	2508	0.5756	2.8140	0.4280	0.0266	0.2062	--	0.1471
	2509	0.6942	2.5770	0.4843	0.0336	0.2303	--	0.1464
	2510	0.6686	2.5361	0.4716	0.0348	0.2452	--	0.1612

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	UTERUS %
1F	1501	0.1527
	1502	0.1818
	1503	0.2211
	1504	0.3768
	1505	0.1266
	1506	0.3429
	1507	0.1636
	1508	0.6633
	1509	0.1924
	1510	0.1817
2F	2501	0.1220
	2502	0.3176
	2503	0.1884
	2504	0.2333
	2505	0.1844
	2506	0.2042
	2507	0.1456
	2508	0.1518
	2509	0.1938
	2510	0.1692

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
3F	3501	0.6244	--	0.01997	0.00470	--	0.00524	0.3924
	3502	0.7013	--	0.02513	0.00678	--	0.00650	0.4000
	3503	0.6920	--	0.02174	0.00621	--	0.00740	0.4090
	3504	0.6530	--	0.01977	0.00560	--	0.00783	0.3867
	3505	0.7023	--	0.02388	0.00655	--	0.00658	0.3479
	3506	0.7055	--	0.02187	0.00651	--	0.00540	0.4284
	3507	0.7307	--	0.02433	0.00617	--	0.00578	0.3791
	3508	0.8249	--	0.03527	0.00776	--	0.00809	0.4344
	3509	0.7056	--	0.02787	0.00566	--	0.00535	0.3720
	3510	0.7718	--	0.02475	0.00606	--	0.00846	0.3880
4F	4501	0.8230	--	0.02943	0.00590	--	0.00541	0.4344
	4502	0.6130	--	0.01959	0.00441	--	0.00658	0.4035
	4503	0.7128	--	0.02390	0.00489	--	0.00415	0.3993
	4504	0.7200	--	0.02287	0.00520	--	0.00520	0.4000
	4505	0.6470	--	0.02865	0.00560	--	0.00731	0.4237
	4506	0.6740	--	0.02428	0.00551	--	0.00551	0.4133
	4507	0.7322	--	0.02539	0.00536	--	0.00597	0.4180
	4508	0.7496	--	0.02615	0.00565	--	0.00612	0.4273
	4509	0.7017	--	0.03459	0.00486	--	0.00510	0.3969
	4510	0.7590	--	0.02701	0.00472	--	0.00642	0.4210

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
3F	3501	0.6076	2.5517	0.4267	0.0276	0.2175	--	0.1708
	3502	0.6729	2.8108	0.4869	0.0357	0.2618	--	0.1796
	3503	0.6177	2.8154	0.4334	0.0328	0.2100	--	0.1797
	3504	0.6557	2.6487	0.4380	0.0327	0.2000	--	0.1430
	3505	0.6635	2.9033	0.4928	0.0316	0.2919	--	0.1756
	3506	0.6218	2.5588	0.4156	0.0291	0.2003	--	0.1637
	3507	0.5791	2.6848	0.4964	0.0282	0.2776	--	0.1455
	3508	0.7237	2.8183	0.4842	0.0365	0.2805	--	0.0983
	3509	0.5129	2.5997	0.4430	0.0385	0.2238	--	0.1238
	3510	0.7375	2.4811	0.5073	0.0363	0.1915	--	0.1012
4F	4501	0.6434	2.9660	0.5033	0.0406	0.2635	--	0.1242
	4502	0.6643	2.7003	0.4484	0.0328	0.2664	--	0.2267
	4503	0.6355	2.8553	0.5117	0.0344	0.2188	--	0.1457
	4504	0.5829	2.8069	0.4651	0.0375	0.2367	--	0.0905
	4505	0.6844	2.8243	0.4395	0.0335	0.2350	--	0.1308
	4506	0.6509	2.7411	0.4400	0.0284	0.2544	--	0.1221
	4507	0.6702	3.0776	0.4936	0.0305	0.2532	--	0.1278
	4508	0.6242	2.6312	0.4696	0.0338	0.2262	--	0.1435
	4509	0.7361	2.8541	0.4779	0.0293	0.2568	--	0.1167
	4510	0.6247	2.9358	0.5332	0.0373	0.2782	--	0.1432

Appendix 21

Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	UTERUS %
3F	3501	0.2022
	3502	0.1946
	3503	0.4051
	3504	0.1743
	3505	0.1391
	3506	0.2913
	3507	0.1780
	3508	0.4851
	3509	0.3441
	3510	0.1483
4F	4501	0.1668
	4502	0.1272
	4503	0.1638
	4504	0.1735
	4505	0.1395
	4506	0.1579
	4507	0.1441
	4508	0.2100
	4509	0.3037
	4510	0.1601

Appendix 21

Appendix 4
Individual Organ Weight Values - Relative to Brain Weight (Day 44)

Appendix 21

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1001	59.5238	3.37912	0.67308	51.4194	0.76007	87.2711	147.0696
	1002	54.9545	3.30909	0.65000	63.5000	0.98636	89.9091	140.8636
	1003	53.3662	3.23609	0.57002	60.2334	0.98743	77.3339	140.1257
	1004	54.1197	2.71899	0.63747	48.9592	1.02342	89.2888	138.4215
	1005	58.6987	3.25318	0.64592	59.4531	0.91938	84.1113	141.3956
	1006	53.6958	2.93118	0.74766	61.4274	1.11725	80.4163	151.0620
	1007	52.3968	3.36497	0.74988	64.7366	1.15330	81.5852	156.0038
	1008	49.2767MPI	2.39150	0.59222	73.7342	1.26582	82.6854	139.8734
	1009	53.1465	2.77905	0.57878	59.8989	0.84520	76.3895	138.8149
	1010	60.1928	2.94766	0.58770	58.2185	1.21671	86.5932	141.1387
2M	2001	56.8695	2.93425	0.59863	68.8420	0.91757	83.2679	142.1492
	2002	54.1818	2.69545	0.67727	48.1818	1.03636	88.9091	152.6818
	2003	56.4436	2.60440	0.60620	47.1486	1.13606	71.8006	146.3404
	2004	50.1504	2.76751	0.57155	58.7022	0.90675	75.5049	129.1792
	2005	54.4521	2.47003	0.59075	57.6199	0.88613	75.8990	141.1387
	2006	50.8936	3.14894	0.70638	57.1064	2.01277MPI	94.0851	141.8298
	2007	55.1507	3.03194	0.60729	46.6037	0.82771	68.2861	129.1948
	2008	55.0208	3.10042	0.65710	61.8232	0.91624	78.1583	137.1587
	2009	56.4727	2.32747	0.53676	55.4353	1.29905	70.1398	142.6703
	2010	57.7211	2.63088	0.65552	61.6806	1.03828	76.0229	126.8808

Appendix 21

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	1001	660.5311	81.3645	--	42.8571	196.7033	16.1172	--
	1002	653.2727	78.0000	--	36.0000	182.2273	15.8636	--
	1003	552.8276	75.1346	--	35.5925	157.0018	18.9408	--
	1004	676.3226	78.6644	--	40.4163	166.5221	19.7311	--
	1005	709.8538	77.1334	--	42.7628	190.6648	19.4719	--
	1006	652.4214	81.3934	--	40.2719	157.9014	16.8224	--
	1007	690.6977	84.7651	--	43.7589	173.3745	28.6664	--
	1008	622.8752	72.3779	--	40.4611	160.9855MPI	23.8698	--
	1009	507.0740	79.0078	--	39.0446	156.9132	25.4479	--
	1010	604.1781	77.5941	--	55.9229	162.1212	23.1405	--
2M	2001	719.9706	75.6624	--	49.8528	193.2777	21.2954	--
	2002	650.8636	79.0909	--	55.2727	168.8636	37.7727MPI	--
	2003	654.1536	79.5240	--	48.7652	194.2973	22.4068	--
	2004	544.3060	74.8174	--	48.7752	154.0610	17.7482	--
	2005	526.7123	71.7466	--	47.6027	172.6027	18.4503	--
	2006	695.3191	77.3191	--	55.2766	153.0213	30.2553	--
	2007	514.4849	74.7638	--	40.2609	174.8088	21.3225	--
	2008	538.4081	70.5692	--	47.8019	175.6131	14.0213	--
	2009	612.5395	73.2521	--	43.9332	198.8724	23.7258	--
	2010	504.3115	73.2072	--	41.6630	159.8768	21.6014	--

