charles river

FINAL REPORT

Test Facility Study No. 5002231

A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
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USA

TEST FACILITY:
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QUALITY ASSURANCE STATEMENT

Study Number: 5002231

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

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
22-Mar-2017	Final Study Plan	23-Mar-2017	23-Mar-2017
28-Mar-2017	Study Plan Amendment 1	28-Mar-2017	28-Mar-2017
03-May-2017	Addition of Study Plan to Provantis	03-May-2017	03-May-2017
03-May-2017 - 04-May-2017	Dose Preparation	04-May-2017	04-May-2017
03-May-2017	Study Plan Amendment 2	03-May-2017	03-May-2017
04-May-2017	Dose Administration	04-May-2017	04-May-2017
04-May-2017	Body Temperature	04-May-2017	04-May-2017
01-Jun-2017	Necropsy	10-Aug-2017	10-Aug-2017
13-Jun-2017	Immunology	20-Jul-2017	20-Jul-2017
13-Jun-2017	Procedural Statement	20-Jul-2017	20-Jul-2017
20-Jun-2017	Study Plan Amendment 3	20-Jun-2017	20-Jun-2017
20-Jun-2017	Study Plan Amendment 4	20-Jun-2017	20-Jun-2017
27-Jun-2017	Study Plan Amendment 5	27-Jun-2017	27-Jun-2017
14-Jul-2017	Data Review - Bioanalysis & Immunology	17-Jul-2017	17-Jul-2017
14-Jul-2017	Final Phase Report - Immunology	17-Jul-2017	17-Jul-2017
02-Aug-2017 - 10-Aug-2017	Data Review - Animal Care	16-Aug-2017	16-Aug-2017
02-Aug-2017 - 10-Aug-2017	Draft Phase Report - Ophthalmology	16-Aug-2017	16-Aug-2017
02-Aug-2017 - 10-Aug-2017	Draft Report - Materials and Methods	16-Aug-2017	16-Aug-2017
02-Aug-2017 - 10-Aug-2017	Report Preparation	16-Aug-2017	16-Aug-2017
02-Aug-2017 - 10-Aug-2017	Data Review - Technical Operations	16-Aug-2017	16-Aug-2017
02-Aug-2017 - 10-Aug-2017	Data Review - Formulations	16-Aug-2017	16-Aug-2017
02-Aug-2017 - 10-Aug-2017	Data Review - Clinical Pathology	16-Aug-2017	16-Aug-2017
02-Aug-2017 - 10-Aug-2017	Data Review - Technical Operations	16-Aug-2017	16-Aug-2017
02-Aug-2017 - 10-Aug-2017	Data Review - Veterinary Services	16-Aug-2017	16-Aug-2017
02-Aug-2017 - 10-Aug-2017	Data Review - Shipping/Receiving	16-Aug-2017	16-Aug-2017
13-Aug-2017 15-Aug-2017	Data Review - Analytical Chemistry	16-Aug-2017	16-Aug-2017
13-Aug-2017 15-Aug-2017	Final Phase Report - Dose Formulation Analysis	16-Aug-2017	16-Aug-2017
28-Aug-2017	Data Review - Necropsy	29-Aug-2017	29-Aug-2017
28-Aug-2017 - 29-Aug-2017	Data Review - Histology	29-Aug-2017	29-Aug-2017

QUALITY ASSURANCE STATEMENT - Study Number: 5002231

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
28-Aug-2017	Data Review - Shipping/Receiving	29-Aug-2017	29-Aug-2017
29-Aug-2017	Report Preparation	29-Aug-2017	29-Aug-2017
29-Aug-2017	Draft Phase Report - Pathology	29-Aug-2017	29-Aug-2017
21-Sep-2017	Study Plan Amendment 6	21-Sep-2017	21-Sep-2017
25-Sep-2017	Study Plan Amendment 7	25-Sep-2017	25-Sep-2017
03-Nov-2017 - 06-Nov-2017	Final Report	07-Nov-2017	07-Nov-2017

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

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

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

30 Nov 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) and Japan (MHLW).

Exceptions from the above regulations are listed below.

- Characterization of the Test Item was performed by the 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 and anti-therapeutic antibody 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: 30 Nov 2017

1. RESPONSIBLE PERSONNEL

1.1. Test Facility

Study Director (b) (6)

Test Facility Management (b) (6)

1.2. Individual Scientists (IS) at Test Facility

Ophthalmology (b) (6)
Senneville, QC, Canada

Pathology (b) (6)
Charles River Laboratories Montreal ULC
Senneville, QC, Canada

Analytical Chemistry
(Concentration and Particle
Size Analysis) (b) (6)
Charles River Laboratories Montreal ULC
Senneville Site (CR MTL), QC, Canada

Immunology
(Purity Analysis) (b) (6)
Charles River Laboratories Montreal ULC
Senneville, QC, Canada

Biomarkers
(IL-1ß, IL-6, TNF-α,
IP-10, MIP-1-α, MCP-1) (b) (6)
Charles River Laboratories Montreal ULC
Senneville, QC, Canada

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

Anti-Drug
Antibody Analysis (ADA) (b) (6)
Integrated BioTherapeutics, Inc.
Rockville, MD, USA

2. SUMMARY

The objective of this study were to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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)	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-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

The following parameters and endpoints were evaluated in this study: clinical observations consisting of twice daily examinations for mortality/moribundity and weekly detailed examinations; detailed examination of the injection sites; weekly body weights and food consumption measurements; ophthalmic examinations; body temperature; clinical pathology assessment (hematology, coagulation, clinical chemistry) at termination; cytokine analysis (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1); Anti-Drug Antibody (ATA – antibody titer) analysis prior to dosing initiation and at termination; gross necropsy findings, organ weights, and histopathologic examinations.

On Day 30, following the last dose injection, all animals (with the exception of animal no.2001) were positive for antibodies against ZIKV lysate, showing a dose responsive increase. On Day 43, following the recovery period, animals dosed at 100 µg/dose showed higher response when compared to Day 30.

There were no mRNA-1706-related changes in food consumption and ophthalmology.

There were no unscheduled deaths during the course of this study.

The primary mRNA-1706-related findings were observed at the site of injection of animals given ≥ 10 µg/dose. A generally dose responsive increase in incidence and/or severity of swelling was noted at the injection site, following dose administration of both males and females. Extension of the injection site swelling to hindlimb and inguinal areas was also noted in animals given 100 µg/dose. In addition, skin redness at the injection site, was noted with a higher incidence throughout the dosing period for animals given ≥ 50 µg/dose. Macroscopically, the injection sites were characterized by firmness, swelling and occasionally by the presence of a clot in the thigh muscle used for the injection. These macroscopic findings were observed in males and females at all dose levels with no clear dose relationship and correlated histologically with inflammation and/or hemorrhage. In addition, enlargement of the draining lymph nodes (inguinal, popliteal and iliac) was observed in males and females at all dose levels with no evidence of dose relationship and correlated histologically with mixed cell infiltration. Clinical signs (i.e. swelling and redness of the skin) observed at the injection site and gross pathology findings as well as microscopic findings observed at the inguinal, iliac and popliteal lymph nodes

were no longer observed in recovery animals, indicating a complete to recovery for these changes and partial recovery for the findings at injection site.

mRNA-1706-related systemic changes associated with inflammation were also observed in animals given ≥ 10 µg/dose and included minimally increased cellularity of the myeloid lineage in the bone marrow. This change was likely a reactive response to the pronounced inflammation observed at the injection site. Other systemic findings included minimal to mild decreased lymphoid cellularity of the splenic periarteriolar lymphoid sheathand the paracortex of the mesenteric lymph node. In the liver, minimal to mild hypertrophy of the Kupffer cell was noted with occasional centrilobular degeneration characterized by the presence of mixed inflammatory cells in the sinusoid accompagnied by single cell necrosis or degeneration of hepatocytes. Clinical pathology changes suggestive of inflammation were also observed in males and/or females given mRNA-1706 at all doses (unless noted otherwise) and included: minimal to moderate increases in neutrophil, monocyte, eosinophil and large unstained cell counts with concomitant increases in white blood cell counts, minimal to moderate decreases in lymphocyte counts and platelet counts (females at ≥50 µg/dose), minimal increases in activated partial thromboplastin time and mild increases in fibrinogen, minimal increases in globulin, minimal decreases in albumin, with concomitant decreases in A/G ratio. Increase in body temperature postdose (≥ 50 µg/dose), along with elevations of cytokine levels IP-10, MIP-1α and MCP-1, were all suggestive of inflammation. All mRNA-1706-related systemic changes returned close to control values and, as such, were considered fully recovered.

Additional findings related to mRNA-1706 were observed in the adrenal glands of animals given ≥ 50 µg/dose and consisted of dose-related to minimal cortical hypertrophy and correlated with increased adrenal weights. This finding showed significance at 100 µg/dose. Single cell necrosis was also observed in the thymus. These findings were all fully recovered following the 2-week recovery period.

When compared to controls, following each dose, a tendency towards lower mean body weight gains was noted in males and females given ≥ 10 µg/dose; these changes sometimes reached statistical significance in both genders. From Day -1 to 28, the changes were down to 0.60X controls in males and 0.78X controls in females. The body weight changes were generally comparable or rebounded during the 2-week recovery period.

In conclusion, administration of mRNA-1706 by intramuscular injection for 1 month (3 doses) was clinically well tolerated (no mortality, no major decreases in body weight and no changes in food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 100 µg/dose. Starting at 10 µg/dose, generally dose-dependent changes in clinical signs at the injection site, clinical pathology parameters and cytokines were consistent with an inflammatory response at the injection site. Dose-related target organ effects were limited to the injection site, the bone marrow, the inguinal, mesenteric, iliac and popliteal lymph nodes, adrenal gland, liver, spleen and thymus of animals given mRNA-1706. At the end of the 2-week recovery period, all changes were fully recovered.

3. INTRODUCTION

The objectives of this study were to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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 Nonclinical Pharmacokinetic Studies*, *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 Nov 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

The Study Director signed the study plan on 15 Mar 2017, and dosing was initiated on 03 May 2017 (males) and 04 May 2017 (females). The in-life phase of the study was completed on 02 Jun 2017 (main animals) and 15 Jun 2017 (recovery animals); the last date of necropsy. The experimental start date was 16 Mar 2017, and the experimental completion date is 31 Oct 2017. The study plan, study plan amendments, and deviations are presented in Appendix 1.

4. MATERIALS AND METHODS

4.1. Test Item

Identification:	mRNA-1706
Batch (Lot) No.:	MTDP17036
Concentration:	2.1 mg/mL
Retest Date:	An end-of-use analysis of the bulk Test Item was performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanoparticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

4.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Supplier:	Life Technologies

Lot Number:	1854892
Expiration Date:	Dec 2018
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

4.3. Test and Reference Item Characterization

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

4.4. Analysis of Test Item

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

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

The second vial was transferred on ice pack to the molecular biology laboratory at the Test Facility for purity analysis.

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

4.5. Reserve Samples

For each batch (lot) of Test and Reference Item components, a reserve sample (1 mL or 1 vial) 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.

4.7. Dose Formulation and Analysis

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

4.7.1. Preparation of Reference Item

The Reference Item, Phosphate Buffered Saline pH 7.2, was dispensed on days of dosing (i.e. Days 1, 15 and 29) for administration to Group 1 control animals and as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots were transferred directly to room temperature.

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

4.7.2. Preparation of Test Item

Test Item dosing formulations were diluted with Phosphate Buffered Saline, pH 7.2, as necessary for administration. The dosing formulations were prepared on each days of dosing (i.e. Days 1, 15 and 29) and were transferred directly to room temperature.

Any residual volumes of formulated Test Item were stored in a refrigerator set at 4°C and were discarded prior to finalisation following approval by the Study Director.

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	Homogeneity	Concentration	Sampling From
Day 1[b]	2 to 4[a]	All groups	Preparation vessel
Day 29[b]	N/A	All groups	Preparation vessel

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 as soon as possible following preparation to the analytical laboratory (CR MTL).

4.7.3.1. Analytical Method

Analyses were performed by HPLC using a validated analytical procedure (Validation Study Number 1801737).

4.7.3.2. Concentration and Homogeneity Analysis

Duplicate sets of samples (0.5 mL) for each sampling time point 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 from the top, middle and bottom of the preparation vessel for each concentration except for Group 1 and on Day 29 (the last preparation of the study) where only concentration analysis was required; the formulation was then only sampled from the middle.

Concentration results were considered acceptable if mean sample concentration results were within or equal to ± 15% of theoretical concentration. Each individual sample concentration result was considered acceptable if it was within or equal to ± 20%.

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

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

4.7.3.3. Stability Analysis

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

4.8. Test System

4.8.1. Receipt

On 16 Mar 2017, one hundred and twenty-one Crl:CD(SD) Sprague-Dawley rats (61 males and 60 females) were received from Charles River Canada Inc., St. Constant, QC, Canada. At the dosing onset, animals were 13 weeks old and males weighed between 375 and 520 g and females weighed between 221 and 295 g.

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 48 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 were not assigned to groups.

No animal were replaced before or after the initiation of dosing.

All rats remaining unassigned to groups after Day 2 were released from the study and their disposition 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 throughout the study. The rooms in which the animals were kept were 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-treated 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 generally maintained. A 12-hour light/12-hour dark cycle was maintained (refer to Appendix 1 for one exception), except when interrupted for designated procedures.

4.8.6.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 (14% protein) was provided ad libitum throughout the study, except during designated procedures (refer to Appendix 1 for one exception). Wet pellets were provided to all animals of Group 4 as warranted by clinical signs.

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

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

4.8.6.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation was freely available to each animal via an automatic watering system (except during designated procedures) (refer to Appendix 1 for one exception). Water bottles were provided, when 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.

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.

Hydrotherapy was provided to Animal No. 4513 from Day 2 to 4, due to swollen at injection site. This treatment was considered necessary for the well-being of the animal.

All veterinary examinations and recommended therapeutic treatments were documented in the study records.

4.9. Experimental Design

Text Table 3
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animals No.			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	1001-1010	1501-1510	1011-1015	1511-1515
2	mRNA-1706	10	200	0.05	2001-2010	2501-2510	-	-
3	mRNA-1706	50	200	0.25	3001-3010	3501-3510	-	-
4	mRNA-1706	100	200	0.5	4001-4010	4501-4510	4011-4015	4511-4515

4.9.1. Administration of Test Materials

The Test and Reference Items were administered to the appropriate animals from Groups 1 to 4 via intramuscular injection into the lateral compartment of the thigh alternating legs on Days 1, 15 and 29 (site 1= left thigh, 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 have been clipped or shaved as required to improve visualization of the injection sites. The injection site was documented in the raw data for each dose administered.

4.9.2. Justification of Route and Dose Levels

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

The dose levels for this toxicology study were chosen to approximate a substantial multiple of the anticipated clinical starting dose and top clinical dose. The highest dose tested was expected to represent the intended maximum human clinical dose and volume and were 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 (refer to Appendix 1 for exceptions). 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 every two weeks during the predosing period and weekly during the dosing and recovery periods, starting Day -1.

In addition detailed examination of the injection sites was performed at predose, 24, 48 and 72 hours post each dose (refer to Appendix 1 for exceptions). Following Day 29 dosing, no assessment was performed on main study animals at 72 hours post dose as animals were sent to necropsy on Day 30. Any clinical signs at the injection site such as swelling, redness, vocalization upon palpation, warm to the touch, etc. were recorded as observed.

4.10.3. Body Weights

Animals were weighed individually every two weeks during the predosing period and weekly during the dosing and recovery periods, starting Day -1. A fasted weight was recorded on the day of necropsy.

4.10.4. Food Consumption

Food consumption was quantitatively measured weekly during the dosing and recovery periods, starting on Day -7.

4.10.5. Ophthalmic Examinations

Animals had funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations once prior to the dosing initiation (all animals) and on Day 23 for males and Day 22 for females of the dosing period. As there were no Test Item-related ophthalmoscopic findings at the end of the dosing period, examinations were not performed on recovery animals. The mydriatic used was 1% tropicamide.

4.10.6. Body Temperature

Rectal body temperature was recorded on un-sedated animals on Day 1 and on Day 29 at predose, 6 and 24 hours post dose (end of each group). Additional body temperature measurement was performed on all Group 4 female animals (Day 1) and on Animals Nos. 4511 to 4513 (Day 29) at 48 hours postdose since the 24 hours postdose values were significantly above normal range.

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
1 to 4[a]	Day 30	X	X	X
1 and 4	Day 43	X	X	X

[a] Samples were collected from animals sent to euthanasia on Day 30.

4.11.1.2. Hematology

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

Text Table 5
Hematology Parameters

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

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

4.11.1.3. Coagulation

Blood samples (target volume of 0.9 mL collected in a 1.0 mL tube containing citrate as anticoagulant) were processed for plasma, and plasma was analyzed for the parameters listed in Text Table 6.

Text Table 6
Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

4.11.1.4. Clinical Chemistry

Blood samples (target volume of 0.7 mL collected in 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	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine Kinase	Glucose
Total bilirubin	Cholesterol
Urea nitrogen	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphorus	Chloride
Sample Quality	

4.11.2. Cytokine Analysis

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

Text Table 8
Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation settings			(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	NAp	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 (processing)			CR-SHB	CR-SHB

X = Sample collected, NAp = 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 for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 were analyzed by the Biomarkers department at CR MTL. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 was 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.

A Biomarkers interpretative report (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) is included as an appendix to the Final Report.

4.11.3. Anti-Drug Antibody (ADA) Sample Collection, Processing and Analysis.

Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for recovery animals), blood was collected from all animals by jugular venipuncture and/or via the abdominal aorta while under isoflurane anesthesia (terminal samples).

Samples were mixed gently and allowed to clot at room temperature until centrifugation which was carried out as soon as practical (not exceeding 60 minutes after collection, refer to Appendix 1 for exceptions). 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. Samples were shipped on dry ice to Integrated BioTherapeutics, Inc., Rockville, MD, USA

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

Residual/retained samples were discarded prior issuance of the Final Report.

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

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[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	30	X	X	X	Full Tissue	Full Tissue
2	10	10					Full Tissue	Gross Lesions Target Tissues
3	10	10					Full Tissue	Gross Lesions Target Tissues
4	10	10					Full Tissue	Full Tissue
1	5	5	43	X	X	X	Full Tissue	Gross Lesions Target Tissues
4	5	5					Full Tissue	Gross Lesions Target Tissues

X = Procedure conducted; - = Not applicable.
[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 clinical pathology, anti-drug antibodies and cytokines 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 study and recovery animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

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

4.12.4. Organ Weights

The organs identified in Text Table 10 were weighed at necropsy for all scheduled euthanasia animals. Paired organs were weighed together. 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 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

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

[a] Preserved in Davidson's fixative.
[b] Preserved in Modified Davidson's fixative.

4.12.6. Histology

Tissues identified in Text Table 11 (except animal identification 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. The following target tissues identified by the study pathologist during microscopic evaluation were communicated to the study Director, evaluated and reported: gland adrenal, liver, spleen, injection site, lymph nodes (inguinal, popliteal and mesenteric), thymus and galt-associated lymphoid tissue.

4.12.8. Peer Review

A pathology peer review was conducted by (b) (6) from Moderna Therapeutics, Cambridge, MA, USA.

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

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

6. STATISTICAL ANALYSIS

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 predose or control values when deemed appropriate. Inferential statistics were performed according to the matrix below when possible, but excluded semi-quantitative data, and any group with less than 3 observations.

Text Table 12
Statistical Matrix

Variables for Inferential Analysis	Statistical Method Parametric/ Non-Parametric
Body Weight	X
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Organ Weights	X
Body Weight Changes	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 No.	Description of Data Collected and/or Analyzed
Provantis	8	In-life; clinical pathology; postmortem
Dispense	8	Test Material receipt, accountability and/or formulation activities
In-house reporting software Nevis 2012 (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 and 4.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Build 3471 SR1	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC and measurement of purity.
BioPlex Manager	6.1	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data collection
Watson LIMS	7.4.2 SP1	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data regression
Dynamics (Wyatt)	7.1.9.3.	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	1.1.0.11	Data acquisition
Excel	2007	Data analyses and tabulation
SRS (PCS-MTL in-house application built with SAS and SAS system for Windows)	1.4	Statistical analyses of cytokines

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 the Test Facility 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 Sponsor-designated subcontractors were returned to the Test Facility for archiving. Archival location and duration are detailed in the applicable PI report(s) or details regarding the retention of the materials were provided to the Study Director for inclusion in the Final Report.

9. RESULTS

9.1. Dose Formulation Analyses

(Appendix 3)

The dose formulations were within specification. Homogeneity testing showed that the formulation technique used produced homogeneous preparations.

In addition, the end of use bulk Test Item analysis demonstrated that the test item was suitable for use during the study period.

9.2. Mortality

(Appendix 4)

There were no unscheduled deaths during the course of this study.

9.3. Clinical Observations

(Table 1 and Appendix 5)

Following each dosing, warm to the touch was observed for females given 100 µg/dose. This observation was also noted following the second dose administration for males given 100 µg/dose and for females given 50 µg/dose. Those observations correlate with higher body temperature observed (Refer to Section 9.7)

During the dosing period, some females given 100 µg/dose were also observed with prominent backbone, thinness, hunched posture and suspected dehydration. Those observations were not observed during the recovery period.

Following each dosing occasions, a dose-related swelling (soft to firm) was noted on the injection site and extended to hindlimb and inguinal areas for some animals given 100 µg/dose. In addition, skin redness at the injection site, was noted with a higher incidence throughout the dosing period for animals given ≥ 50 µg/dose. Given the absence of swelling and redness at the injection site at the end of the recovery period, these clinical observations were considered fully reversed.

9.4. Body Weights and Body Weight Gains

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

When compared to controls, following each dose, a tendency towards lower mean body weight gains was noted in males and females given ≥ 10 µg/dose; these changes sometimes reached statistical significance in both genders. From Day -1 to 28, the changes were down to 0.60X controls in males and 0.78X controls in females. The body weight changes were generally comparable or rebounded during the 2-week recovery period.

9.5. Food Consumption

(Table 4 and Appendix 8)

Given the variability in weekly food consumption results, the occasional weekly changes, with no clear dose-relationship, were considered not mRNA-1706-related.

9.6. Ophthalmic Examinations

(Appendix 13)

There were no mRNA-1706-related ocular changes observed during the course of the study. The findings noted were age-related or incidental in origin and to be expected in this population of animals.

9.7. Body Temperature

(Table 5 and Appendix 9)

In general body temperatures were within normal ranges of 36-38°C. When compared to control animals and pre-dose body temperature measurements, the mean body temperature appeared minimally increased in males and females given ≥ 50 µg/dose at 6 and/or 24 hours post Day 1 and Day 29 doses. These statistically-significant changes were considered mRNA-1706-related.

9.8. Hematology

(Table 6 and Appendix 10)

mRNA-1706-related hematology changes were noted for males and females starting at 10 µg/dose and included increases in neutrophil (NEUT), monocytes (MONO), eosinophil (EOS) and/or large unstained cell (LUC) counts (with concomitant increases in white blood cell [WBC] counts) and decreases in lymphocyte (LYMPH), reticulocytes (RETIC) and platelet (PLT) counts. These changes are illustrated in Text Table 14.