Appendix 21

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
3M	3001	58.5573	2.91843	0.57049	74.8232	0.97595	84.2527	144.8373
	3002	59.6383	2.94663	0.69696	54.5214	0.97486	89.5015	171.4160
	3003	54.2581	2.43635	0.67164	56.5408	0.93942	85.2063	138.7621
	3004	52.1760	3.13447	0.67971	75.5990	1.00244	83.3741	121.4670
	3005	63.1938	3.07205	0.67673	59.6884	0.94450	76.9231	147.6631
	3006	50.6792	2.67447	0.57611	58.7822	0.87588	68.7588	136.1593
	3007	56.3596	2.62921	0.67865	51.1011	1.02472	92.6742	133.5730
	3008	56.2782	2.52484	0.68654	53.3875	1.14724	85.0497	121.0930
	3009	55.2231	2.63185	0.68966	45.8418	0.73022	75.4564	133.8235
	3010	56.4068	3.06900	0.68996	60.0806	1.23208	82.3925	142.7419
4M	4001	54.9978	3.39405	0.56864	63.9716	1.29276	93.8250	158.6850
	4002	53.8902	2.18616	0.50597	47.8282	0.86396	67.3031	125.1551
	4003	53.0110	2.52308	0.47912	50.8132	1.60440	69.0989	112.4835
	4004	56.3037	3.45750	0.81662	62.5597	1.00764	80.0382	156.4470
	4005	54.2731	2.77014	0.60904	47.9862	0.74656	85.9037	143.7132
	4006	56.9302	2.66047	0.52558	48.7442	0.93023	81.1163	144.7442
	4007	50.2852	3.21293	0.71293	66.4924	0.99810	87.8327	158.5076
	4008	61.3726	3.43599	0.80070	70.7435	1.41663	101.1879	152.7497
	4009	55.5145	3.55330	0.75681	55.8837	0.89063	86.5713	151.3152
	4010	55.1464	3.44720	0.51464	61.2245	1.31322	85.5368	127.2848

Appendix 21

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
3M	3001	554.7383	75.5304	--	40.6412	174.4460	13.9557	--
	3002	755.0066	89.5457MPI	--	45.5668	165.3286	21.7027	--
	3003	723.6172	86.4355	--	52.5900	177.5680	20.3248	--
	3004	573.3985	77.3594	--	49.2421	160.3423	12.7628	--
	3005	737.2444	83.7877	--	49.6105	199.3671	23.5638	--
	3006	565.7611	73.3489	--	43.1850	175.1288	19.5785	--
	3007	626.6966	78.3371	--	45.4382	166.8315	25.5281	--
	3008	676.8744	78.3198	--	54.8329	185.3207	34.3270	--
	3009	590.6187	74.8479	--	53.0426	178.0426	21.9574	--
	3010	673.1631	86.5143	--	59.4982	165.7706	20.3853	--
4M	4001	789.2492	85.5620	--	55.8418	173.7006	23.5451	--
	4002	478.6158	62.6730	--	42.2912	167.4463	20.2387	--
	4003	630.4176	78.2857	--	45.0549	178.7692	18.1099	--
	4004	630.9456	79.1309	--	46.3228	170.7259	19.1500	--
	4005	738.8016	75.5894	--	44.6955	178.5855	21.0216	--
	4006	582.7907	79.4419	--	61.1163	160.6512	25.4884	--
	4007	732.8422	93.4411	--	62.5000	168.7262	25.3327	--
	4008	764.5842	87.1975	--	65.0682	191.9490	20.1056	--
	4009	663.5441	83.9409	--	40.3784	156.9912	13.7056	--
	4010	596.0071	78.9707	--	55.9006	164.6406	16.0160	--

Appendix 21

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	1501	--	3.16943	0.72541	--	0.57936	51.3632	84.2259
	1502	--	4.25363	0.90314	--	1.05756	60.7861	90.2199
	1503	--	3.28094	0.98723	--	0.75147	57.9077	95.5796
	1504	--	4.16140	0.92854	--	1.03549	58.9208	101.8474
	1505	--	2.34675	0.48948	--	0.79597	54.8490	76.1208
	1506	--	3.56333	0.87728	--	0.80335	54.2632	83.8344
	1507	--	3.37576	0.91312	--	0.68622	66.5744	102.5457
	1508	--	2.96296	0.89269	--	0.87369	57.8822	88.5565
	1509	--	3.41498	0.89967	--	0.74423	64.6726	88.5068
	1510	--	4.06325	0.88644	--	0.86248	59.3675	99.5688
2F	2501	--	3.26780	0.88204	--	1.04676	64.5058	86.1318
	2502	--	3.39772	0.69341	--	1.05002	56.7608	95.0966
	2503	--	3.83412	0.76161	--	0.74596	53.9384	100.0522
	2504	--	2.97405	0.77345	--	0.80838MPI	60.1297	86.1776
	2505	--	3.27129	0.79572	--	0.93532	68.9158	90.6933
	2506	--	2.45683	0.58214	--	0.78441	73.1130	79.3291
	2507	--	3.66090	0.77393	--	0.72811	54.2261	93.9919
	2508	--	3.18641	0.92287	--	0.96419	66.5289	94.3526
	2509	--	3.03415	0.87805	--	0.88293	56.6829	92.7805
	2510	--	3.96593	0.87080	--	0.90393	57.9271	94.6048

Appendix 21

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	1501	323.2717	56.9133	3.9435	29.6495	--	13.7780	19.1821
	1502	377.3046MPI	57.8381	5.6621	31.0248	--	22.9761	26.2050
	1503	391.9941	68.5167	4.7642	28.8802	--	21.7583	30.8448
	1504	424.7934	67.2338	5.5421	37.7248	--	20.2722	57.5109
	1505	314.7301	52.0586	4.9405	22.6898	--	20.2196	16.9716
	1506	323.3613	58.2553	4.2385	26.9098	--	20.0099	46.1311
	1507	375.5396	62.8113	4.6486	33.8129	--	11.5108MPI	25.3459
	1508	354.6534	53.1339	4.9383	30.9592	--	20.4179	84.0931
	1509	395.2426	63.4008	4.6632	24.5878	--	21.1493	29.8163
	1510	365.7882	67.4173	4.1687	24.9641	--	26.6890	26.1140
2F	2501	404.9947	63.5494	5.1010	35.8130	--	30.1275	19.4474
	2502	361.5651	63.3482	5.2501	30.5102	--	17.2858	43.8831
	2503	375.8477	67.3448	4.7992	32.4987	--	23.3698	27.9082
	2504	355.7884	59.3812	4.6906	32.6347	--	16.8663	31.7864
	2505	425.4072	73.2434	6.2820	39.5998	--	22.5686	30.2932
	2506	388.2585	70.8436	4.4894	29.5511	--	19.5856	29.1071
	2507	397.6069	63.1874	5.0916	35.9470	--	15.6823	22.9124
	2508	461.2489	70.1561	4.3618	33.7925	--	24.1047	24.8852
	2509	344.4390	64.7317	4.4878	30.7805	--	19.5610	25.9024
	2510	358.8736	66.7298	4.9219	34.6900	--	22.8112	23.9470

Appendix 21

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
3F	3501	--	3.19776	0.75241	--	0.83884	62.8368	97.3055
	3502	--	3.58311	0.96730	--	0.92643	57.0391	95.9582
	3503	--	3.14126	0.89684	--	1.06877	59.1078	89.2658
	3504	--	3.02705	0.85758	--	1.19959	59.2139	100.4084
	3505	--	3.39981	0.93228	--	0.93692	49.5362	94.4805
	3506	--	3.09956	0.92202	--	0.76508	60.7160	88.1314
	3507	--	3.33004	0.84486	--	0.79051	51.8775	79.2490
	3508	--	4.27565	0.94064	--	0.98089	52.6660	87.7264
	3509	--	3.94945	0.80278	--	0.75818	52.7255	72.6957
	3510	--	3.20660	0.78539	--	1.09555	50.2751	95.5478
4F	4501	--	3.57570	0.71713	--	0.65737	52.7888	78.1873
	4502	--	3.19622	0.71868	--	1.07329	65.8156	108.3688
	4503	--	3.35323	0.68657	--	0.58209	56.0199	89.1542
	4504	--	3.17677	0.72222	--	0.72222	55.5556	80.9596
	4505	--	4.42851	0.86534	--	1.12911	65.4789	105.7844
	4506	--	3.60229	0.81728	--	0.81728	61.3222	96.5643
	4507	--	3.46759	0.73148	--	0.81481	57.0833	91.5278
	4508	--	3.48897	0.75423	--	0.81580	57.0036	83.2735
	4509	--	4.92971	0.69317	--	0.72710	56.5681	104.8958
	4510	--	3.55858	0.62227	--	0.84589	55.4691	82.3043

Appendix 21

Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
3F	3501	408.6426	68.3274	4.4230	34.8246	--	27.3513	32.3843
	3502	400.8174	69.4369	5.0863	37.3297	--	25.6131	27.7475
	3503	406.8773	62.6394	4.7398	30.3439	--	25.9758	58.5502
	3504	405.6151	67.0750	5.0026	30.6279	--	21.8989	26.6973
	3505	413.4045	70.1763	4.4991	41.5584	--	25.0000	19.8052
	3506	362.6778	58.9014	4.1197	28.3963	--	23.1976	41.2948
	3507	367.4407	67.9348	3.8538	37.9941	--	19.9111	24.3577
	3508	341.6499	58.7022	4.4266	34.0040	--	11.9215	58.8028
	3509	368.4341	62.7849	5.4509	31.7146	--	17.5421	48.7611
	3510	321.4607	65.7329	4.7024	24.8124	--	13.1066	19.2096
4F	4501	360.4084	61.1554	4.9303	32.0219	--	15.0896	20.2689
	4502	440.4728	73.1442	5.3428	43.4515	--	36.9740	20.7565
	4503	400.5970	71.7910	4.8259	30.6965	--	20.4478	22.9851
	4504	389.8485	64.5960	5.2020	32.8788	--	12.5758	24.0909
	4505	436.5109	67.9315	5.1828	36.3258	--	20.2221	21.5641
	4506	406.6632	65.2785	4.2166	37.7408	--	18.1156	23.4253
	4507	420.3241	67.4074	4.1667	34.5833	--	17.4537	19.6759
	4508	351.0005	62.6475	4.5151	30.1693	--	19.1380	28.0144
	4509	406.7378	68.1047	4.1687	36.5972	--	16.6263	43.2865
	4510	386.7769	70.2479	4.9101	36.6553	--	18.8624	21.0987

Appendix 21

Appendix 5
Individual Organ Weight Values -Absolute (Day 57)

Appendix 21

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	589	2.336	1.325	0.0565	0.0117	1.114	0.0166
	1012	635	2.253	1.194	0.0556	0.0127	1.216	0.0153
	1013	568	2.252	1.236	0.0928MPI	0.0142	1.051	0.0183
	1014	657	2.350	1.325	0.0817MPI	0.0130	1.392	0.0218
	1015	532	2.190	1.283	0.0659	0.0135	1.170	0.0155
4M	4011	605	2.219	1.297	0.0613	0.0140	1.294	0.0177
	4012	579	2.288	1.219	0.0590	0.0142	1.174	0.0174
	4013	543	2.141	1.299	0.0685	0.0126	1.292	0.0164
	4014	581	2.328	1.441	0.0904	0.0164	0.991	0.0213
	4015	516	2.190	1.123	0.0483	0.0152	1.225	0.0155

Appendix 21

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	1011	1.824	3.188	16.519	1.772	--	1.113	4.207
	1012	2.093	3.347	17.882	1.515	--	0.947	3.938
	1013	1.762	3.291	20.360	1.766	--	3.613MPI	4.059
	1014	2.000	3.421	17.655	1.845	--	0.898	4.332
	1015	1.707	3.450	14.846	1.699	--	1.460	3.660
4M	4011	1.807	3.304	16.872	1.772	--	1.115	3.910
	4012	1.739	2.980	17.437	1.705	--	1.098	3.805
	4013	1.892	3.067	15.276	1.735	--	1.070	3.859
	4014	1.964	3.758	16.679	1.821	--	1.906	4.173
	4015	1.476	3.193	11.907	1.604	--	0.961	3.798

Appendix 21

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1M	1011	0.395	--
	1012	0.602	--
	1013	0.510	--
	1014	0.362	--
	1015	0.194	--
4M	4011	0.428	--
	4012	0.389	--
	4013	0.456	--
	4014	0.349	--
	4015	0.295	--

Appendix 21

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 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	296	2.001	--	0.0676	0.0189	--	0.0137
	1512	278	2.002	--	0.0615	0.0155	--	0.0155
	1513	306	1.988	--	0.0656	0.0143	--	0.0170
	1514	302	2.180	--	0.0759	0.0187	--	0.0179
	1515	284	1.988	--	0.0606	0.0126	--	0.0148
4F	4511	304	2.097	--	0.0655	0.0164	--	0.0240MPI
	4512	328	2.034	--	0.0735	0.0190	--	0.0149
	4513	289	1.891	--	0.0538	0.0118	--	0.0172
	4514	282	1.994	--	0.0640	0.0174	--	0.0142
	4515	321	2.050	--	0.0656	0.0160	--	0.0159

Appendix 21

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	1511	1.102	1.839	7.770	1.319	0.096	0.653	--
	1512	1.112	1.566	6.703	1.287	0.101	0.638	--
	1513	1.192	1.864	7.398	1.264	0.074	0.475	--
	1514	1.175	1.936	6.861	1.218	0.109	0.530	--
	1515	1.081	1.646	6.224	1.139	0.081	0.558	--
4F	4511	1.171	1.816	7.132	1.355	0.087	0.571	--
	4512	1.207	2.086	9.031	1.367	0.089	0.627	--
	4513	1.028	1.580	6.441	1.052	0.064	0.451	--
	4514	1.105	1.782	6.588	1.225	0.118	0.576	--
	4515	1.203	1.758	7.605	1.311	0.089	0.563	--

Appendix 21

Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1F	1511	0.336	0.674
	1512	0.267	0.935
	1513	0.247	0.404
	1514	0.297	0.479
	1515	0.353	0.481
4F	4511	0.322	0.410
	4512	0.351	0.484
	4513	0.291	0.820
	4514	0.294	1.166
	4515	0.452	0.482

Appendix 21

Appendix 6
Individual Organ Weight Values - Relative to Body Weight (Day 57)

Appendix 21

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1011	0.3966	0.2250	0.00959	0.00199	0.1891	0.00282	0.3097
	1012	0.3548	0.1880	0.00876	0.00200	0.1915	0.00241	0.3296
	1013	0.3965	0.2176	0.01634MPI	0.00250	0.1850	0.00322	0.3102
	1014	0.3577	0.2017	0.01244MPI	0.00198	0.2119	0.00332	0.3044
	1015	0.4117	0.2412	0.01239	0.00254	0.2199	0.00291	0.3209
4M	4011	0.3668	0.2144	0.01013	0.00231	0.2139	0.00293	0.2987
	4012	0.3952	0.2105	0.01019	0.00245	0.2028	0.00301	0.3003
	4013	0.3943	0.2392	0.01262	0.00232	0.2379	0.00302	0.3484
	4014	0.4007	0.2480	0.01556	0.00282	0.1706	0.00367	0.3380
	4015	0.4244	0.2176	0.00936	0.00295	0.2374	0.00300	0.2860

Appendix 21

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	1011	0.5413	2.8046	0.3008	--	0.1890	0.7143	0.0671
	1012	0.5271	2.8161	0.2386	--	0.1491	0.6202	0.0948
	1013	0.5794	3.5845	0.3109	--	0.6361MPI	0.7146	0.0898
	1014	0.5207	2.6872	0.2808	--	0.1367	0.6594	0.0551
	1015	0.6485	2.7906	0.3194	--	0.2744	0.6880	0.0365
4M	4011	0.5461	2.7888	0.2929	--	0.1843	0.6463	0.0707
	4012	0.5147	3.0116	0.2945	--	0.1896	0.6572	0.0672
	4013	0.5648	2.8133	0.3195	--	0.1971	0.7107	0.0840
	4014	0.6468	2.8707	0.3134	--	0.3281	0.7182	0.0601
	4015	0.6188	2.3076	0.3109	--	0.1862	0.7360	0.0572

Appendix 21

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	UTERUS %
1M	1011	--
	1012	--
	1013	--
	1014	--
	1015	--
4M	4011	--
	4012	--
	4013	--
	4014	--
	4015	--

Appendix 21

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	1511	0.6760	--	0.02284	0.00639	--	0.00463	0.3723
	1512	0.7201	--	0.02212	0.00558	--	0.00558	0.4000
	1513	0.6497	--	0.02144	0.00467	--	0.00556	0.3895
	1514	0.7219	--	0.02513	0.00619	--	0.00593	0.3891
	1515	0.7000	--	0.02134	0.00444	--	0.00521	0.3806
4F	4511	0.6898	--	0.02155	0.00539	--	0.00789MPI	0.3852
	4512	0.6201	--	0.02241	0.00579	--	0.00454	0.3680
	4513	0.6543	--	0.01862	0.00408	--	0.00595	0.3557
	4514	0.7071	--	0.02270	0.00617	--	0.00504	0.3918
	4515	0.6386	--	0.02044	0.00498	--	0.00495	0.3748

Appendix 21

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	1511	0.6213	2.6250	0.4456	0.0324	0.2206	--	0.1135
	1512	0.5633	2.4112	0.4629	0.0363	0.2295	--	0.0960
	1513	0.6092	2.4176	0.4131	0.0242	0.1552	--	0.0807
	1514	0.6411	2.2719	0.4033	0.0361	0.1755	--	0.0983
	1515	0.5796	2.1915	0.4011	0.0285	0.1965	--	0.1243
4F	4511	0.5974	2.3461	0.4457	0.0286	0.1878	--	0.1059
	4512	0.6360	2.7534	0.4168	0.0271	0.1912	--	0.1070
	4513	0.5467	2.2287	0.3640	0.0221	0.1561	--	0.1007
	4514	0.6319	2.3362	0.4344	0.0418	0.2043	--	0.1043
	4515	0.5477	2.3692	0.4084	0.0277	0.1754	--	0.1408

Appendix 21

Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	UTERUS %
1F	1511	0.2277
	1512	0.3363
	1513	0.1320
	1514	0.1586
	1515	0.1694
4F	4511	0.1349
	4512	0.1476
	4513	0.2837
	4514	0.4135
	4515	0.1502

Appendix 21

Appendix 7
Individual Organ Weight Values - Relative to Brain Weight (Day 57)