Text Table 14
Hematology Changes

Dose (µg/dose)	10		50		100	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
WBC						
Day 30	**2.1**	**2.5**	**2.3**	**1.8**	**1.8**	0.90
Day 43					1.1	1.1
NEUT						
Day 30	**10.0**	**9.7**	**13.0**	**7.9**	**11.3**	4.0
Day 43					1.7	1.6
MONO						
Day 30	**2.0**	**1.8**	**2.1**	1.3	1.5	0.85
Day 43					1.5	1.2
LYMPH						
Day 30	0.78	0.97	**0.49**	**0.48**	**0.26**	**0.24**
Day 43					1.0	1.1
EOS						
Day 30	**3.0**	**6.5**	**2.3**	**3.8**	1.1	1.6
Day 43					0.86	0.96
LUC						
Day 30	**4.7**	**3.0**	**5.1**	**2.4**	3.0	1.3
Day 43					1.5	1.2
PLT						
Day 30	-	1.01	-	0.96	-	**0.80**
Day 43					-	1.1
RETIC						
Day 30	0.87	0.90	**0.80**	0.98	**0.72**	0.82
Day 43					**1.2**	1.2

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

Mild to moderate increases in WBC counts (up to 2.3X and 2.5X controls, respectively) were noted in males and females given ≥ 10 µg/dose, mainly due to minimal to moderate increases in NEUT, MONO, LUC, and EOS (up to 13.0X, 2.1X, 5.1X and 3.0X controls for males and 9.7X, 1.8X, 3.0X and 6.5X controls for females). Minimal to moderate dose-related decreases in LYMPH and RETIC counts were noted for males and females at ≥ 10 µg/dose (down to 0.26X and 0.24X controls, respectively). Increased observed in WBC, NEUT, MONO, LUC and EOS in animals given ≤ 50 µg/dose were followed by a decreased in the animals given 100 µg/dose. At the end of the recovery period, values for NEUT, MONO, LUC, were almost back to normal and LYMPH and RETIC values return to normal values.

Minimal dose-related decreases in PLT were noted in females given ≥ 50 µg/dose (down to 0.80X controls) with full recovery at the end of 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-1706-related.

9.9. Coagulation

(Table 7 and Appendix 11)

mRNA-1706-related increases in activated partial thromboplastin time (APTT) and in fibrinogen (FIB) were noted in males and females given ≥ 10 µg/dose. The changes are illustrated in Text Table 15.

Text Table 15
Coagulation Changes

Dose (µg/dose)	10		50		100	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
APTT						
Day 30	**1.2**	**1.2**	**1.2**	**1.4**	**1.3**	**1.4**
Day 43					1.0	1.0
FIB						
Day 30	**2.3**	**2.4**	**2.5**	**2.6**	**2.3**	**2.4**
Day 43					**0.9**	1.0

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

Minimal increases in APTT were noted for males and females given ≥ 10 µg/dose (up to 1.3X controls for males and 1.4X controls for females). Mild increases in FIB were noted for males and females given ≥ 10 µg/dose (up to 2.5X controls for males and 2.6X controls in females). At the end of the 2-week recovery period, changes were fully recovered.

Any other differences in the coagulation parameters were judged to be due to individual or biological variability or lacked true dose relationship and therefore were considered not mRNA-1706-related.

9.10. Clinical Chemistry

(Table 8 and Appendix 12)

mRNA-1706-related decreases in albumin (ALB) and increases in globulin (GLOB) were noted for males and females reflected by overall decrease in A/G ratio. Dose-related decrease in glucose concentration (GLUC) and increase in aspartate aminotransferase were also observed. The changes are illustrated in Text Table 16.

Text Table 16
Clinical Chemistry Changes

Dose (µg/dose)	10		50		100	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
ALB						
Day 30	**0.9**	**0.9**	**0.9**	0.9	**0.9**	**0.9**
Day 43					1.0	1.0
GLOB						
Day 30	**1.2**	**1.1**	**1.2**	1.1	**1.2**	1.0
Day 43					0.9	1.0
A/G						
Day 30	**0.8**	**0.8**	**0.8**	**0.8**	**0.8**	**0.8**
Day 43					1.1	1.0
GLUC						
Day 30	**0.8**	0.9	**0.8**	**0.8**	**0.7**	**0.7**
Day 43					1.0	**1.3**

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

Minimal decreases in ALB and minimal increases in GLOB were noted for males and females given ≥ 10 µg/dose (0.9X controls and up to 1.2X controls for each parameter) and affected the A/G ratio (down to 0.8X controls, for both genders). At the end of the 2-week recovery period, changes were fully recovered.

Minimal decreased in GLUC were noted for males and females given ≥ 10 µg/dose (down to 0.7X controls, for both genders). At the end of the recovery period, changes were fully recovered.

Increase in AST was observed for females given 100 µg/dose but is mainly related to the increase in AST level in female no.4501 and is not considered mRNA-1706-related.

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-1706-related.

9.11. Cytokines Analysis

(Appendix 14 and Appendix 15)

When compared to control, statistically-significant higher concentrations of IP-10 were observed in both genders given 100 µg/dose, high incidence and magnitude of change observed for males and females of higher dose group (100 µg/dose) were considered to be mRNA-1706-related.

Higher concentrations of MIP-1α and MCP-1 were also observed in both genders given 100 µg/dose. Concentrations were comparable to control levels on Day 43.

No mRNA-1706 changes were observed for IL-1β, TNF-α and IL-6.

All the mRNA-1706-related increases observed tent to be reversible.

9.12. Anti-Drug Antibody (ADA)

(Appendix 16)

The Day 30 samples from mRNA-1706-treated Main Study animals had detectable antibody responses against ZIKV lysate. The Day 43 samples from Recovery Study animals previously given 100 µg/dose had higher response when compared to Day 30 results.

9.13. Gross Pathology

(Appendix 17)

9.13.1. Terminal Euthanasia Animals (Day 30)

mRNA-1706-related gross pathology findings were observed in lymph nodes (iliac, inguinal, popliteal) and at the injection site and their incidences are summarized in Tox Table 17.

Text Table 17
Summary of Gross Pathology Findings – Scheduled Euthanasia (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**100**	**0**	**10**	**50**	**100**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injections (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Abnormal consistency; firm	0	8	9	9	0	4	9	9
Swelling	0	1	3	2	0	5	6	7
Material accumulation; clot	0	0	2	0	0	0	0	0
Lymph node[a] (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Enlargement	0	0	0	4	0	1	3	4
Lymph node, inguinal (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Enlargement	0	0	1	0	0	0	0	1
Lymph node, popliteal (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Enlargement	1	3	0	1	0	3	0	0

[a] Iliac left as documented in individual animals.

Macroscopic findings attributed to the administration of mRNA-1706 at the injection site were characterized by firmness, swelling and occasionally by the presence of a clot in the thigh muscle used for the injection. These macroscopic findings were observed in males and females at all dose levels with no clear dose relationship and correlated histologically with inflammation and/or hemorrhage.

In addition, enlargement of the draining lymph nodes (inguinal, popliteal and iliac) was observed in males and females at all dose levels with no evidence of dose relationship and correlated histologically with mixed cell infiltration.

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 reference and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

9.13.2. Recovery Euthanasia Animals (Day 43)

mRNA-1706-related gross findings noted at the terminal euthanasia in the injection site and draining lymph nodes were not observed at the end of the recovery period (Day 43). 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 reference and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

9.14. Organ Weights

(Appendix 17)

9.14.1. Terminal Euthanasia Animals (Day 30)

mRNA-1706-related organ weight changes were observed in the adrenal glands and are summarized in Text Table 18.

Text Table 18
Summary of Organ Weight Data – Scheduled Euthanasia (Day 30)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**10**	**50**	**100**	**10**	**50**	**100**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Gland, adrenal (No. Weighed)[a]	(10)	(10)	(10)	(10)	(10)	(10)
Absolute value	7	2	14	4	**13**	**21**
% of body weight	**15**	5	**27**	6	11	**23**
% of brain weight	7	-2	11	3	13	**24**

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

The group means for absolute and relative (to body and brain) weight of the adrenal were significantly higher in females given mRNA-1706 at 100 µg/dose compared to the concurrent reference. There was also a trend toward higher group means for absolute and relative (to body and brain) weight in males given mRNA-1706 at 100 µg/dose and females at 50 µg/dose but these values were statistically significant only in for absolute (females) or relative to body (males) weights. These increases of adrenal weights correlated histologically with cortical hypertrophy.

No other mRNA-1706-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective references. 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 terminal body weight and unrelated to administration of mRNA-1706.

9.14.2. Recovery Euthanasia Animals (Day 43)

mRNA-1706-related organ weight changes noted in the adrenal glands at the terminal euthanasia were not observed at the end of the recovery period (Day 43). There were isolated organ weight values that were statistically different from their respective references. 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 terminal body weight and unrelated to administration of mRNA-1706.

9.15. Histopathology

(Appendix 17)

9.15.1. Terminal Euthanasia Animals (Day 30)

mRNA-1706-related microscopic findings were observed at the injection site, in the draining lymph nodes (inguinal, popliteal, iliac), bone marrow, adrenal glands, liver, mesenteric lymph node, thymus and spleen and their incidence and severity are summarized in Text Table 19.

Text Table 19
Summary of Microscopic Findings – Scheduled Euthanasia (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**100**	**0**	**10**	**50**	**100**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Bone Marrow (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Increased cellularity; myeloid	(0)[a]	(5)	(6)	(7)	(0)	(3)	(5)	(8)
Minimal	0	5	6	7	0	3	5	8
Gland, Adrenal (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Hypertrophy; cortical	(0)[a]	(0)	(5)	(10)	(0)	(0)	(4)	(9)
Minimal	0	0	5	10	0	0	4	9
Liver (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Hypertrophy; Kupffer cell	(0)	(2)	(1)	(2)	(0)	(2)	(2)	(5)
Minimal	0	2	1	2	0	2	2	4
Mild	0	0	0	0	0	0	0	1
Degeneration/necrosis; centrilobular	(0)	(1)	(0)	(0)	(0)	(0)	(1)	(3)
Minimal	0	1	0	0	0	0	1	2
Mild	0	0	0	0	0	0	0	1
Lymph node; inguinal (No. Examined)	(10)	(9)	(8)	(10)	(10)	(10)	(10)	(10)
Infiltration, mixed cell	(0)	(0)	(1)	(1)	(0)	(0)	(1)	(5)
Minimal	0	0	1	1	0	0	1	4
Mild	0	0	0	0	0	0	0	1
Lymph node; popliteal (No. Examined)	(10)	(9)	(9)	(10)	(10)	(10)	(10)	(10)
Infiltration, mixed cell	(0)	(0)	(1)	(3)	(0)	(3)	(5)	(5)
Minimal	0	0	1	2	0	3	5	4
Mild	0	0	0	1	0	0	0	1
Lymph node[b] (No. Examined)	(0)	(0)	(0)	(4)	(0)	(1)	(3)	(4)
Infiltration, mixed cell	-	-	-	(4)	-	(1)	(3)	(4)
Minimal	-	-	-	1	-	1	1	0
Mild	-	-	-	2	-	0	2	3
Moderate	-	-	-	1	-	0	0	1
Lymph node; mesenteric (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Decreased cellularity; lymphoid, paracortex	(0)	(3)	(4)	(4)	(0)	(2)	(4)	(8)
Minimal	0	3	4	4	0	2	4	8

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**100**	**0**	**10**	**50**	**100**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injection (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Inflammation	(0)	(10)	(10)	(9)	(2)	(10)	(10)	(10)
Minimal	0	0	0	0	2	1	0	0
Mild	0	5	1	2	0	3	1	0
Moderate	0	5	6	4	0	6	3	2
Marked	0	0	3	3	0	0	6	8
Hemorrhage	(1)	(1)	(5)	(3)	(0)	(1)	(0)	(0)
Minimal	1	1	0	3	0	1	0	0
Mild	0	0	3	0	0	0	0	0
Moderate	0	0	2	0	0	0	0	0
Spleen (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Decreased cellularity; lymphoid, periarteriolar lymphoid sheath	(0)	(9)	(8)	(10)	(0)	(7)	(8)	(10)
Minimal	0	7	4	8	0	6	5	5
Mild	0	2	4	2	0	1	3	5
Single cell necrosis; lymphoid	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(6)
Minimal	0	0	0	1	0	0	0	6
Thymus (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Single cell necrosis; lymphoid	(0)	(0)	(3)	(3)	(0)	(0)	(0)	(8)
Minimal	0	0	3	3	0	0	0	6
Mild	0	0	0	0	0	0	0	2
Decreased cellularity; lymphoid	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Minimal	0	0	0	1	0	0	0	0

[a] Numbers in parentheses represent the number of animals with the finding.
[b] Iliac lymph node, examined only if gross abnormality observed.

At the injection site, the microscopic findings attributed to the administration of mRNA-1706 were minimal to marked inflammation and minimal to moderate hemorrhage. The inflammation was observed in males and females at all dose levels with no dose relationship between 50 µg/dose and 100 µg/dose but with lower severity of the findings at 10 µg/dose. It was characterized locally by extensive infiltration of mixed inflammatory cells, mainly granulocytes, with associated edema and fibrin exudates and correlated macroscopically with firmness of the thigh (abnormal consistency; firm). It was accompanied by mild to moderate hemorrhage (correlating macroscopically with material accumulation; clot) in some males at 50 µg/dose. This inflammatory process was not otherwise associated with degeneration of the muscle. Similar incidence and severity of minimal degeneration/necrosis of myofiber was observed in reference and mRNA-1706-dosed animals and was considered related to the experimental procedures (intramuscular injection).

In the inguinal, popliteal and iliac lymph nodes (considered as draining injection site), there was minimal to moderate mixed cell infiltration in males and/or females administered mRNA-1706 at all dose levels. The inflammatory infiltrate was composed of clusters of degenerated granulocytes in the lymph node sinuses or in the adjacent adipose/connective tissue.

A dose related minimal increase of myeloid cellularity was observed in the bone marrow of males and females at all dose levels.

In the adrenal glands, a dose related minimal cortical hypertrophy was present in males and females administered mRNA-1706 at ≥ 50 µg/dose and correlated with the increased adrenal weights.

In the liver, a low incidence of minimal to mild hypertrophy of the Kupffer cell was observed in males and females at all dose levels with no clear dose relationship. The hypertrophied Kupffer cells sometimes contained finely granular brownish pigment. In one male at 10 µg/dose, one female at 50 µg/dose and three females at 100 µg/dose, there was minimal to mild degeneration in the centrilobular region characterized by presence of mixed inflammatory cell in the sinusoid with single cell necrosis or degeneration of hepatocytes.

Microscopic findings similar in nature were observed in the spleen and mesenteric lymph nodes at all dose levels as well as in thymus at ≥ 50 µg/dose. They consisted of minimal to mild decreased lymphoid cellularity and/or single cell necrosis of lymphocyte. The decreased lymphoid cellularity was present in the periarteriolar sheath of the spleen, in the cortex of the thymus and in the paracortex of the mesenteric lymph node. In these areas, the lymphoid cells were less densely populated with prominent dendric cells. Single cell lymphoid necrosis was observed in the depleted region in these organs, mainly at 100 µg/dose.

After evaluation of all dose group animals, the GALT was no longer considered as a target organ.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in reference and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

9.15.2. Recovery Euthanasia Animals (Day 43)

Microscopic findings noted in the adrenal glands, bone marrow, lymph nodes (mesenteric, popliteal, inguinal), thymus, spleen and liver at the terminal euthanasia were not observed at the end of the recovery period (Day 43) and therefore, considered completely recovered.

At the injection site, the inflammation and hemorrhage present at the end of dosing were no longer observed but minimal mononuclear cell infiltration was noted in males and females at 100 µg/dose as well as in one control female. This microscopic finding was interpreted to result from the healing process from previous inflammation at the injection site. The incidence and severity are summarized in Text Table 20.

Text Table 20
Summary of Microscopic Findings – Scheduled Euthanasia (Day 43)

	Males		females	
Group	**1**	**4**	**1**	**4**
Dose (µg/dose)	**0**	**100**	**0**	**100**
No. Animals Examined	**5**	**5**	**5**	**5**
Site, injections (No. Examined)	(5)	(5)	(5)	(5)
Infiltration; mononuclear cell	(0)[a]	(5)	(1)	(2)
Minimal	0	5	1	2

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

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in reference and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

10. CONCLUSION

In conclusion, administration of mRNA-1706 by intramuscular injection for 1 month (3 doses) was clinically well tolerated (no mortality, major decreases in body weight and no changes in food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 100 µg/dose. Starting at 10 µg/dose, generally dose-dependent changes in clinical signs at the injection site, clinical pathology parameters and cytokines were consistent with an inflammatory response at the injection site. Dose-related target organ effects were limited to the injection site, the bone marrow, the inguinal, mesenteric, iliac and popliteal lymph nodes, adrenal gland, liver, spleen and thymus of animals given mRNA-1706. At the end of the 2-week recovery period, all changes were partially or fully recovered.

Figure 1

Summary of Body Weights - Males

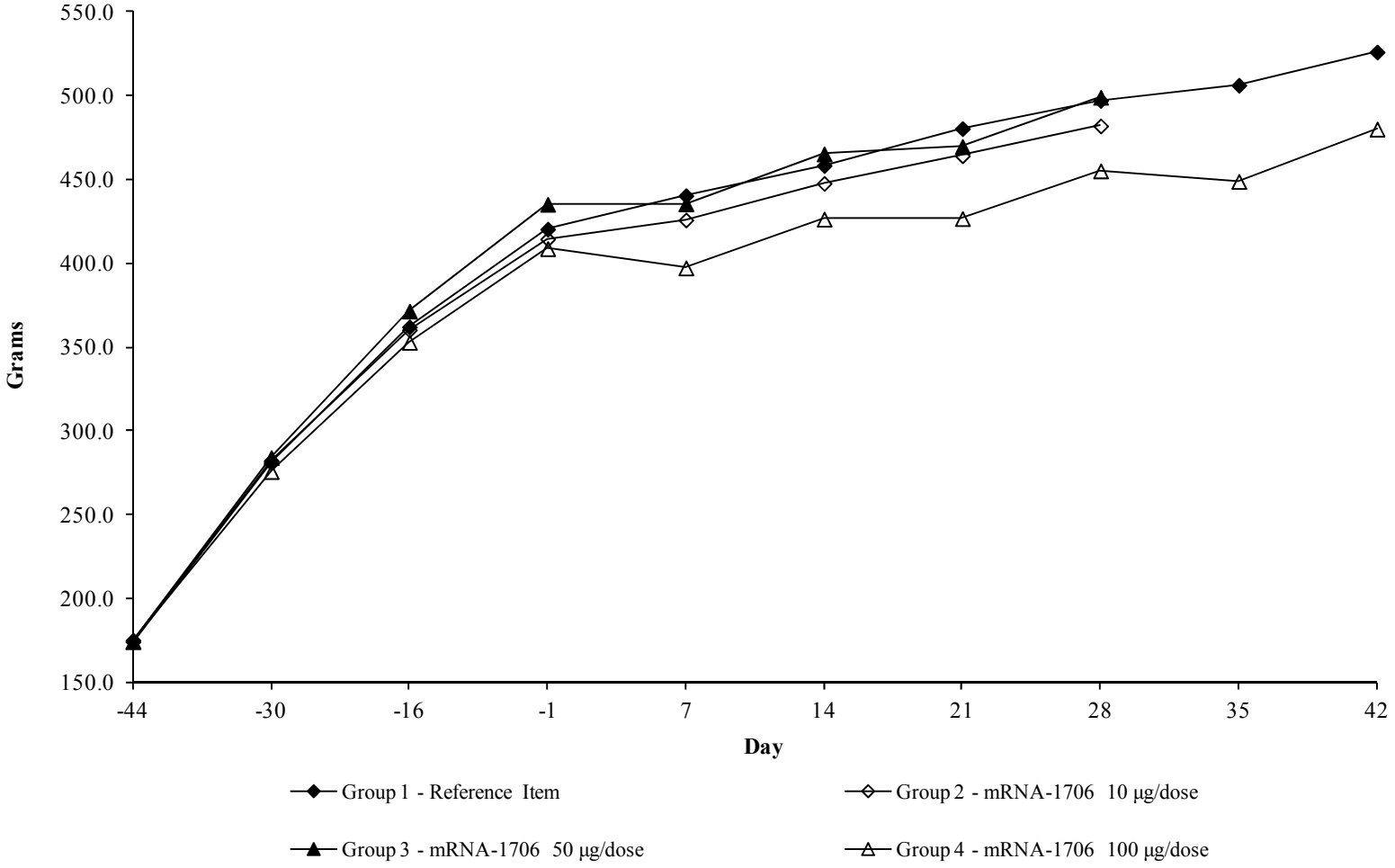

Figure 2

Summary of Body Weights - Females

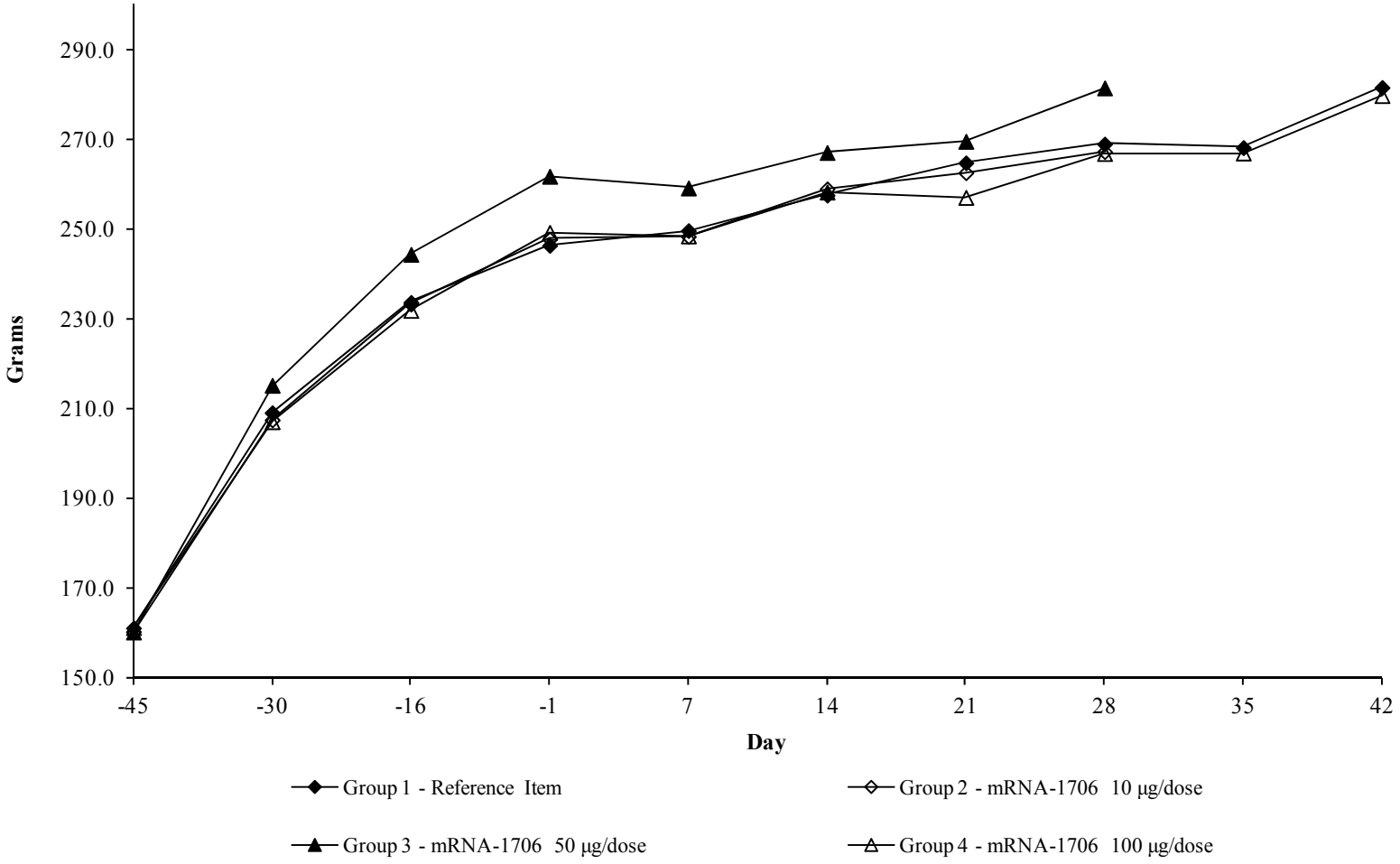

Table 1

Summary of Clinical Observations

5002231

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	10 ug/dose	50 ug/dose	100 ug/dose
Abnormal Gait				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	30 30
Hyperreactive				
Number of Observations	8	.	.	1
Number of Animals	2	.	.	1
Days from - to	-9 30	.	.	30 30
Vocalization Increased				
Number of Observations	7	.	1	1
Number of Animals	2	.	1	1
Days from - to	-1 30	.	2 2	30 30
Hunched Posture				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	30 30
Limited Usage				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	30 30
Swollen Soft				
Number of Observations	7	18	16	14
Number of Animals	7	10	10	6
Days from - to	16 16	16 30	16 30	2 32
Swollen Firm				
Number of Observations	.	15	49	95
Number of Animals	.	10	10	15
Days from - to	.	4 18	-37 30	2 30