Appendix 21

Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1011	56.7209	2.41866	0.50086	47.6884	0.71062	78.0822	136.4726
	1012	52.9960	2.46782	0.56369	53.9725	0.67909	92.8984	148.5575
	1013	54.8845	4.12078MPI	0.63055	46.6696	0.81261	78.2416	146.1368
	1014	56.3830	3.47660MPI	0.55319	59.2340	0.92766	85.1064	145.5745
	1015	58.5845	3.00913	0.61644	53.4247	0.70776	77.9452	157.5342
4M	4011	58.4498	2.76251	0.63091	58.3146	0.79766	81.4331	148.8959
	4012	53.2780	2.57867	0.62063	51.3112	0.76049	76.0052	130.2448
	4013	60.6726	3.19944	0.58851	60.3456	0.76600	88.3699	143.2508
	4014	61.8986	3.88316	0.70447	42.5687	0.91495	84.3643	161.4261
	4015	51.2785	2.20548	0.69406	55.9361	0.70776	67.3973	145.7991

Appendix 21

Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	1011	707.1490	75.8562	--	47.6455	180.0942	16.9092	--
	1012	793.6973	67.2437	--	42.0328	174.7892	26.7199	--
	1013	904.0853	78.4192	--	160.4352MPI	180.2398	22.6465	--
	1014	751.2766	78.5106	--	38.2128	184.3404	15.4043	--
	1015	677.8995	77.5799	--	66.6667	167.1233	8.8584	--
4M	4011	760.3425	79.8558	--	50.2479	176.2055	19.2880	--
	4012	762.1066	74.5192	--	47.9895	166.3024	17.0017	--
	4013	713.4984	81.0369	--	49.9766	180.2429	21.2985	--
	4014	716.4519	78.2216	--	81.8729	179.2526	14.9914	--
	4015	543.6986	73.2420	--	43.8813	173.4247	13.4703	--

Appendix 21

Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	1511	--	3.37831	0.94453	--	0.68466	55.0725	91.9040
	1512	--	3.07193	0.77423	--	0.77423	55.5445	78.2218
	1513	--	3.29980	0.71932	--	0.85513	59.9598	93.7626
	1514	--	3.48165	0.85780	--	0.82110	53.8991	88.8073
	1515	--	3.04829	0.63380	--	0.74447	54.3763	82.7968
4F	4511	--	3.12351	0.78207	--	1.14449MPI	55.8417	86.5999
	4512	--	3.61357	0.93412	--	0.73255	59.3412	102.5565
	4513	--	2.84506	0.62401	--	0.90957	54.3628	83.5537
	4514	--	3.20963	0.87262	--	0.71214	55.4162	89.3681
	4515	--	3.20000	0.78049	--	0.77561	58.6829	85.7561

Appendix 21

Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	1511	388.3058	65.9170	4.7976	32.6337	--	16.7916	33.6832
	1512	334.8152	64.2857	5.0450	31.8681	--	13.3367	46.7033
	1513	372.1328	63.5815	3.7223	23.8934	--	12.4245	20.3219
	1514	314.7248	55.8716	5.0000	24.3119	--	13.6239	21.9725
	1515	313.0785	57.2938	4.0744	28.0684	--	17.7565	24.1952
4F	4511	340.1049	64.6161	4.1488	27.2294	--	15.3553	19.5517
	4512	444.0020	67.2075	4.3756	30.8260	--	17.2566	23.7955
	4513	340.6134	55.6319	3.3845	23.8498	--	15.3887	43.3633
	4514	330.3912	61.4343	5.9178	28.8867	--	14.7442	58.4754
	4515	370.9756	63.9512	4.3415	27.4634	--	22.0488	23.5122

Appendix 21

Appendix 8
Individual Animal Data Gross and Histopathology Findings

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1001	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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 : 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]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Infiltration, mononuclear cell; minimal : with fibrosis
LIVER : Infiltration, mixed cell; mild [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : No Glandular Tissue In Section
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 2, 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, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; 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:

LYMPH NODE, POPLITEAL - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1002	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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; depressed : 1, dark, corticomedullary junction, left. (TGL)
LIVER : Focus; depressed : 2, dark, left lateral. (TGL)
LIVER : Focus; pale : 1, near hilus, right lateral. (TGL)
LUNG : Focus; dark : 1 to 7. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
LYMPH NODE, MESENTERIC : Focus; dark : 1. (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]:

GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal [KIDNEY : Focus; depressed : 1, dark, corticomedullary junction, left. (G)]
LIVER : Infiltration, mixed cell; minimal [LIVER : Focus; pale : 1, near hilus, right lateral. (G)]
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]
SPINAL CORD, LUMBAR : Infiltration, mononuclear cell; perivascular, minimal
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 6. (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; depressed : 2, dark, left lateral. (G) | LYMPH NODE, MESENTERIC : Focus; dark : 1. (G) | LUNG : Focus; dark : 1 to 7. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; 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; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1003	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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)

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 : Murine progressive cardiomyopathy; minimal
KIDNEY : Cast; hyaline, minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, mixed cell; minimal [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; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; 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; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1004	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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 2, right middle, right accessory. (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 : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Hyperplasia; focal, minimal, pneumocyte, type 2
LUNG : Crystal; minimal : with hemorrhage
LUNG : Infiltration, mixed cell; minimal [LUNG : Focus; dark : 1 to 2, right middle, right accessory. (G)]
SITE, INJECTION : Inflammation, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
TRACHEA : Infiltration, mononuclear cell; 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, 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; 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

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.
SKIN - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1005	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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, 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, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (G)]
LIVER : Infiltration, mixed cell; minimal
TONGUE : Infiltration, mononuclear cell; minimal
TRACHEA : Infiltration, mononuclear cell; 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; 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; THYMUS; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1006	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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 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]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Cast; hyaline, minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Crystal; minimal : with hemorrhage [LUNG : Focus; dark : 1 to 5. (G)]
LUNG : Infiltration, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
STOMACH : Infiltration, mixed cell; 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; 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; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1007	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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, 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, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PARATHYROID : Infiltration, mononuclear cell; minimal
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
KIDNEY : Cast; hyaline, minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
STOMACH : Infiltration, mixed cell; minimal
TESTIS : Atrophy; unilateral, mild, seminiferous tubule
URINARY BLADDER : Infiltration, mononuclear cell; minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (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, 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; 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; THYMUS; TONGUE; TRACHEA

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1008	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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 : Small : Right. (TGL)
EPIDIDYMIS : Abnormal consistency; soft : Right. (TGL)
EPIDIDYMIS : Focus; pale : 1, caput, right. (TGL)
EPIDIDYMIS : Focus; raised : 3, pale, caput, right. (TGL)
LIVER : Focus; pale : >10, papillary process of caudate. (TGL)
TESTIS : Abnormal consistency; soft : Right. (TGL)
TESTIS : Focus; pale : 2, 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]:

EPIDIDYMIS : Sperm granuloma; unilateral, regionally extensive, moderate [EPIDIDYMIS : Abnormal consistency; soft : Right. (G) | EPIDIDYMIS : Focus; raised : 3, pale, caput, right. (G) | EPIDIDYMIS : Focus; pale : 1, caput, right. (G)]
EPIDIDYMIS : Infiltration, mononuclear cell; minimal
EPIDIDYMIS : Cribriform change; unilateral, mild
EPIDIDYMIS : Hypospermia; unilateral, moderate [EPIDIDYMIS : Small : Right. (G)]
GLAND, PITUITARY : Pars Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal [LIVER : Focus; pale : >10, papillary process of caudate. (G)]
SITE, INJECTION : Inflammation, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
TESTIS : Vacuolation; unilateral, mild, sertoli cell

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

TESTIS : Atrophy; unilateral, marked, seminiferous tubule : With mononuclear infiltration [TESTIS : Abnormal consistency; soft : Right. (G) | TESTIS : Focus; pale : 2, right. (G)]

THYMUS : Congestion; minimal [THYMUS : Focus; dark : >10, right. (G)]

TRACHEA : Infiltration, mononuclear cell; minimal

URINARY BLADDER : Infiltration, mononuclear cell; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; 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; TONGUE

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1009	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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, 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]:

HEART : Murine progressive cardiomyopathy; minimal
LARGE INTESTINE, COLON : Parasitism; nematode
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (G)]
LIVER : Infiltration, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal
TRACHEA : Infiltration, mononuclear cell; 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; GLAND, THYROID; KIDNEY; LARGE INTESTINE, CECUM; 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; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1010	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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)

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 Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, THYROID : One Of A Pair Available For Evaluation.
GLAND, THYROID : Examined
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Degeneration; hyaline droplets, moderate [KIDNEY : Focus; pale : >10, bilateral. (G)]
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; 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; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1011	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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 : 1 (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, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
PANCREAS : Infiltration, mixed cell; mild : with focal necrosis and minimal chronic mononuclear infiltration with fibrosis
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SPLEEN : Hyperplasia; lymphoid, minimal
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 1 (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; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; 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; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1012	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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)
LYMPH NODE : Discoloration; dark : Mediastinal (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 : Thyroglossal duct remnant, squamous epithelium; minimal
KIDNEY : Cast; hyaline, minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, MEDIASTINAL : Hemorrhage; mild [LYMPH NODE : Discoloration; dark : Mediastinal (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal
URINARY BLADDER : Infiltration, mononuclear cell; 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; 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

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1013	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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:

GLAND, ADRENAL : Enlargement : Bilateral (TGL)
SPLEEN : Focus; raised : 2, pale, firm (TGL)
SPLEEN : Enlargement (TGL)
SPLEEN : Irregular surface (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 : Necrosis; minimal : focal
LIVER : Infiltration, mixed cell; mild : more lymphocytic in periportal regions
LUNG : Hyperplasia; focal, minimal, pneumocyte, type 2
LUNG : Infiltration, mixed cell; minimal
LUNG : Metaplasia; osseous, focal, minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal
SPLEEN : Congestion; moderate [SPLEEN : Enlargement (G)]
SPLEEN : Hyperplasia; lymphoid, mild
SPLEEN : Hyperplasia; stromal, focal, moderate : with mild associated mixed cell inflammation (reactive stromal hyperplasia) [SPLEEN : Focus; raised : 2, pale, firm (G) | SPLEEN : Irregular surface (G)]
NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Enlargement : Bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; 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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 1014	Group: 1		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/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:

GLAND, ADRENAL : Enlargement : 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, HARDERIAN : Infiltration, mononuclear cell; minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
PANCREAS : Infiltration, mixed cell; minimal : with fibrosis
STOMACH : Cyst; epithelial, single
TESTIS : Atrophy; minimal, seminiferous tubule
THYMUS : Hemorrhage; minimal
NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Enlargement : Left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; 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, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1015	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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 : 2, near hilus, right lateral (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 2, 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, MAMMARY : Immaturity; diffuse, marked, alveolus/duct
KIDNEY : Cast; hyaline, minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, mixed cell; minimal [LIVER : Focus; pale : 2, near hilus, right lateral (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 2, bilateral (G)]
PANCREAS : Infiltration, mononuclear cell; minimal : with fibrosis
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : 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, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; 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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1501	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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)

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
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal

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; 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; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1502	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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 : Nodule; [a] : 1, dark, firm, pedunculated, fissure, medial lobe. (TGL)
THYMUS : Focus; dark : 2, 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, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Cast; hyaline, minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal [LIVER : Nodule; [a] : 1, dark, firm, pedunculated, fissure, medial lobe. (G)]

LUNG : Infiltration, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Congestion; minimal [THYMUS : Focus; dark : 2, 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; 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; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1503	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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, 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, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : No Glandular Tissue In Section
LYMPH NODE, POPLITEAL : Examined
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : with mild hemorrhage
SITE, INJECTION : Inflammation, mixed cell; mild
THYMUS : Congestion; minimal [THYMUS : Focus; dark : >10, left (G)]
TRACHEA : Infiltration, mononuclear cell; minimal

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; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1504	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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:

LARGE INTESTINE, RECTUM : Parasite : 5.
LIVER : Focus; pale : 1, fissure, left medial. (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, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Granuloma; focal, mild [LIVER : Focus; pale : 1, fissure, left medial. (G)]
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
STOMACH : Infiltration, mixed cell; minimal
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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5002158 - 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; 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; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1505	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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:

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, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
STOMACH : Infiltration, mixed cell; minimal
THYMUS : Appears to be parathyroid focus
THYMUS : Hemorrhage; minimal
THYMUS : Ectopia; minimal

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; 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; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1506	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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)
THYMUS : 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, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Congestion; minimal [THYMUS : Focus; dark : 1, right. (G)]
URINARY BLADDER : Infiltration, mononuclear cell; minimal

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; 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; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1507	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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 : Small (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
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal : with foamy macrophages
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal
NO CORRELATE : No correlating lesion [THYMUS : Small (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; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1508	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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 : 3 to 4, bilateral. (TGL)
MUSCLE, SKELETAL : Material accumulation; clot : Ventral cervical, 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, HARDERIAN : Infiltration, mononuclear cell; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LARGE INTESTINE, CECUM : Dilatation; minimal, crypt
LARGE INTESTINE, RECTUM : Dilatation; minimal, crypt
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 3 to 4, bilateral. (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal
NO CORRELATE : No correlating lesion [MUSCLE, SKELETAL : Material accumulation; clot : Ventral cervical, left. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, COLON; 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; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1509	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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)
STOMACH : Focus; pale : >10, mucosa, glandular (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
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Cast; hyaline, minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LARGE INTESTINE, RECTUM : Hemorrhage; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10, right (G)]
NO CORRELATE : No correlating lesion [STOMACH : Focus; pale : >10, mucosa, glandular (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; 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; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1510	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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:

KIDNEY : Focus; depressed : 1, dark, cortex, left. (TGL)
LIVER : Focus; pale : 1, near hilus, right lateral. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 3, bilateral. (TGL)
STOMACH : Focus; dark : 2, mucosa, glandular. (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 : Infiltration, lymphocytic; focal, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, PARATHYROID : Fibrosis; interstitial, minimal
KIDNEY : Chronic progressive nephropathy; minimal [KIDNEY : Focus; depressed : 1, dark, cortex, left. (G)]
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Congestion; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 3, bilateral. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
STOMACH : Congestion; minimal [STOMACH : Focus; dark : 2, mucosa, glandular. (G)]
TRACHEA : Dilatation; submucosal, minimal, glandular

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; 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; THYMUS; TONGUE; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1511	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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, PITUITARY : Cyst
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
PANCREAS : Fibrosis; minimal
URINARY BLADDER : Accumulation; granular, minimal, transitional epithelium

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, 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; 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; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1512	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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)

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 : Thyroglossal duct remnant, squamous epithelium; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Infiltration, mixed cell; minimal
MUSCLE, SKELETAL : Infiltration, mononuclear cell; minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, minimal
PANCREAS : Infiltration, mononuclear cell; minimal : with fibrosis

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; NERVE, OPTIC; OVARY; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1513	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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]:

KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
THYMUS : Cyst; epithelial, multiple, minimal
TRACHEA : Infiltration, mononuclear cell; minimal
URINARY BLADDER : Infiltration, mononuclear cell; minimal

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; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1514	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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:

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
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
PANCREAS : Infiltration, mononuclear cell; minimal : with fibrosis
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 3 (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; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	1515	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/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, THYROID : Thyroglossal duct remnant, squamous epithelium; mild
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mononuclear cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

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; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2001	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 9.6 ug/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 : >10, papillary process of caudate (TGL)
SKIN : Scab; dark : 2, 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]:

LIVER : Necrosis; minimal [LIVER : Focus; pale : >10, papillary process of caudate (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SKIN : Pinna skin
SKIN : Hyperkeratosis; moderate : with epithelial hyperplasia and regionally extensive mixed cell infiltration [SKIN : Scab; dark : 2, pinna, bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2002	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 9.6 ug/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 to 5, right middle, right accessory, right caudal. (TGL)
LYMPH NODE, INGUINAL : Focus; dark : 3 to >10, bilateral. (TGL)
STOMACH : Focus; dark : >10, mucosa, glandular. (TGL)
THYMUS : Enlargement (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 : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Crystal; minimal : with hemorrhage [LUNG : Focus; dark : 2 to 5, right middle, right accessory, right caudal. (G)]
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, INGUINAL : Hemorrhage; minimal [LYMPH NODE, INGUINAL : Focus; dark : 3 to >10, bilateral. (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hyperplasia; lymphoid, diffuse, mild [THYMUS : Enlargement (G)]
NO CORRELATE : No correlating lesion [STOMACH : Focus; dark : >10, mucosa, glandular. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN; STOMACH

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2003	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 9.6 ug/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, ADRENAL : Focus; dark : 1, right (TGL)
LIVER : Focus; pale : >10, papillary process of caudate (TGL)
LYMPH NODE, MANDIBULAR : 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]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, ADRENAL : Congestion; mild [GLAND, ADRENAL : Focus; dark : 1, right (G)]
LIVER : Necrosis; mild [LIVER : Focus; pale : >10, papillary process of caudate (G)]
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 1, right (G)]

LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; moderate
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2004	Group: 2		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 9.6 ug/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 : Bilateral. (TGL)
LYMPH NODE, MESENTERIC : Enlargement (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Bilateral. (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, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : Bilateral. (G)]

LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, MESENTERIC : Hyperplasia; lymphoid, moderate [LYMPH NODE, MESENTERIC : Enlargement (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal [LYMPH NODE, POPLITEAL : Enlargement : Bilateral. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; mild, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	2005	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 9.6 ug/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 : Bilateral (TGL)
SITE, INJECTION : Swelling : Right (TGL)
THYMUS : 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 : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : Bilateral (G)]

LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, marked
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 1, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2006	Group: 2		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 9.6 ug/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 : Enlargement : Bilateral. (TGL)
LIVER : Focus; pale : 1, near hilus, right lateral, fissure, right medial. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 1, right. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
STOMACH : Focus; dark : 4, mucosa, glandular. (TGL)
THYMUS : Focus; dark : 3, 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 : Hyperplasia; diffuse, mild, follicle [GLAND, THYROID : Enlargement : Bilateral. (G)]
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral, fissure, right medial. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, moderate
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 1, right. (G)]

LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 3, right. (G)]
NO CORRELATE : No correlating lesion [STOMACH : Focus; dark : 4, mucosa, glandular. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

BONE MARROW; STOMACH

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2007	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 9.6 ug/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:

ESOPHAGUS : Discoloration; dark : Caudal part (TGL)
ESOPHAGUS : Dilatation : Caudal part (TGL)
ESOPHAGUS : Thick : Wall, caudal part (TGL)
LIVER : Focus; pale : 1, fissure, medial 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]:

ESOPHAGUS : Hyperplasia; epithelial, diffuse, mild, lumen
ESOPHAGUS : Hypertrophy; mural, regionally extensive, moderate, myofiber [ESOPHAGUS : Discoloration; dark : Caudal part (G) | ESOPHAGUS : Thick : Wall, caudal part (G)]
ESOPHAGUS : Dilatation; mild [ESOPHAGUS : Dilatation : Caudal part (G)]
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, medial lobe (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; moderate
SITE, INJECTION : Degeneration/necrosis; mild, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2008	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 9.6 ug/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 : Focus; dark : 1, mucosa. (TGL)
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 : 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]:

LARGE INTESTINE, RECTUM : Hemorrhage; mild [LARGE INTESTINE, RECTUM : Focus; dark : 1, mucosa. (G)]

LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; mild, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 1, left. (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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	2009	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 9.6 ug/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:

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
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	2010	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 9.6 ug/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, edge, right caudal. (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, mixed cell; minimal
LUNG : Atelectasis; regionally extensive, mild [LUNG : Focus; dark : 1, edge, right caudal. (G)]
LUNG : Hemorrhage; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2501	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 9.6 ug/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, 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 : Necrosis; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, marked
SITE, INJECTION : Inflammation, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10, right (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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	2502	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 9.6 ug/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 : 5 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]:

LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, MANDIBULAR : Congestion; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 5 to >10, bilateral. (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2503	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 9.6 ug/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:

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]:

LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2504	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 9.6 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death: 44 (7)	

Palpable Mass Details:

Mass 1; Abdominal; Firm; 3 mm

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)
LIVER : Focus; pale : 1, fissure, right medial. (TGL)
SUBCUTIS : Mass; [1] : 4x4x3 mm, dark, firm, abdominal, cut surface: material green thick. (TGL) [Mass 1; Abdominal; Firm; 3 mm (M)]

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 : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, moderate
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SUBCUTIS : Abscess; chronic active, focal, mild [SUBCUTIS : Mass; [1] : 4x4x3 mm, dark, firm, abdominal, cut surface: material green thick. (G) | Mass 1; Abdominal; Firm; 3 mm (M)]
NO CORRELATE : No correlating lesion [GLAND, THYROID : Small : Left. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GLAND, THYROID; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	2505	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 9.6 ug/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 : 4, 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 : Tension lipidosis; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Congestion; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 4, right (G)]

LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate : with edema
SITE, INJECTION : Inflammation, mixed cell; mild [SITE, INJECTION : Abnormal consistency; firm : Right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Congestion; minimal [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, INGUINAL - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2506	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 9.6 ug/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 to 7. (TGL)
LYMPH NODE, POPLITEAL : 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]:

LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Crystal; minimal : with hemorrhage [LUNG : Focus; dark : 1 to 7. (G)]
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]

NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	2507	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 9.6 ug/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)
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]:

LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (G)]

LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate : with edema
SITE, INJECTION : Inflammation, mixed cell; mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 4 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2508	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 9.6 ug/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 : 4 to >10, bilateral. (TGL)
LYMPH NODE, MESENTERIC : Enlargement (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
STOMACH : Focus; dark : 1, linear, mucosa, glandular. (TGL)
STOMACH : Thick : Wall, glandular. (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, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Congestion; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 4 to >10, bilateral. (G)]
LYMPH NODE, MESENTERIC : Hyperplasia; lymphoid, mild [LYMPH NODE, MESENTERIC : Enlargement (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; mild [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
STOMACH : Inflammation, eosinophilic; mild : with abundant macrophages and locally extensive edema [STOMACH : Focus; dark : 1, linear, mucosa, glandular. (G) | STOMACH : Thick : Wall, glandular. (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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2509	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 9.6 ug/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)
LUNG : Focus; dark : 1, 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 : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate : with edema
SITE, INJECTION : Inflammation, mixed cell; mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G) | LUNG : Focus; dark : 1, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LUNG; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 2510	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 9.6 ug/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)

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, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; moderate
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
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; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 3001	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 29 ug/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)
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
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Degeneration/necrosis; mild, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3002	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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, PITUITARY : Focus; dark : 2. (TGL)
KIDNEY : Focus; depressed : 3 to 7, dark, bilateral. (TGL)
KIDNEY : Focus; pale : 3, left. (TGL)
LUNG : Focus; dark : 3 to >10, right cranial, right caudal, left lobe. (TGL)
LUNG : Focus; depressed : 1, dark, edge, left lobe. (TGL)
LUNG : Discoloration; dark : Cranial half, left lobe. (TGL)
LUNG : Abnormal consistency : Spongy, cranial half, left lobe. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
MUSCLE, SKELETAL : Material accumulation; clot : Ventral cervical. (TGL)
SITE, INJECTION : Swelling : 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]:

GLAND, PITUITARY : Pars Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, PITUITARY : Congestion; mild [GLAND, PITUITARY : Focus; dark : 2. (G)]
KIDNEY : Cast; hyaline, minimal
KIDNEY : Cyst; tubular, multiple, mild [KIDNEY : Focus; pale : 3, left. (G)]
KIDNEY : Chronic progressive nephropathy; mild [KIDNEY : Focus; depressed : 3 to 7, dark, bilateral. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LUNG : Atelectasis; regionally extensive, minimal [LUNG : Focus; depressed : 1, dark, edge, left lobe. (G)]
LUNG : Hemorrhage; marked [LUNG : Discoloration; dark : Cranial half, left lobe. (G) | LUNG : Abnormal consistency : Spongy, cranial half, left lobe. (G) | LUNG : Focus; dark : 3 to >10, right cranial, right caudal, left lobe. (G)]

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
MUSCLE, SKELETAL : Ventral cervical.
MUSCLE, SKELETAL : Hemorrhage; acute, regionally extensive, marked [MUSCLE, SKELETAL : Material accumulation; clot : Ventral cervical. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Swelling : right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Congestion; mild [THYMUS : Focus; dark : 2. (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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3003	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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, edge right caudal (TGL)
LYMPH NODE, INGUINAL : Enlargement : Bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
SITE, INJECTION : Swelling : right (TGL)
STOMACH : Focus; dark : >10, mucosa. glandular (TGL)
THYMUS : 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]:

LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LUNG : Atelectasis; regionally extensive, minimal [LUNG : Focus; dark : 1 to 2, right middle, edge right caudal (G)]

LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : Bilateral (G)]

LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G) | SITE, INJECTION : Swelling : right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
STOMACH : Hemorrhage; minimal [STOMACH : Focus; dark : >10, mucosa. glandular (G)]
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 4, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3004	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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, MANDIBULAR : Focus; dark : 2, left. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
SITE, INJECTION : Focus; dark : 1, right (TGL)
STOMACH : Focus; dark : 3, mucosa, glandular. (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 : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LUNG : Atelectasis; regionally extensive, minimal [LUNG : Focus; dark : 1, left lobe (G)]
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Congestion; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 2, left. (G)]

LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : with locally extensive hemorrhage
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G) | SITE, INJECTION : Focus; dark : 1, right (G)]
SITE, INJECTION : Degeneration/necrosis; mild, myofiber
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
STOMACH : Hemorrhage; minimal [STOMACH : Focus; dark : 3, mucosa, glandular. (G)]
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10, right. (G)]

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3005	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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, right accessory (TGL)
LYMPH NODE, MANDIBULAR : 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 : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LUNG : Atelectasis; regionally extensive, mild [LUNG : Focus; dark : 1, right caudal, right accessory (G)]
LUNG : Hemorrhage; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, mild [LYMPH NODE, MANDIBULAR : Enlargement : Right (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild : with edema
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3006	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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)
LUNG : Focus; dark : 1, right accessory. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 4, left. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (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]:

LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Atelectasis; regionally extensive, mild [LUNG : Focus; dark : 1, right accessory. (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; mild [LYMPH NODE, MANDIBULAR : Focus; dark : 4, left. (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 3. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3007	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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)
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]:

LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild : with edema
SITE, INJECTION : with a small amount of locally extensive hemorrhage
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G) | SITE, INJECTION : Focus; dark : >10, right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]
THYMUS : Congestion; mild

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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 3008	Group: 3		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 29 ug/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, MANDIBULAR : Focus; dark : 1, left. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : Focus; dark : 5, 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, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, moderate [LYMPH NODE, INGUINAL : Enlargement : Right. (G)]
LYMPH NODE, MANDIBULAR : Hemorrhage; mild [LYMPH NODE, MANDIBULAR : Focus; dark : 1, left. (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : with a small amount of locally extensive hemorrhage
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Focus; dark : 5, right. (G) | SITE, INJECTION : Swelling : Right. (G) | SITE, INJECTION : Abnormal consistency; firm : Right. (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3009	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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)
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
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G) | SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Degeneration/necrosis; mild, myofiber
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 3010	Group: 3		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 29 ug/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)