Table 1

Summary of Clinical Observations

5002231

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	10 ug/dose	50 ug/dose	100 ug/dose
Warm to Touch				
Number of Observations	.	.	.	7
Number of Animals	.	.	.	6
Days from - to	.	.	.	15 17
Skin, Black				
Number of Observations	.	.	.	2
Number of Animals	.	.	.	1
Days from - to	.	.	.	-37 -23
Skin, Red				
Number of Observations	7	7	13	30
Number of Animals	5	4	9	13
Days from - to	2 14	3 17	-37 17	-48 30
Skin, Dry				
Number of Observations	.	2	.	.
Number of Animals	.	1	.	.
Days from - to	.	7 14	.	.
Skin, Scab				
Number of Observations	14	26	8	27
Number of Animals	5	10	7	11
Days from - to	-37 21	-37 30	-37 30	-48 30
Fur, Staining, Red				
Number of Observations	2	8	10	6
Number of Animals	2	4	5	4
Days from - to	14 28	-23 30	-9 30	-9 30
Fur, Thin Cover				
Number of Observations	11	28	21	24
Number of Animals	4	8	8	11
Days from - to	-37 14	-37 30	-37 30	-37 30

Table 1

Summary of Clinical Observations

5002231

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	10 ug/dose	50 ug/dose	100 ug/dose
Pinna Partly Missing				
Number of Observations	40	.	27	51
Number of Animals	2	.	2	3
Days from - to	-37 43	.	-37 30	-37 30
Tail, Missing				
Number of Observations	.	.	.	19
Number of Animals	.	.	.	1
Days from - to	.	.	.	-48 30

Table 1

Summary of Clinical Observations

5002231

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	10 ug/dose	50 ug/dose	100 ug/dose
Backbone Prominent				
Number of Observations	.	.	.	3
Number of Animals	.	.	.	3
Days from - to	.	.	.	2 30
Dehydrated Suspected				
Number of Observations	.	.	.	7
Number of Animals	.	.	.	6
Days from - to	.	.	.	2 30
Hunched Posture				
Number of Observations	.	.	.	5
Number of Animals	.	.	.	5
Days from - to	.	.	.	2 30
Limited Usage				
Number of Observations	.	.	1	20
Number of Animals	.	.	1	10
Days from - to	.	.	2 2	2 17
Swollen Soft				
Number of Observations	.	32	27	13
Number of Animals	.	10	10	6
Days from - to	.	16 30	16 30	3 32
Swollen Firm				
Number of Observations	.	13	39	104
Number of Animals	.	7	10	15
Days from - to	.	2 30	2 30	2 35
Thin				
Number of Observations	.	.	.	3
Number of Animals	.	.	.	3
Days from - to	.	.	.	2 30

Table 1

Summary of Clinical Observations

5002231

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	10 ug/dose	50 ug/dose	100 ug/dose
Warm to Touch				
Number of Observations	.	.	7	49
Number of Animals	.	.	6	14
Days from - to	.	.	16 17	2 31
Skin, Red				
Number of Observations	4	7	18	50
Number of Animals	3	4	8	14
Days from - to	-37 28	7 29	3 30	-1 32
Skin, Dry				
Number of Observations	.	4	.	.
Number of Animals	.	2	.	.
Days from - to	.	28 30	.	.
Skin, Scab				
Number of Observations	16	2	12	9
Number of Animals	6	2	5	3
Days from - to	-37 43	7 30	-1 30	2 43
Fur, Erected				
Number of Observations	.	.	.	2
Number of Animals	.	.	.	2
Days from - to	.	.	.	2 30
Fur, Staining, Red				
Number of Observations	25	13	3	19
Number of Animals	6	6	2	5
Days from - to	7 43	14 30	28 30	7 43
Fur, Thin Cover				
Number of Observations	30	11	28	37
Number of Animals	7	3	7	7
Days from - to	-9 43	-1 30	-1 30	-37 43

Table 1

Summary of Clinical Observations

5002231

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	10 ug/dose	50 ug/dose	100 ug/dose
Tail, Bent				
Number of Observations	.	.	.	7
Number of Animals	.	.	.	1
Days from - to	.	.	.	-37 3
Pinna Partly Missing				
Number of Observations	.	.	.	4
Number of Animals	.	.	.	1
Days from - to	.	.	.	21 30
Teeth, Clear				
Number of Observations	4	3	.	.
Number of Animals	2	1	.	.
Days from - to	-23 -9	-23 -1	.	.

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day -44	-30	-16	-1	7	14	21	28
1M	Mean	174.3	281.1	362.2	420.5	440.5	458.5	480.5	497.3
	SD	10.0	16.8	26.7	34.2	36.1	37.2	38.4	43.3
	N	15	15	15	15	15	15	15	15
2M	Mean	175.2	282.3	360.4	414.6	426.0	447.8	464.3	482.1
	SD	7.6	12.6	20.7	24.3	25.3	27.4	29.3	30.6
	N	10	10	10	10	10	10	10	10
	%Diff G1	0.5	0.4	-0.5	-1.4	-3.3	-2.3	-3.4	-3.1
3M	Mean	174.4	284.2	371.6	435.3	435.6	465.4	469.8	499.2
	SD	7.1	13.7	23.7	38.4	41.3	42.6	46.2	48.6
	N	10	10	10	10	10	10	10	10
	%Diff G1	0.1	1.1	2.6	3.5	-1.1	1.5	-2.2	0.4
4M	Mean	174.5	275.9	353.0	408.9	397.4b	426.5a	426.8c	455.3a
	SD	10.5	16.0	20.0	23.1	24.6	25.0	27.7	27.3
	N	15	15	15	15	15	15	15	15
	%Diff G1	0.1	-1.9	-2.5	-2.8	-9.8	-7.0	-11.2	-8.4

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

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day 35	Day 42
1M	Mean	506.4	526.2
	SD	22.6	24.1
	N	5	5
2M	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
3M	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
4M	Mean	449.0b	480.2a
	SD	16.4	19.3
	N	5	5
	%Diff G1	-11.3	-8.7

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

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day -45	-30	-16	-1	7	14	21	28
1F	Mean	161.1	209.1	233.7	246.4	249.7	257.6	264.8	269.0
	SD	8.0	12.7	12.4	14.3	17.3	17.3	18.7	16.3
	N	15	15	15	15	15	15	15	15
2F	Mean	160.3	207.5	233.3	247.8	248.4	259.0	262.6	267.3
	SD	4.5	11.8	9.7	10.1	9.9	12.8	10.0	8.5
	N	10	10	10	10	10	10	10	10
	%Diff G1	-0.5	-0.8	-0.2	0.6	-0.5	0.5	-0.8	-0.6
3F	Mean	160.2	215.2	244.4	261.8	259.2	267.1	269.6	281.5
	SD	4.9	8.1	14.4	17.8	16.5	18.6	19.6	17.2
	N	10	10	10	10	10	10	10	10
	%Diff G1	-0.5	2.9	4.6	6.3	3.8	3.7	1.8	4.6
4F	Mean	161.2	207.1	231.9	249.3	248.5	258.3	257.1	266.9
	SD	7.7	9.9	12.8	15.4	17.2	19.5	19.4	19.7
	N	15	15	15	15	15	15	15	15
	%Diff G1	0.1	-1.0	-0.7	1.2	-0.5	0.3	-2.9	-0.8

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day 35	Day 42
1F	Mean	268.2	281.6
	SD	15.0	13.2
	N	5	5
2F	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
3F	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
4F	Mean	267.0	279.8
	SD	11.6	13.4
	N	5	5
	%Diff G1	-0.4	-0.6

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day							
		Change -44 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change -1 - 28
1M	Mean	106.9	81.1	58.3	19.9	18.0	22.1	16.8	76.8
	SD	10.5	14.3	9.9	5.2	6.5	4.4	6.1	14.4
	N	15	15	15	15	15	15	15	15
2M	Mean	107.1	78.1	54.2	11.4e	21.8	16.5d	17.8	67.5
	SD	8.2	10.1	7.1	4.2	5.0	2.6	5.6	11.5
	N	10	10	10	10	10	10	10	10
3M	Mean	109.8	87.4	63.7	0.3f	29.8c	4.4f	29.4f	63.9d
	SD	10.5	12.8	15.1	5.7	3.1	5.4	5.4	12.4
	N	10	10	10	10	10	10	10	10
4M	Mean	101.4	77.1	55.9	-11.5f	29.1c	0.3f	28.5f	46.4f
	SD	7.1	7.5	6.6	6.2	3.2	4.8	6.1	8.3
	N	15	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 (Dunn)
d=p≤0.05,e=p≤0.01,f=p≤0.001 (Dunnett)

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day Change 28 - 35	Change 35 - 42	Change 28 - 42
1M	Mean	16.2	19.8	36.0
	SD	4.9	3.1	4.0
	N	5	5	5
2M	Mean	--	--	--
	SD	--	--	--
	N	--	--	--
3M	Mean	--	--	--
	SD	--	--	--
	N	--	--	--
4M	Mean	1.4b	31.2c	32.6
	SD	7.2	3.6	8.0
	N	5	5	5

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

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day							
		Change -45 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change -1 - 28
1F	Mean	48.1	24.5	12.7	3.3	7.9	7.2	4.2	22.6
	SD	12.5	5.8	6.9	7.8	5.2	7.2	6.7	6.3
	N	15	15	15	15	15	15	15	15
2F	Mean	47.2	25.8	14.5	0.6	10.6	3.6	4.7	19.5
	SD	8.6	7.0	4.9	4.6	9.1	4.9	5.5	6.9
	N	10	10	10	10	10	10	10	10
3F	Mean	55.0	29.2	17.4	-2.6	7.9	2.5	11.9b	19.7
	SD	7.5	8.2	6.6	6.6	5.2	7.8	5.3	5.7
	N	10	10	10	10	10	10	10	10
4F	Mean	45.9	24.9	17.3	-0.7	9.8	-1.3b	9.9a	17.7
	SD	7.9	5.8	5.1	7.1	5.1	6.5	4.4	11.1
	N	15	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-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day Change 28 - 35	Change 35 - 42	Change 28 - 42
1F	Mean	-0.4	13.4	13.0
	SD	5.0	3.0	4.0
	N	5	5	5
2F	Mean	--	--	--
	SD	--	--	--
	N	--	--	--
3F	Mean	--	--	--
	SD	--	--	--
	N	--	--	--
4F	Mean	-3.4	12.8	9.4
	SD	6.4	3.5	6.8
	N	5	5	5

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day (From/To)						
		-7/1	1/8	8/15	15/22	22/29	29/36	36/42
1M	Mean	29.87	28.84	30.93	30.12	29.99	27.32	29.28
	SD	1.79	1.92	1.84	1.97	1.85	0.16	0.16
	N	15	15	15	15	15	5	5
2M	Mean	28.16	26.11	29.07	27.32	28.37	--	--
	SD	1.64	1.17	1.09	1.17	1.14	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	-5.71	-9.47	-6.00	-9.30	-5.39	--	--
3M	Mean	29.98	25.44	30.06	25.52	30.30	--	--
	SD	2.34	2.19	2.08	2.13	2.06	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	0.38	-11.79	-2.80	-15.27	1.04	--	--
4M	Mean	28.69	22.42	33.55	29.14	33.25	27.72	34.80
	SD	1.60	1.49	2.01	2.47	1.78	1.75	1.37
	N	15	15	15	15	15	5	5
	%Diff G1	-3.93	-22.26	8.49	-3.25	10.89	1.46	18.85

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Day (From/To)						
		-7/1	1/8	8/15	15/22	22/29	29/36	36/42
1F	Mean	18.75	18.25	19.02	19.27	19.21	17.06	19.84
	SD	0.89	1.61	1.07	1.31	1.22	0.22	0.88
	N	15	15	15	15	15	5	5
2F	Mean	19.09	17.21	19.03	17.78	18.57	--	--
	SD	0.66	0.68	1.64	0.70	0.90	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	1.80	-5.72	0.05	-7.72	-3.35	--	--
3F	Mean	19.36	16.94	19.33	17.49	19.47	--	--
	SD	1.02	0.93	1.23	0.81	0.57	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	3.23	-7.20	1.63	-9.22	1.34	--	--
4F	Mean	19.75	18.44	25.15	21.81	24.74	21.76	26.24
	SD	1.59	2.62	1.89	2.31	1.92	0.33	0.05
	N	15	15	15	15	15	5	5
	%Diff G1	5.30	1.02	32.21	13.22	28.76	27.55	32.26

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1 (pr)	Day 1 (p)	Day 2	Day 29 (pr)	Day 29 (p)	Day 30
1M	Mean	37.36	37.50	36.52	36.28	37.06	36.65
	SD	0.38	0.53	0.11	0.78	0.44	0.40
	N	15	15	15	15	15	15
2M	Mean	36.97	37.97d	36.75	36.94	37.92f	37.60
	SD	0.49	0.47	0.81	0.87	0.39	0.66
	N	10	10	10	10	10	10
	%Diff G1	-1.04	1.25	0.63	1.82	2.32	2.58
3M	Mean	36.97	38.30f	37.54b	36.40	38.54f	38.70c
	SD	0.34	0.61	0.46	0.60	0.33	0.52
	N	10	10	10	10	10	10
	%Diff G1	-1.04	2.13	2.79	0.33	3.99	5.58
4M	Mean	37.09	38.73f	37.77c	36.81	38.66f	38.86c
	SD	0.50	0.25	0.69	0.51	0.41	0.34
	N	15	15	15	15	15	15
	%Diff G1	-0.71	3.29	3.43	1.45	4.32	6.02

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

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1 (pr)	Day 1 (p)	Day 2	Day 3	Day 29 (pr)	Day 29 (p)	Day 30
1F	Mean	38.58	37.83	37.03	--	38.19	37.01	37.39
	SD	0.44	0.76	0.49	--	0.81	0.87	0.65
	N	15	15	15	--	15	15	15
2F	Mean	38.51	38.36	37.72e	--	38.55	38.06a	38.25f
	SD	0.33	0.65	0.59	--	0.91	0.90	0.44
	N	10	10	10	--	10	10	10
	%Diff G1	-0.18	1.41	1.87	--	0.95	2.83	2.31
3F	Mean	37.88a	38.56	38.54f	--	37.85	38.16a	38.97f
	SD	0.51	0.63	0.38	--	1.04	0.42	0.39
	N	10	10	10	--	10	10	10
	%Diff G1	-1.81	1.94	4.09	--	-0.88	3.10	4.24
4F	Mean	38.06	39.15c	39.30f	37.85	38.04	38.69c	39.21f
	SD	0.64	0.37	0.53	0.45	0.89	0.50	0.41
	N	15	15	15	15	15	15	15
	%Diff G1	-1.35	3.51	6.14	--	-0.38	4.52	4.89

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

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 31
1F	Mean	--
	SD	--
	N	--
2F	Mean	--
	SD	--
	N	--
	%Diff G1	--
3F	Mean	--
	SD	--
	N	--
	%Diff G1	--
4F	Mean	37.40
	SD	0.44
	N	3
	%Diff G1	--

Table 6

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	7.084	0.991	5.814	0.149	0.084	0.008	0.041
	SD	2.122	0.239	1.935	0.040	0.036	0.007	0.021
	N	9	9	9	9	9	9	9
2M	Mean	15.186f	9.890a	4.528	0.305e	0.248f	0.017a	0.194c
	SD	1.821	1.833	0.641	0.106	0.067	0.008	0.108
	N	10	10	10	10	10	10	10
	%Diff G1	114.357	897.870	-22.125	104.851	193.684	118.571	371.892
3M	Mean	16.464f	12.879c	2.844b	0.320e	0.192d	0.016	0.208c
	SD	2.122	1.496	0.881	0.159	0.126	0.010	0.067
	N	10	10	10	10	10	10	10
	%Diff G1	132.396	1199.451	-51.087	114.925	127.368	105.714	405.946
4M	Mean	13.105f	11.159c	1.523c	0.217	0.092	0.008	0.122
	SD	2.661	2.391	0.610	0.085	0.080	0.004	0.037
	N	10	10	10	10	10	10	9
	%Diff G1	84.983	1025.908	-73.807	45.746	8.947	2.857	197.297

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 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	8.488	14.28	42.51	50.13	16.82	33.57	13.30
	SD	0.360	0.63	1.92	1.65	0.50	0.46	0.72
	N	9	9	9	9	9	9	9
2M	Mean	8.329	14.29	42.57	51.16	17.20	33.61	13.89
	SD	0.620	0.93	2.83	1.39	0.57	0.79	0.45
	N	10	10	10	10	10	10	10
	%Diff G1	-1.871	0.09	0.14	2.05	2.25	0.13	4.44
3M	Mean	8.638	14.80	44.18	51.20	17.18	33.55	14.56c
	SD	0.922	1.30	4.72	1.64	0.59	0.78	0.78
	N	10	10	10	10	10	10	10
	%Diff G1	1.770	3.66	3.93	2.13	2.13	-0.05	9.47
4M	Mean	8.600	15.06	44.74	52.03	17.50	33.62	14.44b
	SD	0.294	0.42	1.28	1.07	0.50	0.53	0.58
	N	10	10	10	10	10	10	10
	%Diff G1	1.322	5.48	5.24	3.78	4.03	0.16	8.57

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 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1168.0	235.01
	SD	104.9	27.53
	N	9	9
2M	Mean	1122.6	204.71
	SD	188.8	36.08
	N	10	10
	%Diff G1	-3.9	-12.89
3M	Mean	1033.2	188.54b
	SD	248.2	39.83
	N	10	10
	%Diff G1	-11.5	-19.77
4M	Mean	1100.6	169.55c
	SD	153.2	21.72
	N	10	10
	%Diff G1	-5.8	-27.85

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 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	4.257	0.715	3.373	0.084	0.049	0.004	0.035
	SD	1.366	0.490	0.903	0.052	0.009	0.005	0.029
	N	10	10	10	10	10	10	10
2F	Mean	10.775f	6.904c	3.288	0.147d	0.318c	0.010	0.104e
	SD	2.577	1.569	1.224	0.058	0.134	0.008	0.043
	N	10	10	10	10	10	10	10
	%Diff G1	153.113	865.594	-2.520	75.000	548.980	150.000	197.143
3F	Mean	7.632e	5.640c	1.611a	0.107	0.185b	0.005	0.083d
	SD	2.775	2.417	0.818	0.051	0.115	0.005	0.053
	N	10	10	10	10	10	10	10
	%Diff G1	79.281	688.811	-52.238	27.381	277.551	25.000	137.143
4F	Mean	3.844	2.829	0.820c	0.071	0.080	0.000	0.046
	SD	2.201	1.908	0.333	0.049	0.047	0.000	0.040
	N	10	10	10	10	10	10	9
	%Diff G1	-9.702	295.664	-75.689	-15.476	63.265	-100.000	30.159

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 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.536	13.44	38.98	51.73	17.81	34.45	11.51
	SD	0.278	0.45	0.96	1.30	0.60	0.56	0.49
	N	10	10	10	10	10	10	10
2F	Mean	7.702	13.64	39.61	51.49	17.72	34.42	12.16a
	SD	0.399	0.52	1.35	1.32	0.41	0.27	0.30
	N	10	10	10	10	10	10	10
	%Diff G1	2.203	1.49	1.62	-0.46	-0.51	-0.09	5.65
3F	Mean	8.107b	14.38b	41.90b	51.72	17.75	34.34	12.77c
	SD	0.466	0.71	1.94	1.50	0.56	0.38	0.41
	N	10	10	10	10	10	10	10
	%Diff G1	7.577	6.99	7.49	-0.02	-0.34	-0.32	10.95
4F	Mean	8.294c	14.87c	43.50c	52.47	17.95	34.18	13.01c
	SD	0.430	0.74	2.41	0.85	0.27	0.48	0.69
	N	10	10	10	10	10	10	10
	%Diff G1	10.058	10.64	11.60	1.43	0.79	-0.78	13.03

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 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1123.4	170.35
	SD	83.9	41.20
	N	10	10
2F	Mean	1132.7	152.85
	SD	211.3	26.33
	N	10	10
	%Diff G1	0.8	-10.27
3F	Mean	1081.1	166.54
	SD	178.1	23.41
	N	10	10
	%Diff G1	-3.8	-2.24
4F	Mean	902.5b	139.73
	SD	56.0	26.78
	N	10	10
	%Diff G1	-19.7	-17.97

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 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	7.672	1.184	6.160	0.162	0.086	0.012	0.064
	SD	2.094	0.394	1.925	0.053	0.021	0.004	0.011
	N	5	5	5	5	5	5	5
4M	Mean	8.658	1.966	6.276	0.238	0.074	0.008	0.094
	SD	0.939	0.945	0.607	0.055	0.017	0.004	0.032
	N	5	5	5	5	5	5	5
	%Diff G1	12.852	66.047	1.883	46.914	-13.953	-33.333	46.875

Table 6

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	8.070	13.90	41.98	52.02	17.22	33.12	12.96
	SD	0.099	0.12	0.43	0.66	0.24	0.31	0.53
	N	5	5	5	5	5	5	5
4M	Mean	7.782	13.66	41.48	53.36	17.56	32.88	15.04b
	SD	0.402	0.47	1.63	1.57	0.59	0.30	0.79
	N	5	5	5	5	5	5	5
	%Diff G1	-3.569	-1.73	-1.19	2.58	1.97	-0.72	16.05

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 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1221.6	224.28
	SD	104.7	33.57
	N	5	5
4M	Mean	1251.6	272.36a
	SD	132.3	22.30
	N	5	5
	%Diff G1	2.5	21.44

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 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	4.772	0.754	3.786	0.130	0.050	0.002	0.054
	SD	1.455	0.221	1.206	0.070	0.010	0.004	0.028
	N	5	5	5	5	5	5	5
4F	Mean	5.442	1.186	3.988	0.152	0.048	0.006	0.064
	SD	1.855	0.552	1.327	0.083	0.015	0.005	0.029
	N	5	5	5	5	5	5	5
	%Diff G1	14.040	57.294	5.335	16.923	-4.000	200.000	18.519

Table 6

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.172	12.82	37.82	52.74	17.86	33.90	11.52
	SD	0.329	0.60	1.81	0.34	0.34	0.83	0.19
	N	5	5	5	5	5	5	5
4F	Mean	6.762	12.24	36.60	54.18	18.08	33.44	13.12c
	SD	0.291	0.40	1.03	1.54	0.39	0.29	0.31
	N	5	5	5	5	5	5	5
	%Diff G1	-5.717	-4.52	-3.23	2.73	1.23	-1.36	13.89

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 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1111.0	170.62
	SD	102.5	21.23
	N	5	5
4F	Mean	1174.8	198.28
	SD	116.2	31.31
	N	5	5
	%Diff G1	5.7	16.21

Table 7

Summary of Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	17.20	15.07	280.2
	SD	0.78	0.55	21.9
	N	10	10	10
2M	Mean	16.06e	17.44f	656.2b
	SD	0.74	0.80	94.8
	N	10	10	10
	%Diff G1	-6.63	15.73	134.2
3M	Mean	16.44	18.15f	686.5c
	SD	0.79	1.36	87.6
	N	10	10	10
	%Diff G1	-4.42	20.44	145.0
4M	Mean	16.53	19.06f	652.8c
	SD	0.88	0.96	54.9
	N	10	10	10
	%Diff G1	-3.90	26.48	133.0

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 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.86	14.94	188.1
	SD	0.59	0.65	16.0
	N	10	10	10
2F	Mean	17.22	18.64f	454.1b
	SD	0.54	0.86	38.7
	N	9	9	9
	%Diff G1	-3.57	24.80	141.4
3F	Mean	18.11	20.31f	483.6c
	SD	1.20	1.71	37.5
	N	10	10	10
	%Diff G1	1.40	35.94	157.1
4F	Mean	19.73	20.77f	446.1c
	SD	2.13	1.60	92.1
	N	10	10	10
	%Diff G1	10.47	39.02	137.2