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, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; mild, myofiber

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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 3501	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 29 ug/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 to >10, left lateral, near hilus, right lateral, 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]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Necrosis; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1 to >10, left lateral, near hilus, right lateral, fissure, right medial (G)]
LIVER : Infiltration, mixed cell; minimal [LIVER : Focus; pale : 1 to >10, left lateral, near hilus, right lateral, fissure, right medial (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate : with edema
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3502	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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 : 1 to 2, bilateral. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
SITE, INJECTION : Swelling : Right. (TGL)
SITE, INJECTION : 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, ADRENAL : Congestion; mild [GLAND, ADRENAL : Focus; dark : 1 to 2, bilateral. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; moderate
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : with a moderate amount of locally extensive hemorrhage
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right. (G) | SITE, INJECTION : Swelling : Right. (G) | SITE, INJECTION : Focus; dark : >10, right. (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 3503	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 29 ug/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 : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 3504	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 29 ug/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 : 1 to 2, bilateral. (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]:

GLAND, ADRENAL : Congestion; mild [GLAND, ADRENAL : Focus; dark : 1 to 2, bilateral. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3505	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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)
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 : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal : perinodal;with edema
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild : with edema
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3506	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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:

EYE : Focus; dark : 3, sclera, right. (TGL)
LUNG : Focus; dark : 1, right caudal, left lobe. (TGL)
LUNG : Focus; depressed : 1, dark, ventral, left lobe. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 2 to 3, bilateral. (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 : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Crystal; minimal : with hemorrhage
LUNG : Infiltration, mixed cell; minimal [LUNG : Focus; depressed : 1, dark, ventral, left lobe. (G) | LUNG : Focus; dark : 1, right caudal, left lobe. (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, MANDIBULAR : Congestion; mild [LYMPH NODE, MANDIBULAR : Focus; dark : 2 to 3, bilateral. (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
NO CORRELATE : No correlating lesion [EYE : Focus; dark : 3, sclera, right. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; EYE; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 3507	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 29 ug/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, MANDIBULAR : Focus; dark : >10, bilateral (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]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Hepatodiaphragmatic nodule [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, MANDIBULAR : Congestion; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 5 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	3508	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 29 ug/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 : Enlargement : Iliac, right. (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]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE : Infiltration, mononuclear cell; interstitial, regionally extensive, minimal
LYMPH NODE : Hyperplasia; lymphoid, minimal [LYMPH NODE : Enlargement : Iliac, right. (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Inflammation, mixed cell; moderate [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 3509	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 29 ug/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)
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 : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate : with edema
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, INGUINAL - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 3510	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 29 ug/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 : 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
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

NERVE, SCIATIC; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4001	Group: 4		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 96 ug/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 : 6, 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, HARDERIAN : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mononuclear cell; perivascular, minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SPLEEN : Increased hematopoiesis; minimal
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 6, right (G)]
TONGUE : Infiltration, mononuclear cell; minimal
TRACHEA : Infiltration, mononuclear cell; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; 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; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4002	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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)
SITE, INJECTION : Swelling : right (TGL)
STOMACH : Focus; dark : 5, mucosa, glandular. (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 : Thyroglossal duct remnant, squamous epithelium; minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : right (G) | SITE, INJECTION : Swelling : right (G)]
SITE, INJECTION : Degeneration/necrosis; mild, myofiber
STOMACH : Congestion; minimal [STOMACH : Focus; dark : 5, mucosa, glandular. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; 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; SPLEEN; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4003	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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)
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, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; mild
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, INGUINAL : Plasmacytosis; mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G) | SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
TRACHEA : Dilatation; submucosal, mild, glandular

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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, 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; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4004	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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, edge, papillary process of caudate, near hilus of right lateral, fissure right medial. (TGL)
LYMPH NODE, INGUINAL : Focus; dark : 1, left. (TGL)
LYMPH NODE, INGUINAL : Enlargement : Right. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Right. (TGL)
SITE, INJECTION : Focus; 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, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LARGE INTESTINE, COLON : Parasitism; nematode
LIVER : Necrosis; minimal [LIVER : Focus; pale : 1, edge, papillary process of caudate, near hilus of right lateral, fissure right medial. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : Right. (G)]
LYMPH NODE, INGUINAL : Plasmacytosis; mild
LYMPH NODE, INGUINAL : Inflammation, mixed cell; mild, perinodal
LYMPH NODE, INGUINAL : Congestion; minimal [LYMPH NODE, INGUINAL : Focus; dark : 1, left. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G) | SITE, INJECTION : Focus; pale : 1, right. (G)]

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : 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; GLAND, THYROID; LARGE INTESTINE, CECUM; 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; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4005	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : 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]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; moderate
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G) | SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; 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; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4006	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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 7, right cranial, right middle, right accessory, left lobe. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 1, right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : 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, mild
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
KIDNEY : Cast; hyaline, minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Crystal; minimal : with hemorrhage [LUNG : Focus; dark : 1 to 7, right cranial, right middle, right accessory, left lobe. (G)]
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Congestion; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 1, right. (G)]

LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Swelling : Right. (G) | SITE, INJECTION : Abnormal consistency; firm : Right. (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; 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; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4007	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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, near hilus, right lateral (TGL)
LUNG : Focus; dark : 1 to 2 (TGL)
SITE, INJECTION : Abnormal consistency; firm : 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]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (G)]

LUNG : Crystal; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G) | SITE, INJECTION : Swelling : Right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1 to 2 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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, 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; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4008	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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, fissure, right medial. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : 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]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Necrosis; minimal
LIVER : Tension lipidosis; minimal
LIVER : Fibrosis; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral, fissure, right medial. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LUNG : Crystal; minimal : with hemorrhage
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate, perinodal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
PANCREAS : Infiltration, mononuclear cell; minimal : with fibrosis
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G) | SITE, INJECTION : Swelling : Right. (G)]

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
TRACHEA : Infiltration, mononuclear cell; 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, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; 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:

GLAND, MAMMARY - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4009	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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)
SITE, INJECTION : Abnormal consistency; firm : Right (TGL)
SITE, INJECTION : Swelling : Right (TGL)
SITE, INJECTION : 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]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal [LYMPH NODE, INGUINAL : Enlargement : Right (G)]

LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
PANCREAS : Infiltration, mononuclear cell; minimal
SITE, INJECTION : with regionally extensive hemorrhage
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G) | SITE, INJECTION : Swelling : Right (G) | SITE, INJECTION : Focus; dark : 2, right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Hemorrhage; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; 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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4010	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 96 ug/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)
STOMACH : Focus; dark : 5, mucosa, glandular. (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]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : Infiltration, mononuclear cell; mild
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
STOMACH : Congestion; minimal [STOMACH : Focus; dark : 5, mucosa, glandular. (G)]
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : 1, left. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, MANDIBULAR; 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; SPLEEN; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4011	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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, MESENTERIC : Focus; dark : 1 (TGL)
THYMUS : Focus; dark : 1 (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 : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, MESENTERIC : Hemorrhage; moderate [LYMPH NODE, MESENTERIC : Focus; dark : 1 (G)]
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
MUSCLE, SKELETAL : Infiltration, mononuclear cell; minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, minimal
PANCREAS : Infiltration, mononuclear cell; minimal : with fibrosis
SITE, INJECTION : Infiltration, mononuclear cell; minimal
THYMUS : Congestion; mild [THYMUS : Focus; dark : 1 (G)]
URINARY BLADDER : Infiltration, mononuclear cell; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; NERVE, OPTIC; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4012	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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 : Enlargement : Axillary, 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 Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, AXILLARY, LEFT : Sinus histiocytosis; minimal
LYMPH NODE, AXILLARY, LEFT : Hyperplasia; lymphoid, mild [LYMPH NODE : Enlargement : Axillary, left (G)]

LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, minimal
PANCREAS : Infiltration, mononuclear cell; minimal : with fibrosis
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; 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:

GALT - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4013	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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:

GLAND, ADRENAL : 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]:

GLAND, ADRENAL : Congestion; mild [GLAND, ADRENAL : Focus; dark : 1, left (G)]
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; 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; 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; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4014	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 96 ug/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, near hilus, right lateral (TGL)
LYMPH NODE : Enlargement : Iliac right, Deep cervical 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 : Fibrosis; interstitial, minimal
GLAND, PROSTATE : Infiltration, mononuclear cell; regionally extensive, marked
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, ILIAC, RIGHT : Hemorrhage; interstitial, moderate [LYMPH NODE : Enlargement : Iliac right, Deep cervical right (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Infiltration, mononuclear cell; minimal, perinodal
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, minimal
PANCREAS : Infiltration, mononuclear cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal
SKIN : Crust; serocellular, focal, mild : with associated minimal mononuclear inflammation
THYMUS : Hemorrhage; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; 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 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4015	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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; pale : 1 to 2, bilateral (TGL)
LYMPH NODE, MANDIBULAR : 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, PROSTATE : Infiltration, mononuclear cell; moderate
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, right (G)]
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal
NO CORRELATE : No correlating lesion [KIDNEY : Focus; pale : 1 to 2, 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, 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, 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; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4501	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 96 ug/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)
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
GLAND, PARATHYROID : Fibrosis; interstitial, mild
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; mild
GLAND, THYROID : Fibrosis; interstitial, mild
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Necrosis; minimal [LIVER : Focus; pale : 1, fissure, medial lobe (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; perivascular, minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
THYMUS : Cyst; epithelial, minimal
THYMUS : Infiltration, mixed cell; perivascular, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; 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; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4502	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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 : Discoloration; dark : Mediastinal. (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]:

GLAND, HARDERIAN : Infiltration, mononuclear cell; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mononuclear cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, MEDIASTINAL : Hemorrhage; mild [LYMPH NODE : Discoloration; dark : Mediastinal. (G)]
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
STOMACH : Infiltration, mixed cell; minimal
THYMUS : Hemorrhage; minimal [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; 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; SPLEEN; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4503	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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)
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]:

GLAND, HARDERIAN : Infiltration, mononuclear cell; minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SKIN : Haired skin from recut evaluated
THYMUS : Hemorrhage; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; KIDNEY; 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; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

GALT - Not Present In Section.