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 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	17.08	14.14	273.8
	SD	0.86	0.47	13.7
	N	5	5	5
4M	Mean	17.96	14.60	249.8a
	SD	0.34	0.66	15.4
	N	5	5	5
	%Diff G1	5.15	3.25	-8.8

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

Table 7

Summary of Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.34	15.34	160.8
	SD	0.23	0.85	17.0
	N	5	5	5
4F	Mean	17.80	14.82	162.4
	SD	0.73	1.20	20.5
	N	5	5	5
	%Diff G1	2.65	-3.39	1.0

Table 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	88.8	39.4	96.2	2.0	356.0	0.065	16.5
	SD	23.9	5.9	22.7	0.0	216.2	0.015	3.2
	N	10	10	10	10	9	10	10
2M	Mean	96.0	37.1	88.8	2.0	499.3	0.077	18.6
	SD	23.5	3.9	16.4	0.0	301.4	0.030	2.9
	N	10	10	10	10	10	10	10
	%Diff G1	8.1	-5.8	-7.7	0.0	40.3	18.462	12.7
3M	Mean	107.1	42.8	120.6	2.0	567.9	0.089	16.9
	SD	33.3	8.9	28.3	0.0	438.7	0.016	3.2
	N	10	10	10	10	10	10	10
	%Diff G1	20.6	8.6	25.4	0.0	59.5	36.923	2.4
4M	Mean	116.7	42.4	130.1b	2.0	618.7	0.078	15.9
	SD	32.9	7.0	23.9	0.0	527.7	0.021	2.6
	N	10	10	10	10	9	10	10
	%Diff G1	31.4	7.6	35.2	0.0	73.8	20.000	-3.6

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 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	203.9	67.6	72.4	6.17	3.80	2.37
	SD	0.04	25.0	11.5	26.1	0.23	0.15	0.28
	N	10	10	10	10	10	10	10
2M	Mean	0.42	170.0e	79.5	49.1	6.26	3.48f	2.78e
	SD	0.04	26.4	20.2	12.7	0.26	0.10	0.21
	N	10	10	10	10	10	10	10
	%Diff G1	10.53	-16.6	17.6	-32.2	1.46	-8.42	17.30
3M	Mean	0.45a	163.3f	82.5	69.4	6.30	3.47f	2.83f
	SD	0.05	20.2	18.8	35.8	0.33	0.18	0.28
	N	10	10	10	10	10	10	10
	%Diff G1	18.42	-19.9	22.0	-4.1	2.11	-8.68	19.41
4M	Mean	0.45a	148.0f	78.9	58.2	6.18	3.43f	2.75e
	SD	0.05	16.9	21.6	18.1	0.23	0.08	0.25
	N	10	10	10	10	10	10	10
	%Diff G1	18.42	-27.4	16.7	-19.6	0.16	-9.74	16.03

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 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.63	10.58	6.59	141.2	5.13	100.8
	SD	0.23	0.44	0.45	1.2	0.29	1.4
	N	10	10	10	10	10	10
2M	Mean	1.27b	10.73	7.27d	140.4	5.23	99.6
	SD	0.11	0.31	0.53	0.8	0.31	1.2
	N	10	10	10	10	10	10
	%Diff G1	-22.09	1.42	10.32	-0.6	1.95	-1.2
3M	Mean	1.24b	10.65	7.61e	140.3	5.61e	99.7
	SD	0.13	0.43	0.64	1.9	0.27	2.4
	N	10	10	10	10	10	10
	%Diff G1	-23.93	0.66	15.48	-0.6	9.36	-1.1
4M	Mean	1.26b	10.37	7.52e	140.9	5.57e	100.8
	SD	0.13	0.44	0.75	1.8	0.31	2.0
	N	10	10	10	10	10	10
	%Diff G1	-22.70	-1.98	14.11	-0.2	8.58	0.0

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 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	138.4	59.6	54.5	2.0	333.1	0.056	14.2
	SD	157.7	78.6	12.3	0.0	241.9	0.024	2.4
	N	10	10	10	10	10	10	10
2F	Mean	95.2	37.0	67.5	2.0	397.4	0.065	20.3c
	SD	16.7	8.1	14.2	0.0	251.7	0.021	3.7
	N	10	10	10	10	10	10	10
	%Diff G1	-31.2	-37.9	23.9	0.0	19.3	16.071	43.0
3F	Mean	152.6	50.9	73.0a	2.0	465.7	0.085a	15.5
	SD	129.1	21.9	16.1	0.0	429.0	0.030	2.9
	N	10	10	10	10	10	10	10
	%Diff G1	10.3	-14.6	33.9	0.0	39.8	51.786	9.2
4F	Mean	214.0	61.4	88.6c	2.0	258.5	0.082	15.7
	SD	206.5	31.3	14.2	0.0	154.7	0.021	4.0
	N	10	10	10	10	10	10	10
	%Diff G1	54.6	3.0	62.6	0.0	-22.4	46.429	10.6

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 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	0.43	188.1	74.1	46.4	6.61	4.48	2.13
	SD	0.05	29.2	15.7	15.1	0.34	0.27	0.25
	N	10	10	10	10	10	10	10
2F	Mean	0.45	173.2	78.9	48.4	6.45	4.05b	2.40d
	SD	0.05	21.8	11.3	17.8	0.22	0.05	0.21
	N	10	10	10	10	10	10	10
	%Diff G1	4.65	-7.9	6.5	4.3	-2.42	-9.60	12.68
3F	Mean	0.45	145.4f	79.9	55.9	6.49	4.14	2.35
	SD	0.05	20.6	20.8	18.2	0.53	0.37	0.20
	N	10	10	10	10	10	10	10
	%Diff G1	4.65	-22.7	7.8	20.5	-1.82	-7.59	10.33
4F	Mean	0.44	135.3f	64.6	49.5	6.00e	3.82c	2.18
	SD	0.05	16.8	24.2	25.7	0.44	0.36	0.22
	N	10	10	10	10	10	10	10
	%Diff G1	2.33	-28.1	-12.8	6.7	-9.23	-14.73	2.35

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 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.14	10.77	6.31	142.5	4.49	103.5
	SD	0.33	0.37	0.91	1.5	0.24	2.0
	N	10	10	10	10	10	10
2F	Mean	1.68c	10.86	6.37	141.0d	4.90	101.4
	SD	0.16	0.15	0.76	0.9	0.31	1.6
	N	10	10	10	10	10	10
	%Diff G1	-21.50	0.84	0.95	-1.1	9.13	-2.0
3F	Mean	1.77a	10.80	7.76e	141.9	4.82	101.2
	SD	0.11	0.38	0.92	1.2	0.48	1.8
	N	10	10	10	10	10	10
	%Diff G1	-17.29	0.28	22.98	-0.4	7.35	-2.2
4F	Mean	1.77a	10.32e	7.47e	140.0f	4.64	101.9
	SD	0.23	0.30	0.72	1.2	0.31	2.5
	N	10	10	10	10	10	10
	%Diff G1	-17.29	-4.18	18.38	-1.8	3.34	-1.5

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 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	91.0	43.4	88.4	2.0	445.6	0.058	14.4
	SD	22.2	6.6	17.5	0.0	297.8	0.013	1.9
	N	5	5	5	5	5	5	5
4M	Mean	84.4	37.4	90.6	2.0	355.2	0.058	13.8
	SD	22.6	6.2	5.2	0.0	298.5	0.004	1.8
	N	5	5	5	5	5	5	5
	%Diff G1	-7.3	-13.8	2.5	0.0	-20.3	0.000	-4.2

Table 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	0.32	219.0	91.8	73.0	6.12	3.72	2.40
	SD	0.04	42.4	19.1	14.3	0.23	0.18	0.12
	N	5	5	5	5	5	5	5
4M	Mean	0.36	221.0	65.4a	59.4	5.98	3.76	2.22
	SD	0.05	70.0	13.3	7.5	0.22	0.11	0.20
	N	5	5	5	5	5	5	5
	%Diff G1	12.50	0.9	-28.8	-18.6	-2.29	1.08	-7.50

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 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.56	10.66	7.24	139.2	5.04	101.2
	SD	0.11	0.13	0.56	1.6	0.30	1.5
	N	5	5	5	5	5	5
4M	Mean	1.70	10.44	7.72	139.2	5.28	101.6
	SD	0.20	0.25	0.15	1.9	0.47	1.7
	N	5	5	5	5	5	5
	%Diff G1	8.97	-2.06	6.63	0.0	4.76	0.4

Table 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	120.2	47.8	73.6	2.0	709.0	0.050	17.2
	SD	15.4	5.0	23.4	0.0	273.7	0.012	2.2
	N	5	5	5	5	5	5	5
4F	Mean	83.8b	42.6	71.0	2.0	216.8b	0.036	14.8
	SD	17.1	8.4	9.6	0.0	113.5	0.026	0.8
	N	5	5	5	5	5	5	5
	%Diff G1	-30.3	-10.9	-3.5	0.0	-69.4	-28.000	-14.0

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

Table 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	0.46	173.0	72.8	54.2	6.50	4.50	2.00
	SD	0.09	26.6	20.5	14.3	0.36	0.29	0.16
	N	5	5	5	5	5	5	5
4F	Mean	0.36	217.0a	73.2	59.4	6.30	4.30	2.00
	SD	0.05	23.9	20.6	20.1	0.32	0.23	0.20
	N	5	5	5	5	5	5	5
	%Diff G1	-21.74	25.4	0.5	9.6	-3.08	-4.44	0.00

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 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.26	10.18	6.76	140.0	4.54	102.4
	SD	0.24	0.18	1.07	0.7	0.28	1.8
	N	5	5	5	5	5	5
4F	Mean	2.16	10.38	7.16	139.4	4.76	103.0
	SD	0.27	0.23	0.87	1.1	0.29	1.0
	N	5	5	5	5	5	5
	%Diff G1	-4.42	1.96	5.92	-0.4	4.85	0.6

Appendix 1

FINAL STUDY PLAN

Test Facility Study No. 5002231

A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With 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

15 March 2017

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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:	15 Mar 2017 (First date of study-specific data collection)
Experimental Completion Date:	18 Aug 2017 (Last date data are collected from the study)
Animal Arrival:	15 Mar 2017
Initiation of Dosing:	27 Mar 2017
Completion of In-life:	26 Apr 2017 (main study animals) 09 May 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	06 Jul 2017
Draft Report:	11 Aug 2017
Final Report:	18 Aug 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, *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 and anti-therapeutic antibody 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
22022 Transcanadienne
Senneville Quebec
Canada H9X 3R3
Tel: (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)

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Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)
Fax: (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)
Pathology	To be included by amendment
Analytical Chemistry (Concentration and Particle Size Analysis)	(b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Immunology (Purity Analysis)	(b) (6) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Immunology (Cytokines)	(b) (6) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)

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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

PI at Sponsor-designated Test Site

Anti-Therapeutic
Antibody Analysis (ATA) (b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (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-1706
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17025
Concentration:	To be included by amendment
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle 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 and Reference 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.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Item components, a reserve sample (1 mL, 100 mg or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

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8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned to the Sponsor

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 pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15 and 29) for administration to Group 1 control animals and 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 dosing formulations will be diluted with Phosphate Buffered Saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15 and 29) 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.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and will be discarded prior to finalisation following approval by the Study Director.

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10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

Interval	Homogeneity	Concentration	Sampling From
Day 1[b]	All groups[a]	All groups	Preparation vessel
Day 29[b]	N/A	All groups	Preparation vessel

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 preparation.

All samples to be analyzed will be transferred on ice packs to the analytical laboratory (CR-MTL).

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 HPLC using a validated analytical procedure (Validation Study Number 1801997).

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 (duplicate 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 containers.
Sample Volume:	0.5 mL for analysis and backup samples
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for

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acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study.

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 and weight of animals received will be listed in the Final Report.

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.

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

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

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

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

The alternate animals may be used as replacements on the study within 1 day.

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

12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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

12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.5	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals from Groups 1 to 4 via intramuscular injection into the lateral compartment of the thigh alternating legs on Days 1, 15 and 29 (site 1= left thigh, 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 will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. 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

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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 2 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 29 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 30.
Procedure:	All animals will have the dose injection site examined for signs of erythema/edema. The Local Irritation Assessment scoring will be performed as follows:

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Erythema (Redness)	Score
No erythema	0
Very slight erythema	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	1
Slight edema	2
Moderate edema	3
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 2 weeks during the prestudy 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 at the end 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 1% tropicamide.

Evaluation: A report will be included as an appendix to the Final Report.

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14.7. Body Temperature

Frequency: On Day 1 and Day 29 at predose, 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0C to 38.0C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes, measurement may be taken at the discretion of the Study Director.

Procedure: Body temperature will be recorded via subcutaneous implanted transponder.

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
1-4[a]	Day 30	X	X	X
1 to 4	Day 43	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X

X = Samples to be collected
a Samples will only be collected from those animals scheduled for euthanasia on Day 30.

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

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Hematology Parameters

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

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.

15.1.3. Coagulation

Target Volume: 0.9 mL (in a 1.0 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Clinical Chemistry Parameters

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

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

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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 (ATTACHMENT A).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. 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 settings			(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	NAp	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, NAp = 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 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.

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

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

15.3. Anti-drug Antibody (ADA) Sample Collection, Processing, and Analysis

Blood will be collected from all animals by jugular venipuncture and/or via the abdominal aorta while under isoflurane anesthesia (terminal and unscheduled samples).

Time Points:	Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for 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 (not exceeding 60 minutes after collection). The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the 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.

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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[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	30	X	X	X	Full Tissue	Full Tissue
2	10	10					Full Tissue	Gross Lesions Target Tissues
3	10	10					Full Tissue	Gross Lesions Target Tissues
4	10	10					Full Tissue	Full Tissue
1	5	5	43	X	X	X	Full Tissue	Gross Lesions Target Tissues
4	5	5					Full Tissue	Gross Lesions Target Tissues
Unscheduled Deaths				X	X	-	Full Tissue	Full Tissue
Replaced animals (prestudy)				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.

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis 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 necropsy, 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 necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy 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 clinical pathology, anti-drug antibodies and cytokines 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 study 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 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 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
Organ Weights	X
Body Weight Changes	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.

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

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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. Data regression analysis and measurement of purity.
BioPlex Manager	Cytokine data collection and regression
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
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

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 a CR-MTL archives. At least one year after issue of the draft report, the Sponsor will be contacted.

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 and cytokine sample collection and evaluation
- Anti-drug Antibodies sample collection
- 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) _____ Date: 15 March 2017

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

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

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SPONSOR APPROVAL

The Study Plan was approved by the Sponsor by email on 15 March 2017. The signature below confirms the approval of the Study Plan by the Sponsor Representative

(b) (6) _____ Date: 29Nov17

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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	-	-	-
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	-
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for 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 01

Test Facility Study No. 5002231

A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With 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: 15 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: 27-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To include new schedule following delay in dosing initiation due to test item delivery date.
10.3.Sample Collection and Analysis	To remove homogeneity for Group 1 based on sample collection in section 10.3.1.1.
10.3.1. Analytical Method	To correct the dose formulation analysis validation number.
10.3.1.2. Stability Analysis	To include end of use for bulk test item.
13. EXPERIMENTAL DESIGN	To correct the dose concentration for mid dose group.
15.1.1. Sample Collection	To correct the group numbers to be evaluation on both occasions.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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:	~~**15**~~ **16** Mar 2017 (First date of study-specific data collection)
Experimental Completion Date:	~~**18 Aug 2017**~~ **Week of 25 Sep 2017** (Last date data are collected from the study)
Animal Arrival:	~~**15**~~ **16** Mar 2017
Initiation of Dosing:	~~**27 Mar 2017**~~ **03 May 2017**
Completion of In-life:	~~**26 Apr 2017**~~ **02 Jun 2017** (main study animals) ~~**09 May 2017**~~ **15 Jun 2017** (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	~~**06 Jul 2017**~~ **Will be included by amendment**
Draft Report:	~~**11 Aug 2017**~~ **Will be included by amendment**
Final Report:	~~**18 Aug 2017**~~ **Week of 25 Sep 2017** (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, *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 and anti-therapeutic antibody 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
22022 Transcanadienne
Senneville Quebec
Canada H9X 3R3
Tel: (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)

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Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)
Fax: (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)
Pathology	To be included by amendment
Analytical Chemistry (Concentration and Particle Size Analysis)	(b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Immunology (Purity Analysis)	(b) (6) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Immunology (Cytokines)	(b) (6) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)

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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

PI at Sponsor-designated Test Site

Anti-Therapeutic
Antibody Analysis (ATA) (b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (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-1706
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17025
Concentration:	To be included by amendment
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle 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 and Reference 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.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Item components, a reserve sample (1 mL, 100 mg or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

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8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned to the Sponsor

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 pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15 and 29) for administration to Group 1 control animals and 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 dosing formulations will be diluted with Phosphate Buffered Saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15 and 29) 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.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and will be discarded prior to finalisation following approval by the Study Director.

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10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

Interval	Homogeneity	Concentration	Sampling From
Day 1[b]	~~All groups~~ **2 to 4**[a]	All groups	Preparation vessel
Day 29[b]	N/A	All groups	Preparation vessel

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 preparation.

All samples to be analyzed will be transferred on ice packs to the analytical laboratory (CR-MTL).

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 HPLC using a validated analytical procedure (Validation Study Number ~~**1801997**~~ **1801737**).

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 (duplicate 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 containers.
Sample Volume:	0.5 mL for analysis and backup samples
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for

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acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study**, however, end of use stability analysis on 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 and weight of animals received will be listed in the Final Report.

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.

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

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

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

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

The alternate animals may be used as replacements on the study within 1 day.

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

12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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

12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals from Groups 1 to 4 via intramuscular injection into the lateral compartment of the thigh alternating legs on Days 1, 15 and 29 (site 1= left thigh, 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 will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. 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

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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 2 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 29 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 30.
Procedure:	All animals will have the dose injection site examined for signs of erythema/edema. The Local Irritation Assessment scoring will be performed as follows:

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Erythema (Redness)	Score
No erythema	0
Very slight erythema	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	1
Slight edema	2
Moderate edema	3
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 2 weeks during the prestudy 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 at the end 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 1% tropicamide.

Evaluation: A report will be included as an appendix to the Final Report.

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14.7. Body Temperature

Frequency: On Day 1 and Day 29 at predose, 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0C to 38.0C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes, measurement may be taken at the discretion of the Study Director.

Procedure: Body temperature will be recorded via subcutaneous implanted transponder.

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
~~1~~ ~~4~~[a] **1 to 4**[a]	Day 30	X	X	X
1 ~~to~~ **and** 4	Day 43	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X

X = Samples to be collected
a Samples will only be collected from those animals scheduled for euthanasia on Day 30.

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

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Hematology Parameters

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

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.

15.1.3. Coagulation

Target Volume: 0.9 mL (in a 1.0 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Clinical Chemistry Parameters

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

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

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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 (ATTACHMENT A).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. 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 settings			(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	NAp	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, NAp = 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 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.

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

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

15.3. Anti-drug Antibody (ADA) Sample Collection, Processing, and Analysis

Blood will be collected from all animals by jugular venipuncture and/or via the abdominal aorta while under isoflurane anesthesia (terminal and unscheduled samples).

Time Points:	Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for 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 (not exceeding 60 minutes after collection). The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the 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.

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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[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	30	X	X	X	Full Tissue	Full Tissue
2	10	10					Full Tissue	Gross Lesions Target Tissues
3	10	10					Full Tissue	Gross Lesions Target Tissues
4	10	10					Full Tissue	Full Tissue
1	5	5	43	X	X	X	Full Tissue	Gross Lesions Target Tissues
4	5	5					Full Tissue	Gross Lesions Target Tissues
Unscheduled Deaths				X	X	-	Full Tissue	Full Tissue
Replaced animals (prestudy)				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.

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis 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 necropsy, 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 necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy 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 clinical pathology, anti-drug antibodies and cytokines 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 study 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 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 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
Organ Weights	X
Body Weight Changes	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.

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

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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. Data regression analysis and measurement of purity.
BioPlex Manager	Cytokine data collection and regression
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
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

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 a CR-MTL archives. At least one year after issue of the draft report, the Sponsor will be contacted.

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 and cytokine sample collection and evaluation
- Anti-drug Antibodies sample collection
- 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: 27 Mar 2017

As authorized by the Sponsor on 27 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	-	-	-
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for 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 02

Test Facility Study No. 5002231

A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With 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: 15 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: 27-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To include new schedule following delay in dosing initiation due to test item delivery date.
10.3.Sample Collection and Analysis	To remove homogeneity for Group 1 based on sample collection in section 10.3.1.1.
10.3.1. Analytical Method	To correct the dose formulation analysis validation number.
10.3.1.2. Stability Analysis	To include end of use for bulk test item.
13. EXPERIMENTAL DESIGN	To correct the dose concentration for mid dose group.
15.1.1. Sample Collection	To correct the group numbers to be evaluation on both occasions.
Amendment 2	**Date: 02-May-2017**
2. PROPOSED STUDY SCHEDULE	To include reporting schedule.
7. RESPONSIBLE PERSONNEL	To update PIs description based on wording used in section 15.3.
8.1. Test Item	To include information from Summary of Analysis.
14.2.1. Detailed Clinical Observations	To include detailed examination of the injection site following each dosing.
14.3. Local Irritation Assessment	Section deleted. Replaced by detailed examination of the injection site (refer to section 14.2.1.)
14.7. Body Temperature	To update the procedure as animals were not identified with the appropriate microship for body weight recording with scanner.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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:	16 Mar 2017 (First date of study-specific data collection)
Experimental Completion Date:	Week of 25 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	16 Mar 2017
Initiation of Dosing:	03 May 2017
Completion of In-life:	02 Jun 2017 (main study animals) 15 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	**14 Aug 2017** ~~**Will be included by amendment**~~
Draft Report:	**19 Sep 2017** ~~**Will be included by amendment**~~
Final Report:	**26 Sep 2017** ~~**Week of 25 Sep 2017**~~ (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, *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 and anti-therapeutic antibody 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
22022 Transcanadienne
Senneville Quebec
Canada H9X 3R3
Tel: (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)

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Management Contact

(b) (6)
Address as cited for Test Facility
Tel: (b) (6)
Fax: (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)
Pathology	To be included by amendment
Analytical Chemistry (Concentration and Particle Size Analysis)	(b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Immunology (Purity Analysis)	(b) (6) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Immunology (Cytokines)	(b) (6) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)

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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

PI at Sponsor-designated Test Site

Anti-~~**Therapeutic**~~ **Drug**
Antibody Analysis (A~~**T**~~**DA**) (b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (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-1706
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP170~~**25**~~**536**
Concentration:	**2.1 mg/mL** ~~**To be included by amendment**~~
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle 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 and Reference 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.

8.5. Reserve Samples

For each batch (lot) of Test and Reference Item components, a reserve sample (1 mL, 100 mg or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

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8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned to the Sponsor

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 pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15 and 29) for administration to Group 1 control animals and 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 dosing formulations will be diluted with Phosphate Buffered Saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15 and 29) 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.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and will be discarded prior to finalisation following approval by the Study Director.

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10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

Interval	Homogeneity	Concentration	Sampling From
Day 1[b]	2 to 4[a]	All groups	Preparation vessel
Day 29[b]	N/A	All groups	Preparation vessel

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 preparation.

All samples to be analyzed will be transferred on ice packs to the analytical laboratory (CR-MTL).

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 HPLC using a validated analytical procedure (Validation Study Number 1801737).

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 (duplicate 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 containers.
Sample Volume:	0.5 mL for analysis and backup samples
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for

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acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study, however, end of use stability analysis on 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 and weight of animals received will be listed in the Final Report.

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.

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

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

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

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

The alternate animals may be used as replacements on the study within 1 day.

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

12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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

12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals from Groups 1 to 4 via intramuscular injection into the lateral compartment of the thigh alternating legs on Days 1, 15 and 29 (site 1= left thigh, 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 will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. 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

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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 2 weeks during the predosing period. **In addition detailed examination of the injection sites will be performed at predose, 24, 48 and 72 hours post each dose. Following Day 29 dosing, no assessment will be perfomed on main study animals at 72 hours post dose as animals will be sent to necropsy on Day 30. Any clinical signs at the injection site (e.g. erythema/redness, skin thickening, edema/swelling, vocalization upon palpation, ulceration, necrosis, warm to the touch, etc...) will be recorded as observed.**
Procedure:	Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Section deleted

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every 2 weeks during the prestudy 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.

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Procedure: Food consumption will be quantitatively measured except for on the day of scheduled euthanasia.

14.6. Ophthalmic Examinations

Frequency: Once prestudy and again at the end 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 1% tropicamide.

Evaluation: A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency: On Day 1 and Day 29 at predose, 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0C to 38.0C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes, measurement may be taken at the discretion of the Study Director.

Procedure: ~~**Body temperature will be recorded via subcutaneous implanted transponder.**~~ **Rectal body temperature will be recorded on un-sedated animals.**

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
1 to 4[a]	Day 30	X	X	X
1 and 4	Day 43	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X

X = Samples to be collected

a Samples will only be collected from those animals scheduled for euthanasia on Day 30.

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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) Other cells (as appropriate)

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.

15.1.3. Coagulation

Target Volume: 0.9 mL (in a 1.0 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 tubes

Processing: To serum

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Clinical Chemistry Parameters

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

[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 (ATTACHMENT A).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. 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 settings			(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	NAp	5/5	X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			All volume	All volume
Number of aliquot(s)			1	1
Storage condition			-80°C	-80°C

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Target Blood Volume (mL)			0.5	0.5
Anticoagulant			None (SST)	EDTA
Centrifugation settings			(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
(set to maintain)				
Responsible Lab			CR-SHB	CR-SHB

X = Sample to be collected, NAp = 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 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 will be included as an appendix to the Final Report.

15.3. Anti-drug Antibody (ADA) Sample Collection, Processing, and Analysis

Blood will be collected from all animals by jugular venipuncture and/or via the abdominal aorta while under isoflurane anesthesia (terminal and unscheduled samples).

Time Points:	Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for 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 (not exceeding 60 minutes after collection). 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

Appendix 1

(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-ZIKA antibodies using a qualified ELISA method.

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the 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.

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[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	30	X	X	X	Full Tissue	Full Tissue
2	10	10					Full Tissue	Gross Lesions Target Tissues
3	10	10					Full Tissue	Gross Lesions Target Tissues
4	10	10					Full Tissue	Full Tissue
1	5	5	43	X	X	X	Full Tissue	Gross Lesions Target Tissues
4	5	5					Full Tissue	Gross Lesions Target Tissues
Unscheduled Deaths				X	X	-	Full Tissue	Full Tissue
Replaced animals (prestudy)				X	Standard Diagnostic List	-	-	-
Replaced animals (after dosing start)				X	X	-	-	-

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

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Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		

[a] See Tissue Collection and Preservation table for listing of tissues.

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis 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 necropsy, 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 necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy 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 clinical pathology, anti-drug antibodies and cytokines 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 study 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.

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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.

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 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 pathology peer review will be conducted by:

(b) (6)
Moderna Therapeutics

Appendix 1

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

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
Organ Weights	X
Body Weight Changes	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. Data regression analysis and measurement of purity.
BioPlex Manager	Cytokine data collection and regression
Softmax Pro GxP	IFN-α data collection
Watson LIMS	Biomarker data analysis

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Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

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 a CR-MTL archives. At least one year after issue of the draft report, the Sponsor will be contacted.

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 and cytokine sample collection and evaluation
- Anti-drug Antibodies sample collection
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

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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.

24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

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AMENDMENT APPROVAL

(b) (6) Date: 02 May 2017

As authorized by the Sponsor on 02 May 2017

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ATTACHMENT A

Tissue Collection and Preservation

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

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for 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 03

Test Facility Study No. 5002231

A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With 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: 15 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: 27-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To include new schedule following delay in dosing initiation due to test item delivery date.
10.3.Sample Collection and Analysis	To remove homogeneity for Group 1 based on sample collection in section 10.3.1.1.
10.3.1. Analytical Method	To correct the dose formulation analysis validation number.
10.3.1.2. Stability Analysis	To include end of use for bulk test item.
13. EXPERIMENTAL DESIGN	To correct the dose concentration for mid dose group.
15.1.1. Sample Collection	To correct the group numbers to be evaluation on both occasions.
Amendment 2	**Date: 02-May-2017**
2. PROPOSED STUDY SCHEDULE	To include reporting schedule.
7. RESPONSIBLE PERSONNEL	To update PIs description based on wording used in section 15.3.
8.1. Test Item	To include information from Summary of Analysis.
14.2.1. Detailed Clinical Observations	To include detailed examination of the injection site following each dosing.
14.3. Local Irritation Assessment	Section deleted. Replaced by detailed examination of the injection site (refer to section 14.2.1.)
14.7. Body Temperature	To update the procedure as animals were not identified with the appropriate microship for body weight recording with scanner.
Amendment 3	**Date: 07-Jun-2017**
7. RESPONSIBLE PERSONNEL	To include the pathology IS.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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:	16 Mar 2017 (First date of study-specific data collection)
Experimental Completion Date:	Week of 25 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	16 Mar 2017
Initiation of Dosing:	03 May 2017
Completion of In-life:	02 Jun 2017 (main study animals) 15 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	14 Aug 2017
Draft Report:	19 Sep 2017
Final Report:	26 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, *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 and anti-therapeutic antibody 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
22022 Transcanadienne
Senneville Quebec
Canada H9X 3R3
Tel: (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)

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Management Contact

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

Pathology

~~**To be included by amendment**~~
(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)

Analytical Chemistry (Concentration and Particle Size Analysis)

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

Immunology (Purity Analysis)

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

Immunology (Cytokines)

(b) (6)

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(b) (6)
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

PI at Sponsor-designated Test Site

Anti-Drug
Antibody Analysis (ADA)

(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (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-1706
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17036
Concentration:	2.1 mg/mL

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Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle 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 and Reference 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 Item components, a reserve sample (1 mL, 100 mg 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

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 pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15 and 29) for administration to Group 1 control animals and 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 dosing formulations will be diluted with Phosphate Buffered Saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing

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(i.e. Days 1, 15 and 29) 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.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and will be discarded prior to finalisation following approval by the Study Director.

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	Homogeneity	Concentration	Sampling From
Day 1[b]	2 to 4[a]	All groups	Preparation vessel
Day 29[b]	N/A	All groups	Preparation vessel

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 preparation.

All samples to be analyzed will be transferred on ice packs to the analytical laboratory (CR-MTL).

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 HPLC using a validated analytical procedure (Validation Study Number 1801737).

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 (duplicate 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 containers.

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Sample Volume:	0.5 mL for analysis and backup samples
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study, however, end of use stability analysis on 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 and weight of animals received will be listed in the Final Report.

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.

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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.

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 1 day.

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%

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Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

12.3. Food

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

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

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

12.4. Water

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

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

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

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

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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.

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-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals from Groups 1 to 4 via intramuscular injection into the lateral compartment of the thigh alternating legs on Days 1, 15 and 29 (site 1= left thigh, 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.

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14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. 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.

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 2 weeks during the predosing period. In addition detailed examination of the injection sites will be performed at predose, 24, 48 and 72 hours post each dose. Following Day 29 dosing, no assessment will be perfomed on main study animals at 72 hours post dose as animals will be sent to necropsy on Day 30. Any clinical signs at the injection site (e.g. erythema/redness, skin thickening, edema/swelling, vocalization upon palpation, ulceration, necrosis, warm to the touch, etc...) will be recorded as observed.
Procedure:	Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Section deleted

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every 2 weeks during the prestudy period.

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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 at the end 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 1% tropicamide.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 29 at predose, 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0C to 38.0C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes, measurement may be taken at the discretion of the Study Director.
Procedure:	Rectal body temperature will be recorded on un-sedated animals.

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.

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Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry
1 to 4[a]	Day 30	X	X	X
1 and 4	Day 43	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X

X = Samples to be collected
a Samples will only be collected from those animals scheduled for euthanasia on Day 30.

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

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.

15.1.3. Coagulation

Target Volume: 0.9 mL (in a 1.0 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

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Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Clinical Chemistry Parameters

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine Kinase	Glucose
Total bilirubin[a]	Cholesterol
Urea nitrogen	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphorus	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 (ATTACHMENT A).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. 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 settings			(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	NAp	5/5	X	X
Matrix			Serum	Plasma

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Target Blood Volume (mL)			0.5	0.5
Anticoagulant			None (SST)	EDTA
Centrifugation settings			(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
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, NAp = 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 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 will be included as an appendix to the Final Report.

15.3. Anti-drug Antibody (ADA) Sample Collection, Processing, and Analysis

Blood will be collected from all animals by jugular venipuncture and/or via the abdominal aorta while under isoflurane anesthesia (terminal and unscheduled samples).

Time Points: Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for 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 (not exceeding 60 minutes after collection). 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.

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Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the 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.

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[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	30	X	X	X	Full Tissue	Full Tissue
2	10	10					Full Tissue	Gross Lesions Target Tissues
3	10	10					Full Tissue	Gross Lesions Target Tissues
4	10	10					Full Tissue	Full Tissue
1	5	5	43	X	X	X	Full Tissue	Gross Lesions Target Tissues
4	5	5					Full Tissue	Gross Lesions Target Tissues
Unscheduled Deaths				X	X	-	Full Tissue	Full Tissue
Replaced animals (prestudy)				X	Standard Diagnostic	-	-	-

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Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
					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.

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section **Error! Reference source not found.**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 necropsy, 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 necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy 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 clinical pathology, anti-drug antibodies and cytokines 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 study 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.

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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 **Error! Reference source not found.**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 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.

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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

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
Organ Weights	X
Body Weight Changes	X

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Variables for Inferential Analysis	Statistical Method Parametric/ Non-Parametric
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.

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

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	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. Data regression analysis and measurement of purity.
BioPlex Manager	Cytokine data collection and regression
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
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

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 a CR-MTL archives. At least one year after issue of the draft report, the Sponsor will be contacted.

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 and cytokine sample collection and evaluation
- Anti-drug Antibodies sample collection

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- 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.

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: 07 Jun 2017

As authorized by the Sponsor on 07 Jun 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	-	-	-
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for 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 04

Test Facility Study No. 5002231

A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With 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

Appendix 1

SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 15 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: 27-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To include new schedule following delay in dosing initiation due to test item delivery date.
10.3.Sample Collection and Analysis	To remove homogeneity for Group 1 based on sample collection in section 10.3.1.1.
10.3.1. Analytical Method	To correct the dose formulation analysis validation number.
10.3.1.2. Stability Analysis	To include end of use for bulk test item.
13. EXPERIMENTAL DESIGN	To correct the dose concentration for mid dose group.
15.1.1. Sample Collection	To correct the group numbers to be evaluation on both occasions.
Amendment 2	**Date: 02-May-2017**
2. PROPOSED STUDY SCHEDULE	To include reporting schedule.
7. RESPONSIBLE PERSONNEL	To update PIs description based on wording used in section 15.3.
8.1. Test Item	To include information from Summary of Analysis.
14.2.1. Detailed Clinical Observations	To include detailed examination of the injection site following each dosing.
14.3. Local Irritation Assessment	Section deleted. Replaced by detailed examination of the injection site (refer to section 14.2.1.)
14.7. Body Temperature	To update the procedure as animals were not identified with the appropriate microship for body weight recording with scanner.
Amendment 3	**Date: 07-Jun-2017**
7. RESPONSIBLE PERSONNEL	To include the pathology IS.
Amendment 4	
7. RESPONSIBLE PERSONNEL	To include clarification for immunology analysis and to include a biomarker IS.
15.2. Cytokines Analysis	To include clarification for cytokine analysis..

Appendix 1

TABLE OF CONTENTS

Appendix 1

1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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:	16 Mar 2017 (First date of study-specific data collection)
Experimental Completion Date:	Week of 25 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	16 Mar 2017
Initiation of Dosing:	03 May 2017
Completion of In-life:	02 Jun 2017 (main study animals) 15 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	14 Aug 2017
Draft Report:	19 Sep 2017
Final Report:	26 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, *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 and anti-therapeutic antibody 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
22022 Transcanadienne
Senneville Quebec
Canada H9X 3R3
Tel: (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)

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Management Contact

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

Pathology — (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)

Analytical Chemistry (Concentration and Particle Size Analysis) — (b) (6)
Charles River Laboratories Montreal ULC
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Immunology (Purity Analysis) — (b) (6)
Address as cited for Test Facility
Tel: (b) (6)
E-mail: (b) (6)

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Biomarkers
(IL-1ß, IL-6, TNF-α,
IP-10, MIP-1-α, MCP-1)

(b) (6)

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

Immunology
(**~~Cytokines~~ INF-α**)

(b) (6)

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

PI at Sponsor-designated Test Site

Anti-Drug
Antibody Analysis (ADA)

(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1706
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17036
Concentration:	2.1 mg/mL
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle 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 and Reference Item Characterization

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

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

8.4. Analysis of Test Item

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

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

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

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

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

8.5. Reserve Samples

For each batch (lot) of Test and Reference Item components, a reserve sample (1 mL, 100 mg 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

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

9. SAFETY

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

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

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

The Reference Item, Phosphate Buffered Saline pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15 and 29) for administration to Group 1 control animals and 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 dosing formulations will be diluted with Phosphate Buffered Saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15 and 29) 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.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and will be discarded prior to finalisation following approval by the Study Director.

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	Homogeneity	Concentration	Sampling From
Day 1[b]	2 to 4[a]	All groups	Preparation vessel
Day 29[b]	N/A	All groups	Preparation vessel

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 preparation.

All samples to be analyzed will be transferred on ice packs to the analytical laboratory (CR-MTL).

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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 HPLC using a validated analytical procedure (Validation Study Number 1801737).

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 (duplicate 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 containers.
Sample Volume:	0.5 mL for analysis and backup samples
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study, however, end of use stability analysis on 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

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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 and weight of animals received will be listed in the Final Report.

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.

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 1 day.

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

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12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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

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12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals from Groups 1 to 4 via intramuscular injection into the lateral compartment of the thigh alternating legs on Days 1, 15 and 29 (site 1= left thigh, 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

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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 will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. 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.

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 2 weeks during the predosing period.

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	In addition detailed examination of the injection sites will be performed at predose, 24, 48 and 72 hours post each dose. Following Day 29 dosing, no assessment will be perfomed on main study animals at 72 hours post dose as animals will be sent to necropsy on Day 30. Any clinical signs at the injection site (e.g. erythema/redness, skin thickening, edema/swelling, vocalization upon palpation, ulceration, necrosis, warm to the touch, etc...) will be recorded as observed.
Procedure:	Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Section deleted

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every 2 weeks during the prestudy 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 at the end 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 1% tropicamide.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 29 at predose, 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0C to 38.0C) the temperature will be monitored daily till

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return to normal. If clinical observations indicate a possible body temperature changes, measurement may be taken at the discretion of the Study Director.

Procedure: Rectal body temperature will be recorded on un-sedated animals.

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
1 to 4[a]	Day 30	X	X	X
1 and 4	Day 43	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X

X = Samples to be collected
a Samples will only be collected from those animals scheduled for euthanasia on Day 30.

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

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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.

15.1.3. Coagulation

Target Volume: 0.9 mL (in a 1.0 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 tubes

Processing: To serum

Clinical Chemistry Parameters

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

[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 (ATTACHMENT A).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. 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

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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 settings			(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	NAp	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 **(processing)**			CR-SHB	CR-SHB

X = Sample to be collected, NAp = Not applicable

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

The samples **for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1** will be analyzed by the ~~**Immunology**~~ **Biomarkers** department **at CR MTL**. 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.

The samples for IFN- α will be analyzed by the Immunology department (CR SHB). 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.

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A Biomarkers interpretative report (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) and ~~A~~an Immunology Report **(IFN- α)** will be included as an appendix to the Final Report.

15.3. Anti-drug Antibody (ADA) Sample Collection, Processing, and Analysis

Blood will be collected from all animals by jugular venipuncture and/or via the abdominal aorta while under isoflurane anesthesia (terminal and unscheduled samples).

Time Points:	Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for 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 (not exceeding 60 minutes after collection). The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4)
The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the 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.

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

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Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	30	X	X	X	Full Tissue	Full Tissue
2	10	10					Full Tissue	Gross Lesions Target Tissues
3	10	10					Full Tissue	Gross Lesions Target Tissues
4	10	10					Full Tissue	Full Tissue
1	5	5	43	X	X	X	Full Tissue	Gross Lesions Target Tissues
4	5	5					Full Tissue	Gross Lesions Target Tissues
Unscheduled Deaths				X	X	-	Full Tissue	Full Tissue
Replaced animals (prestudy)				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.

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section **Error! Reference source not found.**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 necropsy, 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 necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy 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 clinical pathology, anti-drug antibodies and cytokines 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 study 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 **Error! Reference source not found.**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 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 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
Organ Weights	X
Body Weight Changes	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.

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

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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. Data regression analysis and measurement of purity.
BioPlex Manager	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data collection
Softmax Pro GxP	IFN-α data collection
Watson LIMS	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data regression
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

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

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of final report issue. All materials generated by Charles River from this study will be transferred to a CR-MTL archives. At least one year after issue of the draft report, the Sponsor will be contacted.

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 and cytokine sample collection and evaluation
- Anti-drug Antibodies sample collection
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

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

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

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

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

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AMENDMENT APPROVAL

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

As authorized by the Sponsor on 15 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	-	-	-
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for 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 05

Test Facility Study No. 5002231

A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With 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: 15 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: 27-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To include new schedule following delay in dosing initiation due to test item delivery date.
10.3.Sample Collection and Analysis	To remove homogeneity for Group 1 based on sample collection in section 10.3.1.1.
10.3.1. Analytical Method	To correct the dose formulation analysis validation number.
10.3.1.2. Stability Analysis	To include end of use for bulk test item.
13. EXPERIMENTAL DESIGN	To correct the dose concentration for mid dose group.
15.1.1. Sample Collection	To correct the group numbers to be evaluation on both occasions.
Amendment 2	**Date: 02-May-2017**
2. PROPOSED STUDY SCHEDULE	To include reporting schedule.
7. RESPONSIBLE PERSONNEL	To update PIs description based on wording used in section 15.3.
8.1. Test Item	To include information from Summary of Analysis.
14.2.1. Detailed Clinical Observations	To include detailed examination of the injection site following each dosing.
14.3. Local Irritation Assessment	Section deleted. Replaced by detailed examination of the injection site (refer to section 14.2.1.)
14.7. Body Temperature	To update the procedure as animals were not identified with the appropriate microship for body weight recording with scanner.
Amendment 3	**Date: 07-Jun-2017**
7. RESPONSIBLE PERSONNEL	To include the pathology IS.
Amendment 4	**Date: 15-Jun-2017**
7. RESPONSIBLE PERSONNEL	To include clarification for immunology analysis and to include a biomarker IS.
15.2. Cytokines Analysis	To include clarification for cytokine analysis..
Amendment 5	
8.6. Test and Reference Items Disposition and Inventory	To update shipping contact information.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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:	16 Mar 2017 (First date of study-specific data collection)
Experimental Completion Date:	Week of 25 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	16 Mar 2017
Initiation of Dosing:	03 May 2017
Completion of In-life:	02 Jun 2017 (main study animals) 15 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	14 Aug 2017
Draft Report:	19 Sep 2017
Final Report:	26 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, *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 and anti-therapeutic antibody 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
22022 Transcanadienne
Senneville Quebec
Canada H9X 3R3
Tel: (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)

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Management Contact

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

Pathology

(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)

Analytical Chemistry (Concentration and Particle Size Analysis)

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

Immunology (Purity Analysis)

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

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Biomarkers
(IL-1ß, IL-6, TNF-α,
IP-10, MIP-1-α, MCP-1)

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

Immunology
(INF-α)

(b) (6)
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

PI at Sponsor-designated Test Site

Anti-Drug
Antibody Analysis (ADA)

(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1706
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17036
Concentration:	2.1 mg/mL
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle 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 and Reference Item Characterization

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

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

8.4. Analysis of Test Item

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

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

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

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

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

8.5. Reserve Samples

For each batch (lot) of Test and Reference Item components, a reserve sample (1 mL, 100 mg 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

Shipping Contact
(b) (6)
Moderna Therapeutics
~~**800**~~ **500** Technology Sq, 8th Floor
Cambridge MA ~~**02476**~~ **02138**
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

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

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

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

The Reference Item, Phosphate Buffered Saline pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15 and 29) for administration to Group 1 control animals and 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 dosing formulations will be diluted with Phosphate Buffered Saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15 and 29) 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.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and will be discarded prior to finalisation following approval by the Study Director.

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	Homogeneity	Concentration	Sampling From
Day 1[b]	2 to 4[a]	All groups	Preparation vessel
Day 29[b]	N/A	All groups	Preparation vessel

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 preparation.

All samples to be analyzed will be transferred on ice packs to the analytical laboratory (CR-MTL).

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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 HPLC using a validated analytical procedure (Validation Study Number 1801737).

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 (duplicate 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 containers.
Sample Volume:	0.5 mL for analysis and backup samples
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study, however, end of use stability analysis on 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

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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 and weight of animals received will be listed in the Final Report.

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.

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 1 day.

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

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12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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

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12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals from Groups 1 to 4 via intramuscular injection into the lateral compartment of the thigh alternating legs on Days 1, 15 and 29 (site 1= left thigh, 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

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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 will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. 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.

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 2 weeks during the predosing period.

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	In addition detailed examination of the injection sites will be performed at predose, 24, 48 and 72 hours post each dose. Following Day 29 dosing, no assessment will be perfomed on main study animals at 72 hours post dose as animals will be sent to necropsy on Day 30. Any clinical signs at the injection site (e.g. erythema/redness, skin thickening, edema/swelling, vocalization upon palpation, ulceration, necrosis, warm to the touch, etc...) will be recorded as observed.
Procedure:	Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Section deleted

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every 2 weeks during the prestudy 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 at the end 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 1% tropicamide.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 29 at predose, 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0C to 38.0C) the temperature will be monitored daily till

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return to normal. If clinical observations indicate a possible body temperature changes, measurement may be taken at the discretion of the Study Director.

Procedure: Rectal body temperature will be recorded on un-sedated animals.

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
1 to 4[a]	Day 30	X	X	X
1 and 4	Day 43	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X

X = Samples to be collected
a Samples will only be collected from those animals scheduled for euthanasia on Day 30.

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

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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.

15.1.3. Coagulation

Target Volume: 0.9 mL (in a 1.0 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 tubes

Processing: To serum

Clinical Chemistry Parameters

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

[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 (ATTACHMENT A).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. 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

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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 settings			(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	NAp	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 (processing)			CR-SHB	CR-SHB

X = Sample to be collected, NAp = Not applicable

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

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

The samples for IFN- α will be analyzed by the Immunology department (CR SHB). 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.

A Biomarkers interpretative report (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) and an Immunology Report (IFN- α) will be included as an appendix to the Final Report.

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15.3. Anti-drug Antibody (ADA) Sample Collection, Processing, and Analysis

Blood will be collected from all animals by jugular venipuncture and/or via the abdominal aorta while under isoflurane anesthesia (terminal and unscheduled samples).

Time Points:	Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for 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 (not exceeding 60 minutes after collection). The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the 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.

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

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Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	30	X	X	X	Full Tissue	Full Tissue
2	10	10					Full Tissue	Gross Lesions Target Tissues
3	10	10					Full Tissue	Gross Lesions Target Tissues
4	10	10					Full Tissue	Full Tissue
1	5	5	43	X	X	X	Full Tissue	Gross Lesions Target Tissues
4	5	5					Full Tissue	Gross Lesions Target Tissues
Unscheduled Deaths				X	X	-	Full Tissue	Full Tissue
Replaced animals (prestudy)				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.

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section **Error! Reference source not found.**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 necropsy, 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 necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy 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 clinical pathology, anti-drug antibodies and cytokines 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 study 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 **Error! Reference source not found.**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 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 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
Organ Weights	X
Body Weight Changes	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.

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

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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. Data regression analysis and measurement of purity.
BioPlex Manager	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data collection
Softmax Pro GxP	IFN-α data collection
Watson LIMS	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data regression
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

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

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of final report issue. All materials generated by Charles River from this study will be transferred to a CR-MTL archives. At least one year after issue of the draft report, the Sponsor will be contacted.