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4504	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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 to 2, right caudal, left lobe. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : 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]:

KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Necrosis; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LUNG : Atelectasis; regionally extensive, mild [LUNG : Focus; dark : 1 to 2, right caudal, left lobe. (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G) | SITE, INJECTION : Swelling : Right. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; 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; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4505	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 96 ug/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]:

GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LARGE INTESTINE, RECTUM : Parasitism; nematode
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SKIN : Infiltration, mixed cell; minimal
THYMUS : Hemorrhage; minimal
TRACHEA : Dilatation; submucosal, mild, glandular

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4506	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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 : Bilateral. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right. (TGL)
SITE, INJECTION : Abnormal consistency; firm : 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, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal [LYMPH NODE, INGUINAL : Enlargement : Bilateral. (G)]
LYMPH NODE, POPLITEAL : Plasmacytosis; mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G) | SITE, INJECTION : Swelling : Right. (G)]
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4507	Group: 4		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 96 ug/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, right cranial, right accessory, edge left (TGL)
LUNG : Focus; depressed : dark, 1, left (TGL)
SITE, INJECTION : Abnormal consistency; firm : 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]:

GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Atelectasis; regionally extensive, mild [LUNG : Focus; dark : 1, right cranial, right accessory, edge left (G) | LUNG : Focus; depressed : dark, 1, left (G)]
LUNG : Infiltration, mononuclear cell; perivascular, minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G) | SITE, INJECTION : Focus; dark : 4, right (G)]
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
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 21

5002158 - 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; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4508	Group: 4		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 96 ug/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)

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
KIDNEY : Infiltration, mononuclear cell; minimal : with fibrosis
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild [LYMPH NODE, POPLITEAL : Enlargement : Right. (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, mild
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SPINAL CORD, LUMBAR : Cyst; epithelial, mild, subdural space
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath
TRACHEA : Dilatation; submucosal, minimal, glandular

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; 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, THORACIC; STOMACH; THYMUS; TONGUE; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4509	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 96 ug/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 : 3, right (TGL)
LYMPH NODE, MANDIBULAR : 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]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 3, right (G)]

LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, moderate [LYMPH NODE, MANDIBULAR : Enlargement : Right (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, moderate
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
TRACHEA : Dilatation; submucosal, minimal, glandular
UTERUS : Dilatation; unilateral, moderate

Appendix 21

5002158 - 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; 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; SPLEEN; STOMACH; THYMUS; TONGUE; URINARY BLADDER; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4510	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 96 ug/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)
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 : Fibrosis; interstitial, minimal
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Tension lipidosis; minimal [LIVER : Focus; pale : 1, near hilus, right lateral. (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; moderate
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Plasmacytosis; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate, perinodal
NERVE, SCIATIC : Inflammation, mixed cell; perineurial, minimal
SITE, INJECTION : Inflammation, mixed cell; marked [SITE, INJECTION : Abnormal consistency; firm : Right. (G)]

SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SPLEEN : Decreased cellularity; minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4511	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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 : Enlargement : Left (TGL)
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]:

GLAND, HARDERIAN : Infiltration, mononuclear cell; minimal
GLAND, PITUITARY : Pars Distalis Available For Evaluation.
GLAND, PITUITARY : Examined
GLAND, THYROID : Hyperplasia; diffuse, mild, follicle [GLAND, THYROID : Enlargement : Left (G)]
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
MUSCLE, SKELETAL : Infiltration, mononuclear cell; minimal
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
URINARY BLADDER : Infiltration, mononuclear cell; minimal
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, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; 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; UTERUS; VAGINA

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4512	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
LARGE INTESTINE, RECTUM : Parasitism; nematode
LIVER : Vacuolation, microvesicular, periportal to midzonal; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, minimal
PANCREAS : Infiltration, mononuclear cell; minimal : with fibrosis
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal

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; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal: 4513	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 96 ug/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:

LUNG : Focus; dark : 1, right caudal (TGL)
LYMPH NODE, MANDIBULAR : 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, MAMMARY : Small portion of mammary glandular tissue on slide 18
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; minimal
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Congestion; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, right (G)]

LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, minimal
SITE, INJECTION : Infiltration, mononuclear cell; minimal
THYMUS : Hemorrhage; minimal
UTERUS : Infiltration, mononuclear cell; minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1, right caudal (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

5002158 - 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; LYMPH NODE, INGUINAL; 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; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4514	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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 : Discoloration; dark : Pancreatique (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 : Thyroglossal duct remnant, squamous epithelium; minimal
HEART : Murine progressive cardiomyopathy; minimal
LIVER : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Plasmacytosis; mild
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
LYMPH NODE, POPLITEAL : Infiltration, mononuclear cell; minimal, perinodal
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, mild
SITE, INJECTION : Degeneration/necrosis; minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; minimal
NO CORRELATE : No correlating lesion [LYMPH NODE : Discoloration; dark : Pancreatique (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; 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; VAGINA

Histo Pathology - The following Tissues were Not Examined:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

Animal:	4515	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 96 ug/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:

LUNG : Focus; pale : 1, 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]:

GLAND, MAMMARY : Vacuolation; epithelial, diffuse, moderate
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
GLAND, THYROID : Thyroglossal duct remnant, squamous epithelium; mild
LIVER : Vacuolation, microvesicular, periportal to midzonal; mild
LIVER : Infiltration, mixed cell; minimal
LUNG : Infiltration, mixed cell; minimal [LUNG : Focus; pale : 1, left lobe (G)]
LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, minimal
MUSCLE, SKELETAL : Infiltration, mononuclear cell; minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; perineurial, mild
PANCREAS : Infiltration, mononuclear cell; mild : with fibrosis
SITE, INJECTION : Infiltration, mononuclear cell; minimal
URINARY BLADDER : Accumulation; granular, minimal, transitional epithelium

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, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; 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; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

Appendix 21

5002158 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 22

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Toxicology/Pathology Department
200 Tech Square • Cambridge, MA 02139
Phone 617-714-6500 • Fax 617-583-1998

PEER-REVIEW STATEMENT

Study Number: 5002158

Study Title: A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

EXPERIMENTAL DESIGN:

Group No.	Test Material	Dose Level (µg/dose)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Article	0	200	0	10	10	5	5
2	mRNA-1443	10 / 9.6	200	0.05 / 0.048	10	10	-	-
3	mRNA-1443	30 / 29	200	0.15 / 0.145	10	10	-	-
4	mRNA-1443	100 / 96	200	0.5 /0.48	10	10	5	5

- : Not applicable
[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 30 May 2017.

PURPOSE: The purpose of this peer review was to assess the overall quality and consistency of the microscopic data and determine the validity of the study pathologist's conclusions.

METHODS:

1. Study plan and amendments, narrative pathology report, histology records, clinical observations, and organ weight data were reviewed
2. Review of all tissues from the Male and Female Groups 1 and Group 4, animal numbers: 1003, 1007, 1014, 1501, 1508, 1512, 4002, 4004, 4009, 4012, 4013, 4503, 4505, 4510, 4511 and 4515.
3. The following organs from all animals in all Groups were reviewed: Bone Marrow, Sciatic Nerve, Injection Site, Liver, Spleen and lymph node popliteal and inguinal.
4. In addition, Heart from animals 4008 and 4514, Eye from animals 4005 and 4006, Brain from animals 4001, Kidney from animals 1012 and 3002, Spleen from animal 1013 and Lung from animals 4007 and 4008.

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5. Following review of the histological sections and corresponding histopathology-related study data, findings were discussed with the study pathologist.

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RESULTS:

Differences of opinion were resolved and mutual agreement on terminology and diagnoses were achieved. The histopathology tables and corresponding narrative contained in the pathology report reflect diagnoses and conclusions agreed to by the peer reviewer and study pathologist

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

Date :
September 1 2017

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

15-SEP-2017
Date :