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 and cytokine sample collection and evaluation
- Anti-drug Antibodies sample collection
- 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: 26 Jun 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	-	-	-
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for 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 06

Test Facility Study No. 5002231

A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With 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: 15 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: 27-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To include new schedule following delay in dosing initiation due to test item delivery date.
10.3.Sample Collection and Analysis	To remove homogeneity for Group 1 based on sample collection in section 10.3.1.1.
10.3.1. Analytical Method	To correct the dose formulation analysis validation number.
10.3.1.2. Stability Analysis	To include end of use for bulk test item.
13. EXPERIMENTAL DESIGN	To correct the dose concentration for mid dose group.
15.1.1. Sample Collection	To correct the group numbers to be evaluation on both occasions.
Amendment 2	**Date: 02-May-2017**
2. PROPOSED STUDY SCHEDULE	To include reporting schedule.
7. RESPONSIBLE PERSONNEL	To update PIs description based on wording used in section 15.3.
8.1. Test Item	To include information from Summary of Analysis.
14.2.1. Detailed Clinical Observations	To include detailed examination of the injection site following each dosing.
14.3. Local Irritation Assessment	Section deleted. Replaced by detailed examination of the injection site (refer to section 14.2.1.)
14.7. Body Temperature	To update the procedure as animals were not identified with the appropriate microship for body weight recording with scanner.
Amendment 3	**Date: 07-Jun-2017**
7. RESPONSIBLE PERSONNEL	To include the pathology IS.
Amendment 4	**Date: 15-Jun-2017**
7. RESPONSIBLE PERSONNEL	To include clarification for immunology analysis and to include a biomarker IS.
15.2. Cytokines Analysis	To include clarification for cytokine analysis..
Amendment 5	**Date: 26-Jun-2017**
8.6. Test and Reference Items Disposition and Inventory	To update shipping contact information.
Amendment 6	
7. RESPONSIBLE PERSONNEL	To change the IS for Analytical Chemistry due to workload reassignment and to update Study Director's phone extension number.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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:	16 Mar 2017 (First date of study-specific data collection)
Experimental Completion Date:	Week of 25 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	16 Mar 2017
Initiation of Dosing:	03 May 2017
Completion of In-life:	02 Jun 2017 (main study animals) 15 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	14 Aug 2017
Draft Report:	19 Sep 2017
Final Report:	26 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, *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 and anti-therapeutic antibody 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
22022 Transcanadienne
Senneville Quebec
Canada H9X 3R3
Tel: (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)

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Management Contact

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

Pathology

(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)

Analytical Chemistry (Concentration and Particle Size Analysis)

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

Immunology (Purity Analysis)

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

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Biomarkers
(IL-1ß, IL-6, TNF-α,
IP-10, MIP-1-α, MCP-1)

(b) (6)

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

Immunology
(INF-α)

(b) (6)

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

PI at Sponsor-designated Test Site

Anti-Drug
Antibody Analysis (ADA)

(b) (6)

Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1706
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17036
Concentration:	2.1 mg/mL
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle 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 and Reference Item Characterization

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

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

8.4. Analysis of Test Item

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

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

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

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

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

8.5. Reserve Samples

For each batch (lot) of Test and Reference Item components, a reserve sample (1 mL, 100 mg 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

Shipping Contact
(b) (6)
Moderna Therapeutics
500 Technology Sq, 8th Floor
Cambridge MA 02138
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

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

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

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

The Reference Item, Phosphate Buffered Saline pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15 and 29) for administration to Group 1 control animals and 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 dosing formulations will be diluted with Phosphate Buffered Saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15 and 29) 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.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and will be discarded prior to finalisation following approval by the Study Director.

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	Homogeneity	Concentration	Sampling From
Day 1[b]	2 to 4[a]	All groups	Preparation vessel
Day 29[b]	N/A	All groups	Preparation vessel

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 preparation.

All samples to be analyzed will be transferred on ice packs to the analytical laboratory (CR-MTL).

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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 HPLC using a validated analytical procedure (Validation Study Number 1801737).

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 (duplicate 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 containers.
Sample Volume:	0.5 mL for analysis and backup samples
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study, however, end of use stability analysis on 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

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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 and weight of animals received will be listed in the Final Report.

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.

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 1 day.

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

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12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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

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12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals from Groups 1 to 4 via intramuscular injection into the lateral compartment of the thigh alternating legs on Days 1, 15 and 29 (site 1= left thigh, 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

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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 will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. 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.

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 2 weeks during the predosing period.

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	In addition detailed examination of the injection sites will be performed at predose, 24, 48 and 72 hours post each dose. Following Day 29 dosing, no assessment will be perfomed on main study animals at 72 hours post dose as animals will be sent to necropsy on Day 30. Any clinical signs at the injection site (e.g. erythema/redness, skin thickening, edema/swelling, vocalization upon palpation, ulceration, necrosis, warm to the touch, etc...) will be recorded as observed.
Procedure:	Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Section deleted

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every 2 weeks during the prestudy 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 at the end 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 1% tropicamide.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 29 at predose, 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0C to 38.0C) the temperature will be monitored daily till

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return to normal. If clinical observations indicate a possible body temperature changes, measurement may be taken at the discretion of the Study Director.

Procedure: Rectal body temperature will be recorded on un-sedated animals.

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
1 to 4[a]	Day 30	X	X	X
1 and 4	Day 43	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X

X = Samples to be collected
a Samples will only be collected from those animals scheduled for euthanasia on Day 30.

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

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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.

15.1.3. Coagulation

Target Volume: 0.9 mL (in a 1.0 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 tubes

Processing: To serum

Clinical Chemistry Parameters

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

[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 (ATTACHMENT A).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. 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

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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 settings			(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	NAp	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 (processing)			CR-SHB	CR-SHB

X = Sample to be collected, NAp = Not applicable

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

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

The samples for IFN- α will be analyzed by the Immunology department (CR SHB). 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.

A Biomarkers interpretative report (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) and an Immunology Report (IFN- α) will be included as an appendix to the Final Report.

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15.3. Anti-drug Antibody (ADA) Sample Collection, Processing, and Analysis

Blood will be collected from all animals by jugular venipuncture and/or via the abdominal aorta while under isoflurane anesthesia (terminal and unscheduled samples).

Time Points:	Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for 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 (not exceeding 60 minutes after collection). The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4)). The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the 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.

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

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Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	30	X	X	X	Full Tissue	Full Tissue
2	10	10					Full Tissue	Gross Lesions Target Tissues
3	10	10					Full Tissue	Gross Lesions Target Tissues
4	10	10					Full Tissue	Full Tissue
1	5	5	43	X	X	X	Full Tissue	Gross Lesions Target Tissues
4	5	5					Full Tissue	Gross Lesions Target Tissues
Unscheduled Deaths				X	X	-	Full Tissue	Full Tissue
Replaced animals (prestudy)				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.

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section **Error! Reference source not found.**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 necropsy, 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 necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy 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 clinical pathology, anti-drug antibodies and cytokines 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 study 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 **Error! Reference source not found.**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 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 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
Organ Weights	X
Body Weight Changes	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.

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

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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. Data regression analysis and measurement of purity.
BioPlex Manager	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data collection
Softmax Pro GxP	IFN-α data collection
Watson LIMS	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data regression
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

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

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of final report issue. All materials generated by Charles River from this study will be transferred to a CR-MTL archives. At least one year after issue of the draft report, the Sponsor will be contacted.

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 and cytokine sample collection and evaluation
- Anti-drug Antibodies sample collection
- 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: 21 Sep 2017

As authorized by the Sponsor on 21 Sep 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	-	-	-
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for 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 07

Test Facility Study No. 5002231

A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With 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: 15 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: 27-Mar-2017**
2. PROPOSED STUDY SCHEDULE	To include new schedule following delay in dosing initiation due to test item delivery date.
10.3.Sample Collection and Analysis	To remove homogeneity for Group 1 based on sample collection in section 10.3.1.1.
10.3.1. Analytical Method	To correct the dose formulation analysis validation number.
10.3.1.2. Stability Analysis	To include end of use for bulk test item.
13. EXPERIMENTAL DESIGN	To correct the dose concentration for mid dose group.
15.1.1. Sample Collection	To correct the group numbers to be evaluation on both occasions.
Amendment 2	**Date: 02-May-2017**
2. PROPOSED STUDY SCHEDULE	To include reporting schedule.
7. RESPONSIBLE PERSONNEL	To update PIs description based on wording used in section 15.3.
8.1. Test Item	To include information from Summary of Analysis.
14.2.1. Detailed Clinical Observations	To include detailed examination of the injection site following each dosing.
14.3. Local Irritation Assessment	Section deleted. Replaced by detailed examination of the injection site (refer to section 14.2.1.)
14.7. Body Temperature	To update the procedure as animals were not identified with the appropriate microship for body weight recording with scanner.
Amendment 3	**Date: 07-Jun-2017**
7. RESPONSIBLE PERSONNEL	To include the pathology IS.
Amendment 4	**Date: 15-Jun-2017**
7. RESPONSIBLE PERSONNEL	To include clarification for immunology analysis and to include a biomarker IS.
15.2. Cytokines Analysis	To include clarification for cytokine analysis..
Amendment 5	**Date: 26-Jun-2017**
8.6. Test and Reference Items Disposition and Inventory	To update shipping contact information.
Amendment 6	**Date: 21-Sep-2017**
7. RESPONSIBLE PERSONNEL	To change the IS for Analytical Chemistry due to workload reassignment and to update Study Director's phone extension number.
Amendment 6	
7. RESPONSIBLE PERSONNEL	To remove the IS for immunology (cytokine IFN-α Analysis) as analysis will not be conducted.
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-1706, when given by intramuscular injection for 1 month (3 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:	16 Mar 2017 (First date of study-specific data collection)
Experimental Completion Date:	Week of 25 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	16 Mar 2017
Initiation of Dosing:	03 May 2017
Completion of In-life:	02 Jun 2017 (main study animals) 15 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	14 Aug 2017
Draft Report:	19 Sep 2017
Final Report:	26 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, *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 and anti-therapeutic antibody 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
22022 Transcanadienne
Senneville Quebec
Canada H9X 3R3
Tel: (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)

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Management Contact

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

Pathology
(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)

Analytical Chemistry (Concentration and Particle Size Analysis)
(b) (6)
Charles River Laboratories Montreal ULC
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
E-mail: (b) (6)

Immunology (Purity Analysis)
(b) (6)
Address as cited for Test Facility
Tel: (b) (6)
E-mail: (b) (6)

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Biomarkers
(IL-1ß, IL-6, TNF-α,
IP-10, MIP-1-α, MCP-1) (b) (6)

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

~~**Immunology**~~
~~**(INF-α)**~~ (b) (6)

~~**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

PI at Sponsor-designated Test Site

Anti-Drug
Antibody Analysis (ADA) (b) (6)

Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1706
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP17036
Concentration:	2.1 mg/mL
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle 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 and Reference Item Characterization

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

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

8.4. Analysis of Test Item

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

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

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

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

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

8.5. Reserve Samples

For each batch (lot) of Test and Reference Item components, a reserve sample (1 mL, 100 mg 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

Shipping Contact
(b) (6)
Moderna Therapeutics
500 Technology Sq, 8th Floor
Cambridge MA 02138
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

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

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

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

The Reference Item, Phosphate Buffered Saline pH 7.2, will be dispensed on days of dosing (i.e. Days 1, 15 and 29) for administration to Group 1 control animals and 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 dosing formulations will be diluted with Phosphate Buffered Saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each days of dosing (i.e. Days 1, 15 and 29) 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.

Any residual volumes of formulated Test Item will be stored in a refrigerator set at 4°C and will be discarded prior to finalisation following approval by the Study Director.

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	Homogeneity	Concentration	Sampling From
Day 1[b]	2 to 4[a]	All groups	Preparation vessel
Day 29[b]	N/A	All groups	Preparation vessel

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 preparation.

All samples to be analyzed will be transferred on ice packs to the analytical laboratory (CR-MTL).

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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 HPLC using a validated analytical procedure (Validation Study Number 1801737).

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 (duplicate 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 containers.
Sample Volume:	0.5 mL for analysis and backup samples
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study, however, end of use stability analysis on 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

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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 and weight of animals received will be listed in the Final Report.

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.

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 1 day.

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

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12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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

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12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals from Groups 1 to 4 via intramuscular injection into the lateral compartment of the thigh alternating legs on Days 1, 15 and 29 (site 1= left thigh, 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

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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 will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. 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.

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 2 weeks during the predosing period.

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	In addition detailed examination of the injection sites will be performed at predose, 24, 48 and 72 hours post each dose. Following Day 29 dosing, no assessment will be perfomed on main study animals at 72 hours post dose as animals will be sent to necropsy on Day 30. Any clinical signs at the injection site (e.g. erythema/redness, skin thickening, edema/swelling, vocalization upon palpation, ulceration, necrosis, warm to the touch, etc...) will be recorded as observed.
Procedure:	Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Section deleted

14.4. Body Weights

Frequency:	Weekly during the dosing and recovery periods, and at least every 2 weeks during the prestudy 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 at the end 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 1% tropicamide.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

Frequency:	On Day 1 and Day 29 at predose, 6 and 24 hours post dose (end of each group). If body temperature is significantly above normal range (36.0C to 38.0C) the temperature will be monitored daily till

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return to normal. If clinical observations indicate a possible body temperature changes, measurement may be taken at the discretion of the Study Director.

Procedure: Rectal body temperature will be recorded on un-sedated animals.

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
1 to 4[a]	Day 30	X	X	X
1 and 4	Day 43	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X

X = Samples to be collected
a Samples will only be collected from those animals scheduled for euthanasia on Day 30.

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

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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.

15.1.3. Coagulation

Target Volume: 0.9 mL (in a 1.0 mL tube)

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Clinical Chemistry Parameters

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine Kinase	Glucose
Total bilirubin[a]	Cholesterol
Urea nitrogen	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphorus	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 (ATTACHMENT A).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. 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

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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 settings			(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	NAp	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 (processing)			CR-SHB	CR-SHB

X = Sample to be collected, NAp = 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.

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

~~**The samples for IFN- α will be analyzed by the Immunology department (CR SHB). 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.

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A Biomarkers interpretative report (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) and an Immunology Report (IFN- α) will be included as an appendix to the Final Report.

15.3. Anti-drug Antibody (ADA) Sample Collection, Processing, and Analysis

Blood will be collected from all animals by jugular venipuncture and/or via the abdominal aorta while under isoflurane anesthesia (terminal and unscheduled samples).

Time Points:	Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for 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 (not exceeding 60 minutes after collection). The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4)
The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court
Suite 300
Rockville, MD 20850, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the 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.

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

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Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology[a]	Histopathology[a]
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	30	X	X	X	Full Tissue	Full Tissue
2	10	10					Full Tissue	Gross Lesions Target Tissues
3	10	10					Full Tissue	Gross Lesions Target Tissues
4	10	10					Full Tissue	Full Tissue
1	5	5	43	X	X	X	Full Tissue	Gross Lesions Target Tissues
4	5	5					Full Tissue	Gross Lesions Target Tissues
Unscheduled Deaths				X	X	-	Full Tissue	Full Tissue
Replaced animals (prestudy)				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.

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section **Error! Reference source not found.**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 necropsy, 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 necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy 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 clinical pathology, anti-drug antibodies and cytokines 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 study 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 **Error! Reference source not found.**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 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 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
Organ Weights	X
Body Weight Changes	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.

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

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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. Data regression analysis and measurement of purity.
BioPlex Manager	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data collection
Softmax Pro GxP	IFN-α data collection
Watson LIMS	Cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1) data regression
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

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

Appendix 1

of final report issue. All materials generated by Charles River from this study will be transferred to a CR-MTL archives. At least one year after issue of the draft report, the Sponsor will be contacted.

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 and cytokine sample collection and evaluation
- Anti-drug Antibodies sample collection
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

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

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

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

Appendix 1

24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

Appendix 1

AMENDMENT APPROVAL

(b) (6) Date: 25 Sep 2017

As authorized by the Sponsor on 25 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	-	-	-
Bone marrow smear	-	X	-	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin.
Bone marrow	-	X	X	X	-
Bone, femur	-	X	X	X	-
Bone, sternum	-	X	X	X	-
Brain	X	X	X	X	Seven brain levels to be examined to include olfactory bulb (Examine in Body cavity, nasal section level 4)
Cervix	-	X	X	X	-
Epididymis	X	X	X	X	-
Esophagus	-	X	X	X	-
Eye	-	X	X	X	-
Gland, adrenal	X	X	X	X	-
Gland, harderian	-	X	X	X	-
Gland, mammary	-	X	X	X	-
Gland, parathyroid	-	X	X	X	-
Gland, pituitary	X	X	X	X	-
Gland, prostate	X	X	X	X	-
Gland, salivary	-	X	X	X	-
Gland, seminal vesicle	-	X	X	X	-
Gland, thyroid	X	X	X	X	-
Gross lesions/masses	-	X	X	X	-
Gut-associated lymphoid tissue	-	X	X	X	-
Heart	X	X	X	X	-
Kidney	X	X	X	X	-
Large intestine, cecum	-	X	X	X	-
Large intestine, colon	-	X	X	X	-

Appendix 1

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration sites used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Thigh site used for 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 and those SOP deviations that could have impacted the quality or integrity of the study are listed below.

None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Husbandry

- As per study plan, the light cycle is 12 hours light and 12 hours dark. On one occasion during the prestudy period, this cycle was not followed and the lights were temporary turned off during the light cycle. This deviation is considered to have no impact on the study and animal's health as it occurred only once and was of short duration.
- On one occasion, high dose female animal no.4506 was found out of home cage and did not have access to food and water during this time. This deviation is considered to have no impact on the study and animal's health due short time excursion (around 4 hours).

In-life Observations, Measurements, and Evaluations

- On two occasions, the mortality/moribundity check was not performed during the morning for males or for all animals with no impact on the study and animal's health as animals were monitored at the end of the day and were observed during the daily activities.
- On some occasions, detailed examination of the injection sites were performed outside the acceptance time range of ± 30 minutes. These deviations are considered to have no impact on the study due to minor time excursion. In addition, all injection sites were examined.

Laboratory Evaluations

- On Day 30 ADA sample for animal Nos. 1001 and 4001 were not centrifuged within 60 minutes of collection. These deviations are considered to have no impact on the study due to minor time excursions.
- On Day 30, collection tubes for animal nos.1001 and 4001 were centrifuged outside the 60-minute stability for creatinine kinase analysis. This deviation will be taken in consideration during clinical pathology evaluation. As this deviation occurred only for two animals from different groups, it is considered to have no impact on the study.

Appendix 2

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

eurofins | Advantar

Summary of Analysis ***DATE: 28 April 2017***

Part I Release Testing Results for mRNA-1706 LNP Drug Product Lot MTDP17036

Protocol Number: MRA-C0019-RTP0005.00 **Document Number:** MRA-C0019-RTR0011.00 (CPR15095)	**Date Received at Eurofins Advantar:** March 31, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion (20mM Tris Buffer, 8% Sucrose, pH 7.4)
Time point: Release **Storage Condition:** -20°C	**Product Lot #:** MTDP17036	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATION (Specifications per protocol)	TEST DATE	RESULTS
RNA Content (mg/mL) (Draft MRA-C0000-GTM0023)	(b) (4)	04/27/2017	(b) (4)
[1]Bacterial Endotoxins (USP <85>)		04/04/2017	
[2]Bioburden (USP <61>)		03/31/2017	

[1] Testing performed at Associates of Cape Cod Incorporated
[2]Testing performed at Nelson Laboratories
[3]Three samples tested and all sample results are (b) (4)

The data generated at Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Advantar has archived the raw data.

(b) (6)

28 APR 2017
Date

Appendix 2

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

eurofins | Advantar

Summary of Analysis ***DATE: 6 July 2017***

Part II Release Testing Results for mRNA-1706 LNP Drug Product Lot MTDP17036

Protocol Number: MRA-C0019-RTP0005.00 **Document Number:** MRA-C0019-RTR0012.00 (CPR15101)	**Date Received at Eurofins Advantar:** March 31, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion (20mM Tris Buffer, 8% Sucrose, pH 7.4)
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17036	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Appearance (MRA-C0000-GTM0016.00)	White to off-white dispersion, no visible particulates	04/27/2017	Conforms (CPR15097 Page 10)
Identity (Sanger Sequencing)	Sequence matches 100% description of the coding region	04/28/2017	Conforms (CPR15097 ADR C1)
Purity (MRA-C0000-GTM0019.01)	(b) (4)	05/01/2017	(b) (4)
Related Impurities (MRA-C0000-GTM0019.01)	Report % Pre-main peak and % Post main peak areas	05/01/2017	
Encapsulated RNA (MRA-C0000-GTM0014.00)	(b) (4)	04/24/2017 05/04/2017 05/05/2017	
Lipid Identification		05/22/2017	
SM-102	Matches retention time of standard		Conforms
Cholesterol	Matches retention time of standard		Conforms
DSPC	Matches retention time of standard		Conforms
PEG2000-DMG	Matches retention time of standard		Conforms
(UHPLC-CAD)			(CPR15097 ADR C1)
Lipid Content	Lipid (mg/mL)	05/22/2017	(b) (4)
SM-102	(b) (4)		
Cholesterol			
DSPC			
PEG2000-DMG			
(UHPLC-CAD)			

Appendix 2

Eurofins Advantar Laboratories, Inc.
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Summary of Analysis ***DATE: 6 July 2017***

Part II Release Testing Results for mRNA-1706 LNP Drug Product Lot MTDP17036

Protocol Number: MRA-C0019-RTP0005.00 **Document Number:** MRA-C0019-RTR0012.00 (CPR15101)	**Date Received at Eurofins Advantar:** March 31, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion (20mM Tris Buffer, 8% Sucrose, pH 7.4)
Time point: Release **Storage Condition:** -20°C	**Product Lot #:** MTDP17036	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Lipid Impurities (UHPLC-CAD)	Report total % Area and RRT	05/22/2017	(b) (4)
Mean Particle Size (nm) (MRA-C0000-GTM0015.02)	Report result	04/27/2017	
Polydispersity (MRA-C0000-GTM0015.02)	Report result	04/27/2017	
Particulate Matter[1] (USP <788> method 2)	(b) (4)	04/07/2017	
Residual Solvents from Formulation: Ethanol (MRA-C0000-GTM0018.01)		05/04/2017	
Osmolality (USP <785>)	Report Result	04/27/2017	
pH (MRA-C0000-GTM0017.01)	Report result	04/27/2017	

[1] Testing performed at Nelson Laboratories.
[2] This is a composite mean coming from 3 data sets (below) as requested by the Sponsor (CPR15099, ADR F1-F2):
T=0 (n=1, 84%), CPR15099, ADR D5
Method Qualification-Linearity (n=6 preps, 90%, 90%, 89%, 90%, 90%, 89%), CPR14795, ADR E7
Method Qualification-Stability (n=1, 88%), CPR14796, ADR F5

The data generated at Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Advantar has archived the raw data.

(b) (6)

06JUL2017
Date

Appendix 3

FINAL REPORT

Study Phase: Analytical Chemistry

Test Facility Study No. 5002231

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

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Appendix 3

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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-1706.

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. 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-1706 in dose formulations (phosphate-buffered saline (PBS) pH 7.2) in the bulk test item from Study 5002231.

For the work detailed in this report, the analytical phase experimental start date was 02 May 2017, and the analytical phase experimental completion date was 23 Jun 2017.

3. EXPERIMENTAL DESIGN

3.1. Dose Formulation Analysis

Analysis of dose formulations was carried out with regard to concentration and homogeneity.

On Day 1 of the study, duplicate samples were collected from the top, middle and bottom strata of Group 2 to 4 for concentration and homogeneity verification while duplicate samples were collected from the middle strata of Group 1. Duplicate samples were also collected from the middle strata of all Groups for concentration verification on Day 29 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-000171 mRNA
Physical Description:	Clear, colorless solution
Batch/Lot No.:	MTDS16017
Concentration:	2.04 mg/mL (used for calculations)
Retest Date:	Aug 2017
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

4.1.2. Reference Material (Bulk Test Item)

Identification:	mRNA-1706
Physical Description:	White to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP17036
Concentration:	2.1 mg/mL (used for calculations)
Manufacture Date:	24 Mar 2017
Retest Date:	24 Mar 2018 (12 months from date of manufacture)
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

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 Summaries of Analysis (SoA) or equivalent documentation are presented in Appendix 2.

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.

Appendix 3

4.2. Methods

4.2.1. Analytical Procedures

The method for concentration analysis is documented in Analytical Procedure AP.5002231.SP.01 (Appendix 1) and was previously validated under Study Nos. 1801737. Concentration stability data were generated by the department of Analytical Chemistry, Charles River, CR MTL for 8 days, for formulation samples stored in a refrigerator set to maintain 4°C, over the concentration range of 0.0100 – 1.20 mg/mL, under Study No. 2100442.

The method for particle size analysis is documented in Analytical Procedure AP.5002231.DLS.01 (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 were calculated using non-rounded values as per the raw data rounding procedure and may not be exactly reproduced from the individual data presented.

5.1. Dose Formulation Analysis

All study samples analyzed had mean concentrations within or equal to the acceptance criteria of ± 15% (individual values within or equal to ± 20%) of their theoretical concentrations. Results are presented in Table 1.

For homogeneity, the RSD of concentrations for all samples in each group tested was within the acceptance criteria of ≤ 5%. Results are presented in Table 1.

Appendix 3

5.2. Bulk Test Item Analysis

The concentration and the particle size was measured. Concentration and particle size results were consistent with the initial Summary of Analysis provided by the Sponsor. Results are presented in Table 2 and Table 3.

6. CONCLUSION

The dose formulations were within specification. Homogeneity testing showed that the formulation technique used produced homogeneous preparations.

The bulk Test Item analysis demonstrated that the test item was suitable for use during the study period.

Appendix 3

7. REPORT APPROVAL

(b) (6) Date: 30 Nov 2017

Appendix 3

Table 1 Study Samples - Concentration and Homogeneity

Occasion (Sampling Date)	Group	Theoretical Concentration	Sampling Location	Measured Concentration (mg/mL)	Percent of Theoretical	RSD (%)
Day 1 (03 May 2017)	1	(b) (4)	Middle	ND	-	-
				ND	-	
			Mean	ND	-	
	2		Top	(b) (4)		(b) (4)
			Middle			
			Bottom			
			Mean			
	3		Top			
			Middle			
			Bottom			
			Mean			
	4		Top			
			Middle			
			Bottom			
			Mean			
Day 29 (01 Jun 2017)	1		Middle			-
			Mean			
	2		Middle			-
			Mean			
	3		Middle			-
			Mean			
	4		Middle			-
			Mean			

ND = None detected.
(b) (4)

Appendix 3

Table 2 Bulk Test Item - Concentration

Occasion (Analysis Date)	Theoretical Concentration (mg/mL)	Measured Concentration (mg/mL)	Mean Measured Concentration (mg/mL)	Percent of Theoretical	Mean Percent of Theoretical (mg/mL)
End of study (23 Jun 2017)	(b) (4)				

Table 3 Bulk Test Item - Particle Size Analysis

Occasion (Analysis Date)	Theoretical Diameter (nm)	Measured Diameter (nm)	PD Index	% Difference Between Duplicate	Mean Measured Diameter (nm)
End of study (23 Jun 2017)	(b) (4)				

Appendix 3

Appendix 1
Analytical Procedures

Appendix 3

Analytical Procedure (AP.5002231.SP.01)

Determination of mRNA-1706 in Dose Formulations by Ion Exchange High Performance Chromatography Using Ultraviolet/Visible Detection

Reference Standard, Reference Material and Vehicle

Reference Standard	CX-000171 (formely mRNA-1325)
Lot number	MTDS16017
Concentration (actual)	2.04 mg/mL
Reference Material	mRNA-1706 *
Description	White to off-white lipid nanoparticle dispersion
Lot number	MTDP17036
Concentration (nominal)	2.1 mg/mL (to be used for calculations)
Vehicle	Phosphate-buffered Saline (PBS) pH 7.2

* mRNA-1706 and mRNA-1325 have the same mRNA construct.

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 1801737.

Appendix 3

Analytical Procedure (AP.5002231.SP.01)

(b) (4)

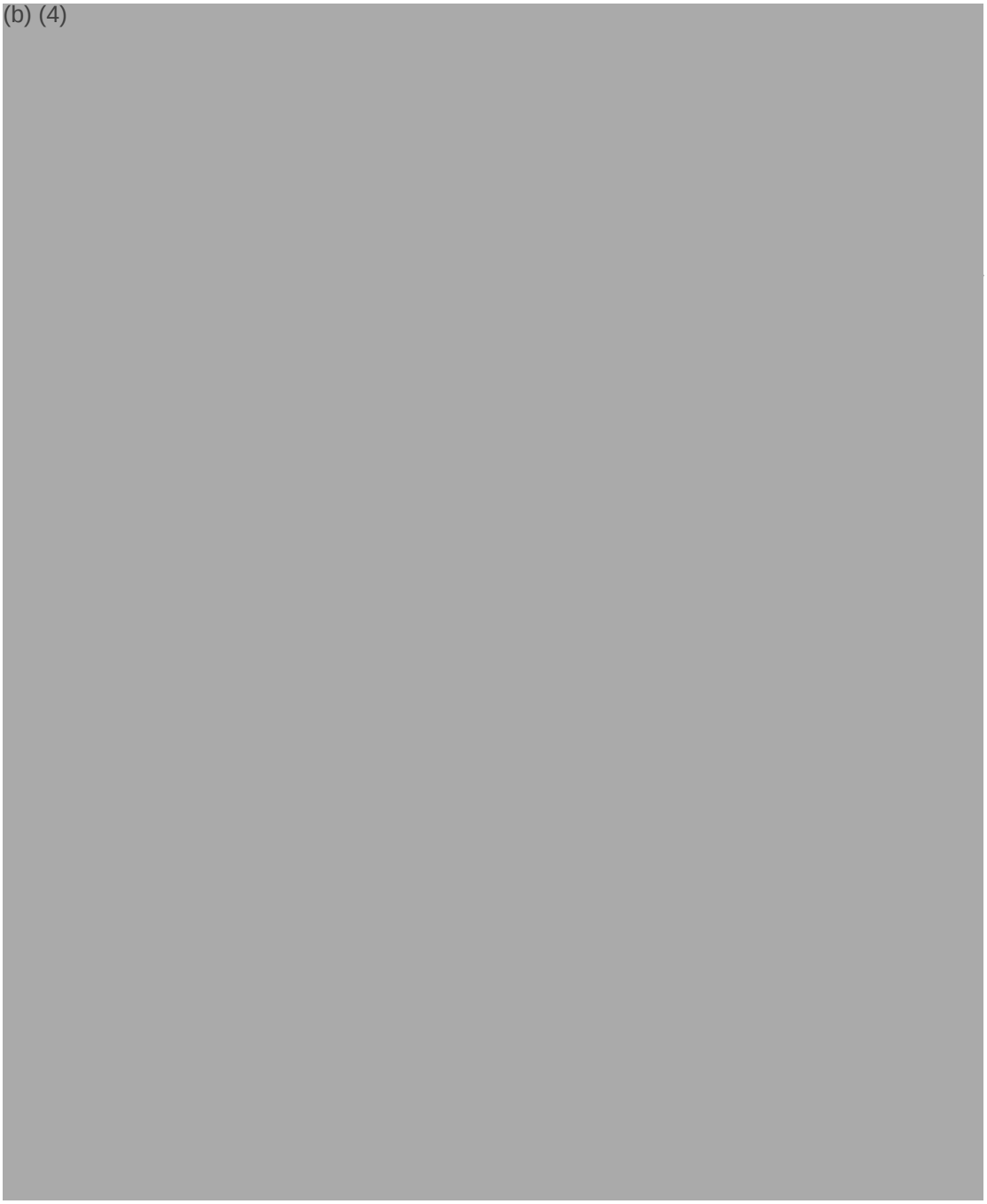
Appendix 3

Analytical Procedure (AP.5002231.SP.01)

(b) (4)

Appendix 3

(b) (4)



Appendix 3

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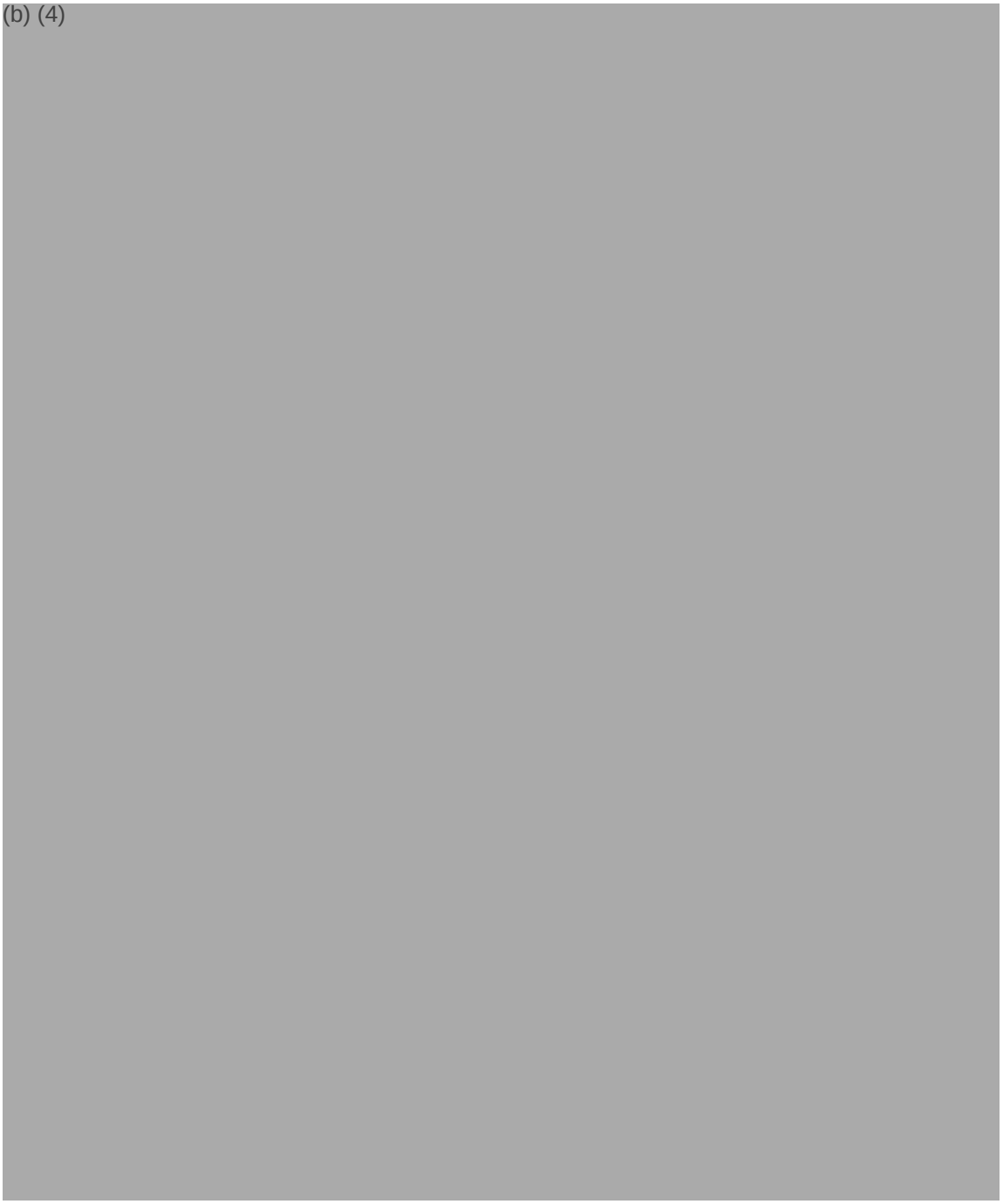
Appendix 3

(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.

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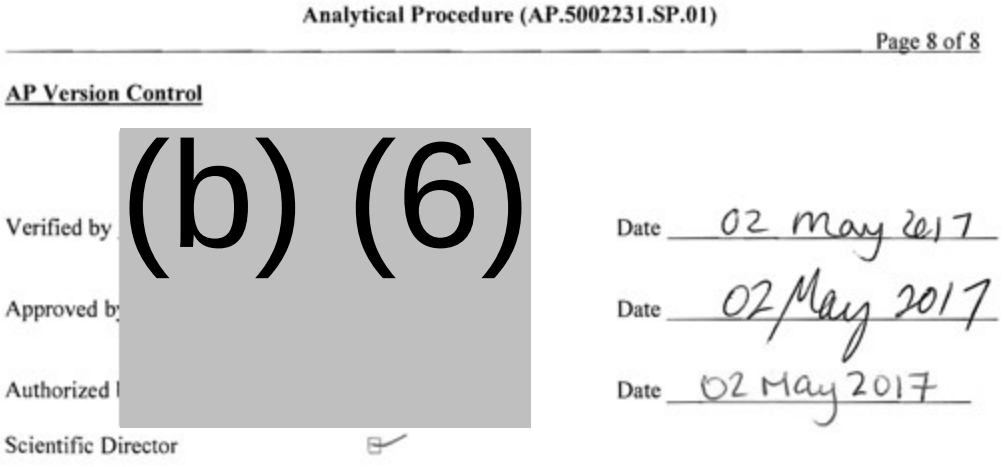

Analytical Procedure (AP.5002231.SP.01)

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AP Version Control

Verified by (b) (6) Date 02 May 2017

Approved by Date 02 May 2017

Authorized by Date 02 May 2017

Scientific Director

Appendix 3

Analytical Procedure (AP.5002231.DLS.01)

Determination of the Particle Size Distribution of mRNA-1706 Drug Product by Dynamic Light Scattering (DLS) using Wyatt DynaPro NanoStar.

Bulk Test Item

Identity	mRNA-1706
Description	White dispersion in lipid nanoparticles
Lot number	MTDP17036
Concentration (nominal)	2.1 mg/mL (to be used for calculations)

For storage conditions for test item supplied by the Sponsor, refer to the corresponding log sheets.

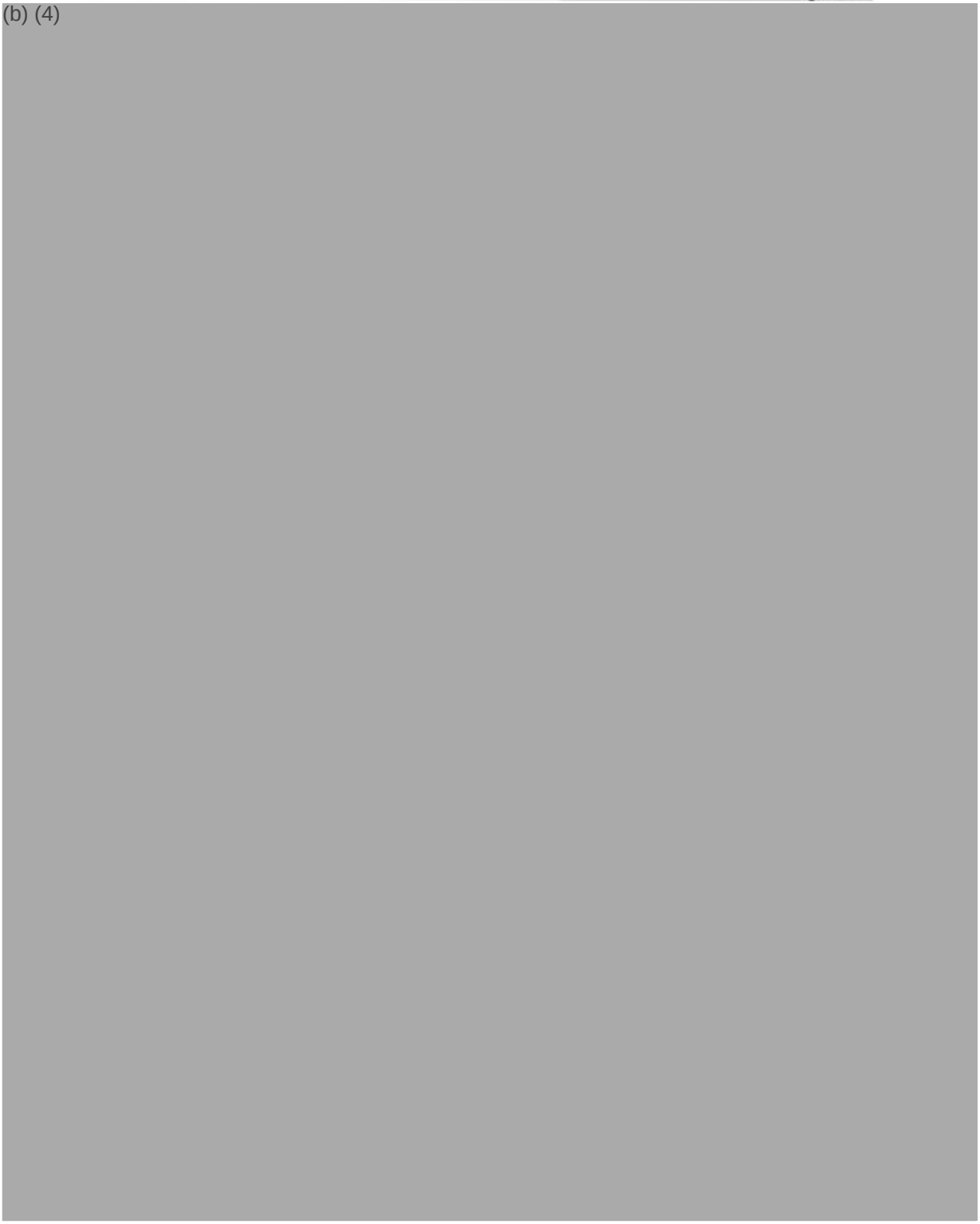
NOTES:

- ❑ 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.5002231.DLS.01)

Instrument Parameters for Sample Reading

Save all settings as a preset on location D:\Dynamics\Projects\5002231.

(b) (4)

Appendix 3

Analytical Procedure (AP.5002158.DLS.01)

(b) (4)

AP Version Control

Initial version.

Verified by (b) (6) Date 23 Jun 2017

Approved by Date 23 Jun 2017

Authorized b Date 23 Jun 2017

Scientific Director

Appendix 3

Appendix 2
Summaries of Analysis

Appendix 3

moderna
messenger therapeutics

200 Technology Square • Cambridge, MA 02139
Phone 617.714.6500 • Fax 617.583.1998

SUMMARY OF ANALYSIS

Sample Description:	**CX-000171 (formerly mRNA-1325)** (mRNA API)
mRNA length:	(b) (4)
SCC:	33.54 µg/mL
Lot or Batch No:	MTDS16017
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	August 2016
Date of Analysis:	August 2016
Storage:	Shipping Temperature: ≤ - 15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	August 2017

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Appearance	SOP-0045, v1.0	Clear, colorless solution, no visible particulates	Clear, colorless solution, no visible particulates	ELN 2016_08_08-049-(b) (6)
Identity	RT/Sanger Sequencing TSOP134.03	Sequence matches 100% description of the coding region	(b) (4)	209-TSOP134-115.00
Total RNA content	DSAD-TM-0019*	(b) (4)		ELN 2016_08_08-049-(b) (6)
Purity	SOP-0067, v1.0 (Capillary electrophoresis)			ELN 2016_08_08-049-(b) (6)
Product related impurities	SOP-0067, v1.0 (Capillary electrophoresis)	Report % Pre-main peak and % Post-main areas		ELN 2016_08_08-049-(b) (6)
pH	SOP-0046, v1.0	(b) (4)		ELN 2016_08_08-049-(b) (6)
Residual DNA template	qPCR TSOP344.01			209-TSOP344-112.00
Residual total protein	SOP-0182, v0.1			2017_04_04-075-(b) (6)

CX-000171 Page 1 of 2 version 04

Appendix 3

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Residual solvents TEA	SOP-0185, v0.1	Report results	(b) (4)	ELN 2016_08_30-024 (b) (6)
IPA	SOP-0183, v0.1			ELN 2016_09_23-039 (b) (6)
Ethanol	SOP-0183, v0.1			ELN 2016_09_23-039- (b) (6)
Hexylene glycol	SOP-0184, v0.1			ELN 2016_08_18-064 (b) (6)
% Poly A tailed RNA (% Tailless RNA)	SOP-0089, v0.3 (RP-HPLC)	(b) (4)	(b) (4)	ELN 2016_08_08-049- (b) (6)
% 5' Capped	SOP-0123, v0.1			ELN 2016_08_19-084- (b) (6)
Bacterial Endotoxins	USP<85>			PD Batch Record MTDS16017
Bioburden	USP<61>			16-07998

(b) (4) (b) (6)

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

05 Apr 2017
Date:

Reviewed by: (b) (6)

05 APR 2017
Date:

CX-000171 Page 2 of 2 version 04

Appendix 3

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

eurofins | Advantar

Summary of Analysis ***DATE: 28 April 2017***

Part I Release Testing Results for mRNA-1706 LNP Drug Product Lot MTDP17036

Protocol Number: MRA-C0019-RTP0005.00 **Document Number:** MRA-C0019-RTR0011.00 (CPR15095)	**Date Received at Eurofins Advantar:** March 31, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion (20mM Tris Buffer, 8% Sucrose, pH 7.4)
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17036	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATION (Specifications per protocol)	TEST DATE	RESULTS
RNA Content (mg/mL) (Draft MRA-C0000-GTM0023)	(b) (4)	04/27/2017	(b) (4)
[1]Bacterial Endotoxins (USP <85>)		04/04/2017	
[2]Bioburden (USP <61>)		03/31/2017	

[1] Testing performed at Associates of Cape Cod Incorporated
[2]Testing performed at Nelson Laboratories
[3]Three samples tested and all sample results are (b) (4)

The data generated at Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Advantar has archived the raw data.

(b) (6)

28 APR 2017
Date

Appendix 3

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
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Summary of Analysis ***DATE: 6 July 2017***

Part II Release Testing Results for mRNA-1706 LNP Drug Product Lot MTDP17036

Protocol Number: MRA-C0019-RTP0005.00 **Document Number:** MRA-C0019-RTR0012.00 (CPR15101)	**Date Received at Eurofins Advantar:** March 31, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion (20mM Tris Buffer, 8% Sucrose, pH 7.4)
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17036	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Appearance (MRA-C0000-GTM0016.00)	White to off-white dispersion, no visible particulates	04/27/2017	Conforms (CPR15097 Page 10)
Identity (Sanger Sequencing)	Sequence matches 100% description of the coding region	04/28/2017	Conforms (CPR15097 ADR C1)
Purity (MRA-C0000-GTM0019.01)	(b) (4)	05/01/2017	(b) (4)
Related Impurities (MRA-C0000-GTM0019.01)	Report % Pre-main peak and % Post main peak areas	05/01/2017	
Encapsulated RNA (MRA-C0000-GTM0014.00)	(b) (4)	04/24/2017 05/04/2017 05/05/2017	
Lipid Identification		05/22/2017	
SM-102	Matches retention time of standard		Conforms
Cholesterol	Matches retention time of standard		Conforms
DSPC	Matches retention time of standard		Conforms
PEG2000-DMG	Matches retention time of standard		Conforms
(UHPLC-CAD)			(CPR15097 ADR C1)
Lipid Content	Lipid (mg/mL)		(b) (4)
SM-102	(b) (4)	05/22/2017	
Cholesterol			
DSPC			
PEG2000-DMG			
(UHPLC-CAD)			

Appendix 3

Eurofins Advantar Laboratories, Inc.
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Summary of Analysis ***DATE: 6 July 2017***

Part II Release Testing Results for mRNA-1706 LNP Drug Product Lot MTDP17036

Protocol Number: MRA-C0019-RTP0005.00 **Document Number:** MRA-C0019-RTR0012.00 (CPR15101)	**Date Received at Eurofins Advantar:** March 31, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion (20mM Tris Buffer, 8% Sucrose, pH 7.4)
Time point: Release **Storage Condition:** -20°C	**Product Lot #:** MTDP17036	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Lipid Impurities (UHPLC-CAD)	Report total % Area and RRT	05/22/2017	(b) (4)
Mean Particle Size (nm) (MRA-C0000-GTM0015.02)	Report result	04/27/2017	
Polydispersity (MRA-C0000-GTM0015.02)	Report result	04/27/2017	
Particulate Matter[1] (USP <788> method 2)	(b) (4)	04/07/2017	
Residual Solvents from Formulation: Ethanol (MRA-C0000-GTM0018.01)		05/04/2017	
Osmolality (USP <785>)	Report Result	04/27/2017	
pH (MRA-C0000-GTM0017.01)	Report result	04/27/2017	

[1] Testing performed at Nelson Laboratories.
[2] This is a composite mean coming from 3 data sets (below) as requested by the Sponsor (CPR15099, ADR F1-F2):
T=0 (n=1, 84%), CPR15099, ADR D5
Method Qualification-Linearity (n=6 preps, 90%, 90%, 89%, 90%, 90%, 89%), CPR14795, ADR E7
Method Qualification-Stability (n=1, 88%), CPR14796, ADR F5

The data generated at Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Advantar has archived the raw data.

(b) (6)

06JUL 2017
Date

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)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 4

Individual Animal Mortality

5002231

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	30	5	01JUN2017	14:40	.	.	TERM
			1002	1001	30	5	01JUN2017	14:37	.	.	TERM
			1003	1001	30	5	01JUN2017	15:57	.	.	TERM
			1004	1004	30	5	01JUN2017	15:41	.	.	TERM
			1005	1004	30	5	01JUN2017	17:04	.	.	TERM
			1006	1004	30	5	01JUN2017	16:45	.	.	TERM
			1007	1007	30	5	01JUN2017	19:35	.	.	TERM
			1008	1007	30	5	01JUN2017	18:42	.	.	TERM
			1009	1009	30	5	01JUN2017	20:46	.	.	TERM
			1010	1009	30	5	01JUN2017	19:36	.	.	TERM
			1011	1011	43	7	14JUN2017	10:24	.	.	REC
			1012	1011	43	7	14JUN2017	12:52	.	.	REC
			1013	1011	43	7	14JUN2017	13:42	.	.	REC
			1014	1014	43	7	14JUN2017	14:32	.	.	REC
			1015	1014	43	7	14JUN2017	15:25	.	.	REC
1	0 ug/dose	Female	1501	1501	30	5	02JUN2017	14:36	.	.	TERM
			1502	1501	30	5	02JUN2017	14:35	.	.	TERM
			1503	1501	30	5	02JUN2017	15:40	.	.	TERM
			1504	1504	30	5	02JUN2017	15:36	.	.	TERM
			1505	1504	30	5	02JUN2017	16:42	.	.	TERM
			1506	1504	30	5	02JUN2017	16:33	.	.	TERM
			1507	1507	30	5	02JUN2017	17:34	.	.	TERM
			1508	1507	30	5	02JUN2017	17:24	.	.	TERM
			1509	1509	30	5	02JUN2017	19:43	.	.	TERM
			1510	1509	30	5	02JUN2017	19:21	.	.	TERM
			1511	1511	43	7	15JUN2017	8:54	.	.	REC
			1512	1511	43	7	15JUN2017	9:42	.	.	REC
			1513	1511	43	7	15JUN2017	10:21	.	.	REC
			1514	1514	43	7	15JUN2017	11:03	.	.	REC
			1515	1514	43	7	15JUN2017	11:41	.	.	REC
2	10 ug/dose	Male	2001	2001	30	5	01JUN2017	15:38	.	.	TERM
			2002	2001	30	5	01JUN2017	15:28	.	.	TERM
			2003	2001	30	5	01JUN2017	16:48	.	.	TERM
			2004	2004	30	5	01JUN2017	16:30	.	.	TERM
			2005	2004	30	5	01JUN2017	19:18	.	.	TERM

Appendix 4

Individual Animal Mortality

5002231

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
2	10 ug/dose	Male	2006	2004	30	5	01JUN2017	18:26	.	.	TERM
			2007	2007	30	5	01JUN2017	20:29	.	.	TERM
			2008	2007	30	5	01JUN2017	19:24	.	.	TERM
			2009	2009	30	5	01JUN2017	20:44	.	.	TERM
			2010	2009	30	5	01JUN2017	20:21	.	.	TERM
2	10 ug/dose	Female	2501	2501	30	5	02JUN2017	15:24	.	.	TERM
			2502	2501	30	5	02JUN2017	15:23	.	.	TERM
			2503	2501	30	5	02JUN2017	16:27	.	.	TERM
			2504	2504	30	5	02JUN2017	16:19	.	.	TERM
			2505	2504	30	5	02JUN2017	17:22	.	.	TERM
			2506	2504	30	5	02JUN2017	17:12	.	.	TERM
			2507	2507	30	5	02JUN2017	19:26	.	.	TERM
			2508	2507	30	5	02JUN2017	19:09	.	.	TERM
			2509	2509	30	5	02JUN2017	20:30	.	.	TERM
			2510	2509	30	5	02JUN2017	20:02	.	.	TERM
3	50 ug/dose	Male	3001	3001	30	5	01JUN2017	15:20	.	.	TERM
			3002	3001	30	5	01JUN2017	15:11	.	.	TERM
			3003	3001	30	5	01JUN2017	16:30	.	.	TERM
			3004	3004	30	5	01JUN2017	16:15	.	.	TERM
			3005	3004	30	5	01JUN2017	18:59	.	.	TERM
			3006	3004	30	5	01JUN2017	17:15	.	.	TERM
			3007	3007	30	5	01JUN2017	20:10	.	.	TERM
			3008	3007	30	5	01JUN2017	19:10	.	.	TERM
			3009	3009	30	5	01JUN2017	21:16	.	.	TERM
			3010	3009	30	5	01JUN2017	20:05	.	.	TERM
3	50 ug/dose	Female	3501	3501	30	5	02JUN2017	15:09	.	.	TERM
			3502	3501	30	5	02JUN2017	15:09	.	.	TERM
			3503	3501	30	5	02JUN2017	16:12	.	.	TERM
			3504	3504	30	5	02JUN2017	16:06	.	.	TERM
			3505	3504	30	5	02JUN2017	17:10	.	.	TERM
			3506	3504	30	5	02JUN2017	16:59	.	.	TERM
			3507	3507	30	5	02JUN2017	19:08	.	.	TERM
			3508	3507	30	5	02JUN2017	18:56	.	.	TERM
			3509	3509	30	5	02JUN2017	20:14	.	.	TERM

Appendix 4

Individual Animal Mortality

5002231

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
3	50 ug/dose	Female	3510	3509	30	5	02JUN2017	19:49	.	.	TERM
4	100 ug/dose	Male	4001	4001	30	5	01JUN2017	15:00	.	.	TERM
			4002	4001	30	5	01JUN2017	14:57	.	.	TERM
			4003	4001	30	5	01JUN2017	16:12	.	.	TERM
			4004	4004	30	5	01JUN2017	16:00	.	.	TERM
			4005	4004	30	5	01JUN2017	17:20	.	.	TERM
			4006	4004	30	5	01JUN2017	17:00	.	.	TERM
			4007	4007	30	5	01JUN2017	19:52	.	.	TERM
			4008	4007	30	5	01JUN2017	18:57	.	.	TERM
			4009	4009	30	5	01JUN2017	21:02	.	.	TERM
			4010	4009	30	5	01JUN2017	19:50	.	.	TERM
			4011	4011	43	7	14JUN2017	12:28	.	.	REC
			4012	4011	43	7	14JUN2017	13:17	.	.	REC
			4013	4011	43	7	14JUN2017	14:06	.	.	REC
			4014	4014	43	7	14JUN2017	15:00	.	.	REC
			4015	4014	43	7	14JUN2017	15:51	.	.	REC
4	100 ug/dose	Female	4501	4501	30	5	02JUN2017	14:53	.	.	TERM
			4502	4501	30	5	02JUN2017	14:56	.	.	TERM
			4503	4501	30	5	02JUN2017	15:56	.	.	TERM
			4504	4504	30	5	02JUN2017	15:52	.	.	TERM
			4505	4504	30	5	02JUN2017	16:56	.	.	TERM
			4506	4504	30	5	02JUN2017	16:46	.	.	TERM
			4507	4507	30	5	02JUN2017	18:54	.	.	TERM
			4508	4507	30	5	02JUN2017	18:42	.	.	TERM
			4509	4509	30	5	02JUN2017	19:58	.	.	TERM
			4510	4509	30	5	02JUN2017	19:34	.	.	TERM
			4511	4511	43	7	15JUN2017	9:18	.	.	REC
			4512	4511	43	7	15JUN2017	10:01	.	.	REC
			4513	4511	43	7	15JUN2017	10:41	.	.	REC
			4514	4514	43	7	15JUN2017	11:22	.	.	REC
			4515	4514	43	7	15JUN2017	12:01	.	.	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)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	3	4
1	m	1001	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
		1002	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
		1003	Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.	.
		1005	Hyperreactive		.	.	.	.	.	.	.	.
			Vocalization Increased		.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	X	X	X	X
			Fur, Thin Cover	Dorsal Cervical	X	X	X	.	.	.	.	.
		1006	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	X	X	X	X	X
			Pinna Partly Missing	Left	X	X	X	X	X	X	X	X
		1007	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	X
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	X	.
		1008	Hyperreactive		.	.	X	X	.	.	.	.
			Vocalization Increased		.	.	.	X	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	X	X	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	X	X	X	.	.	.	.
			Fur, Thin Cover	Cranium	X	X	X	.	.	.	.	.
		1009	Skin, Red	Treatment Site No.01	.	.	.	.	.	X	X	.
		1010	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
		1011	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
		1012	Skin, Scab	Treatment Site No.02	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	X	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	X	.	.	.	.
		1013	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	.	X	X	X	X	X	X	X
			Pinna Partly Missing	Left	.	X	X	X	X	X	X	X
		1014	Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	7 DE	14 DE	15	16	17	18	21 DE	28 DE
1	m	1001	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
		1002	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
		1003	Skin, Red	Hindpaw, Left	X	.	.	.	.	.	.	.
		1005	Hyperreactive		.	.	.	.	.	.	.	.
			Vocalization Increased		.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.	.
		1006	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	X	X	X	X	X
			Pinna Partly Missing	Left	X	X	X	X	X	X	X	X
		1007	Swollen Soft	Treatment Site No.02	.	.	.	2	.	.	.	.
			Skin, Red	Treatment Site No.01	X	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.
		1008	Hyperreactive		X	X	.	.	.	.	X	X
			Vocalization Increased		X	X	.	.	.	.	X	X
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	X
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.
		1009	Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
		1010	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
		1011	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
		1012	Skin, Scab	Treatment Site No.02	.	.	.	.	X	X	X	.
			Skin, Scab	Cranium	X	X	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	X	X	.	.	.	.	.	.
		1013	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
			Skin, Red	Hindpaw, Right	X	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	X	X	X	X	X
			Pinna Partly Missing	Left	X	X	X	X	X	X	X	X
		1014	Skin, Red	Hindpaw, Right	.	X	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	X	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	X	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 PreRx	30	30 DE	31	32	35 DE	42 DE	43 DE
1	m	1001	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
		1002	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
		1003	Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.	.
		1005	Hyperreactive		.	.	X	.	.	.	.	.
			Vocalization Increased		.	.	X	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.	.
		1006	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	.	.	.	.	.
			Pinna Partly Missing	Left	X	X	X	.	.	.	.	.
		1007	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.
		1008	Hyperreactive		.	.	X	.	.	.	.	.
			Vocalization Increased		.	.	X	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.
		1009	Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
		1010	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
		1011	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
		1012	Skin, Scab	Treatment Site No.02	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.
		1013	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	.	X	X	X	X	X
			Pinna Partly Missing	Left	X	X	.	X	X	X	X	X
		1014	Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	3	4
1	m	1015	Skin, Scab	Cranium	X	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	7 DE	14 DE	15	16	17	18	21 DE	28 DE
1	m	1015	Skin, Scab	Cranium	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 PreRx	30	30 DE	31	32	35 DE	42 DE	43 DE
1	m	1015	Skin, Scab	Cranium	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	3	4	7 DE	14 DE	16
2	m	2001	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	2
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	.	.	.
			Skin, Scab	Pinna, Right	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.	.
		2002	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	2
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	X	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	.	.	.	.	.
		2003	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	2
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	X	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Hindlimb, Right	.	.	.	.	.	.	.	X	.
			Fur, Thin Cover	Cranium	X	.	.	.	.	.	.	.	.
		2004	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Skin, Scab	Treatment Site No.01	.	.	.	.	X	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	17	18	21 DE	28 DE	29 PreRx	30	30 DE
2	m	2001	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Right	.	.	.	.	.	.	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.	X	.	.	X
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	X
		2002	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.
		2003	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	X	X	X
			Skin, Scab	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Hindlimb, Right	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.
		2004	Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	X	X
			Fur, Staining, Red	Cranium	.	.	X	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	3	4	7 DE	14 DE	16
2	m	2005	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	2
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	X	.	.
			Skin, Scab	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	X	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	X	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	X	X	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	X	X	X	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	X	X	.	.	X	X	.
		2006	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	2
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	X	.	.
			Skin, Scab	Cranium	.	X	.	X	.	.	X	X	.
			Fur, Thin Cover	Cranium	.	X	X	X	.	.	X	X	.
		2007	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	2
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	.	.	.
			Skin, Scab	Cranium	.	.	.	X	.	.	.	.	.
			Fur, Staining, Red	Urogenital	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	X	X	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.	X	.
			Fur, Thin Cover	Cranium	.	.	.	X	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	17	18	21 DE	28 DE	29 PreRx	30	30 DE
2	m	2005	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	1
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.02	X	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	X
		2006	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	X	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	X	X	.	.	.
		2007	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.
			Fur, Staining, Red	Urogenital	.	.	.	X	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	3	4	7 DE	14 DE	16
2	m	2008	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	2
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	X	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	X	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.	X	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	X	X	.	.	.	.	.	.	.
		2009	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.	X	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.	X	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	X	X	.	.	.
			Skin, Scab	Forepaw, Left	.	.	.	.	.	.	X	.	.
			Skin, Scab	Cranium	.	.	.	X	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	X	X	.
			Fur, Thin Cover	Cranium	.	.	.	X	.	.	.	.	.
		2010	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	2
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.	X	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	X	X	.
			Skin, Dry	Hindpaw, Right	.	.	.	.	.	.	.	X	.
			Skin, Dry	Hindpaw, Left	.	.	.	.	.	.	X	X	.
			Skin, Scab	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Scab	Tail	X	.	.	.	.	.	.	.	.
			Skin, Scab	Lumbar	.	.	.	.	.	.	X	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.	X	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	17	18	21 DE	28 DE	29 PreRx	30	30 DE
2	m	2008	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	X	X
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.
		2009	Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Scab	Forepaw, Left	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.
		2010	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	1	1	.	.	.	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.
			Skin, Dry	Hindpaw, Right	.	.	.	.	.	.	.
			Skin, Dry	Hindpaw, Left	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.02	.	.	X	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.	.	.
			Skin, Scab	Lumbar	.	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	X	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	X	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	3	4
3	m	3001	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	1	1
			Swollen Firm	Dorsal Cervical	1	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	X
			Skin, Red	Forepaw, Right	.	X	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	X	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	X	X	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	X	X	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	X	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.	X	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	X	X	.	.	.	.	.	.
		3002	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	1
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	X	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	.	.	.	.
		3003	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	1
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	X
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	.	.
		3004	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	1	1
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	X
			Fur, Staining, Red	Cranium	.	.	X	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	7 DE	14 DE	15	16	17	18	21 DE	28 DE
3	m	3001	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	1	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Dorsal Cervical	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Forepaw, Right	.	.	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	X	X	.	.	.	.	X	X
			Fur, Thin Cover	Forelimb, Left	X	X	.	.	.	.	X	X
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.	.
		3002	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	1	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	X	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.
		3003	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	1	2	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	X	.
		3004	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	1	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	X
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 PreRx	30	30 DE
3	m	3001	Swollen Soft	Treatment Site No.02	.	.	.
			Swollen Soft	Treatment Site No.01	.	1	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	1
			Swollen Firm	Dorsal Cervical	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.
			Skin, Red	Forepaw, Right	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	X
			Fur, Thin Cover	Forelimb, Left	.	.	X
			Fur, Thin Cover	Dorsal Cervical	.	.	.
		3002	Swollen Soft	Treatment Site No.01	.	1	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	1
			Skin, Red	Treatment Site No.02	.	.	.
			Skin, Scab	Cranium	.	.	.
			Fur, Thin Cover	Cranium	.	.	.
		3003	Swollen Soft	Treatment Site No.01	.	1	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	1
			Skin, Red	Treatment Site No.01	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.
		3004	Swollen Soft	Treatment Site No.02	.	.	.
			Swollen Soft	Treatment Site No.01	.	1	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	1
			Skin, Red	Treatment Site No.01	.	.	.
			Fur, Staining, Red	Cranium	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	3	4
3	m	3005	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	1	1
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	X
			Skin, Scab	Tail	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	X	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	X	X	.	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	.	.	.	.
		3006	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	1	2
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X	X
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	.	.
		3007	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	1	2
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	X
			Skin, Red	Hindpaw, Right	.	.	.	X	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	X	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	7 DE	14 DE	15	16	17	18	21 DE	28 DE
3	m	3005	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	1	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.
		3006	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	1	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	X	X	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	X	X	.	.	.	.	X	X
		3007	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	1	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 PreRx	30	30 DE
3	m	3005	Swollen Soft	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	2
			Skin, Red	Treatment Site No.01	.	.	.
			Skin, Scab	Tail	.	.	X
			Skin, Scab	Cranium	.	.	.
			Fur, Staining, Red	Cranium	.	.	.
			Fur, Thin Cover	Cranium	.	.	.
		3006	Swollen Soft	Treatment Site No.02	.	.	.
			Swollen Soft	Treatment Site No.01	.	1	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	2
			Skin, Red	Treatment Site No.01	.	.	.
			Skin, Scab	Treatment Site No.01	.	X	X
			Fur, Thin Cover	Forelimb, Right	.	.	X
			Fur, Thin Cover	Forelimb, Left	.	.	X
		3007	Swollen Soft	Treatment Site No.02	.	.	.
			Swollen Soft	Treatment Site No.01	.	2	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	1
			Skin, Red	Treatment Site No.01	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.
			Skin, Scab	Treatment Site No.01	.	X	X
			Fur, Staining, Red	Cranium	.	.	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	3	4
3	m	3008	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	2	1	1
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	X
			Skin, Scab	Pinna, Right	.	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Left	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	X	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	X	X	X	X	X
		3009	Vocalization Increased		.	.	.	.	.	X	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	1	1
			Skin, Scab	Treatment Site No.02	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	X	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	X	.	.	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	.	.	.	.
		3010	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	1	1
			Skin, Red	Pinna, Right	X	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	X	X	X	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	7 DE	14 DE	15	16	17	18	21 DE	28 DE
3	m	3008	Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	1	2	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Right	.	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Left	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	X	.	.	.	.	.	.	.
		3009	Vocalization Increased		.	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	1	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	1	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.02	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.
		3010	Swollen Soft	Treatment Site No.02	.	.	.	2	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	1	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	X	X	X	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 PreRx	30	30 DE
3	m	3008	Swollen Soft	Treatment Site No.02	.	.	.
			Swollen Soft	Treatment Site No.01	.	1	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	1
			Skin, Red	Treatment Site No.01	.	.	.
			Skin, Scab	Pinna, Right	.	.	X
			Skin, Scab	Pinna, Left	.	.	X
			Fur, Staining, Red	Cranium	.	.	X
			Fur, Thin Cover	Cranium	.	.	X
			Pinna Partly Missing	Right	.	.	.
		3009	Vocalization Increased		.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	2
			Skin, Scab	Treatment Site No.02	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	X
			Fur, Staining, Red	Muzzle	.	.	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.
			Fur, Thin Cover	Cranium	.	.	.
		3010	Swollen Soft	Treatment Site No.02	.	.	.
			Swollen Soft	Treatment Site No.01	.	1	.
			Swollen Firm	Treatment Site No.02	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	2
			Skin, Red	Pinna, Right	.	.	.
			Pinna Partly Missing	Right	X	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-48 Vet Aid	-37 DE	-23 DE	-9 DE	-1 DE	1
4	m	4001	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Pinna, Right	X	.	.	.	.	.
			Skin, Red	Pinna, Left	.	X	X	.	.	.
			Skin, Scab	Treatment Site No.02	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	X	.	.	.	.
			Pinna Partly Missing	Right	.	X	X	X	X	X
			Pinna Partly Missing	Left	.	X	X	X	X	X
		4002	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	X
			Skin, Scab	Cranium	.	.	.	.	X	.
			Fur, Thin Cover	Cranium	.	.	.	.	X	.
		4003	Abnormal Gait		.	.	.	.	.	.
			Hyperreactive		.	.	.	.	.	.
			Vocalization Increased		.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.
			Limited Usage	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	X	.	.	.	.
		4004	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	3	4	7 DE	14 DE	15
4	m	4001	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	1	2	.	.	.
			Skin, Red	Treatment Site No.01	.	X	X	X	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.02	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	X	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	X	X	.
			Pinna Partly Missing	Right	X	X	X	X	X	X
			Pinna Partly Missing	Left	X	X	X	X	X	X
		4002	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	1	2	.	.	.
			Skin, Red	Treatment Site No.01	.	X	X	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	X	X	.
			Fur, Thin Cover	Cranium	.	.	.	X	X	.
		4003	Abnormal Gait		.	.	.	.	.	.
			Hyperreactive		.	.	.	.	.	.
			Vocalization Increased		.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.
			Limited Usage	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	1	3	.	.	.
			Skin, Red	Treatment Site No.01	.	X	X	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
		4004	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	1	2	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	15 Unsc	16	17	18	21 DE	28 DE
4	m	4001	Swollen Firm	Treatment Site No.02	.	1	2	2	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.02	.	.	.	.	X	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	X
			Skin, Scab	Cranium	.	.	.	.	X	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	X
			Fur, Thin Cover	Cranium	.	.	.	.	X	X
			Pinna Partly Missing	Right	.	X	X	X	X	X
			Pinna Partly Missing	Left	.	X	X	X	X	X
		4002	Swollen Firm	Treatment Site No.02	.	1	1	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
		4003	Abnormal Gait		.	.	.	.	.	.
			Hyperreactive		.	.	.	.	.	.
			Vocalization Increased		.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.
			Limited Usage	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	2	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
		4004	Swollen Firm	Treatment Site No.02	.	1	1	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	X	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 PreRx	30	30 DE	31	32
4	m	4001	Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	1	1	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.
			Skin, Scab	Treatment Site No.02	.	.	X	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.
			Skin, Scab	Cranium	.	.	X	.	.
			Fur, Staining, Red	Cranium	.	.	X	.	.
			Fur, Thin Cover	Cranium	.	.	X	.	.
			Pinna Partly Missing	Right	X	X	X	.	.
			Pinna Partly Missing	Left	X	X	X	.	.
		4002	Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	2	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.
		4003	Abnormal Gait		.	.	X	.	.
			Hyperreactive		.	.	X	.	.
			Vocalization Increased		.	.	X	.	.
			Hunched Posture		.	.	X	.	.
			Limited Usage	Treatment Site No.01	.	1	1	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	2	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	X	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.
		4004	Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	1	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-48 Vet Aid	-37 DE	-23 DE	-9 DE	-1 DE	1
4	m	4005	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
		4006	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	X
		4007	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	X	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	X	X	.	.	.
		4008	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	X	.
			Skin, Scab	Pinna, Left	X	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	X	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	X	.	.	.	.
			Pinna Partly Missing	Left	.	X	X	X	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	3	4	7 DE	14 DE	15
4	m	4005	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	2	2	.	.	.
			Skin, Red	Treatment Site No.01	.	X	X	.	.	.
		4006	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	1	1	2	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	X	X	X	.	.	.
		4007	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	1	2	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.
		4008	Swollen Soft	Treatment Site No.01	2	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	3	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	X	X	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.
			Skin, Scab	Pinna, Left	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.
			Pinna Partly Missing	Left	X	X	X	X	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	15 Unsc	16	17	18	21 DE	28 DE
4	m	4005	Swollen Firm	Treatment Site No.02	.	2	2	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
		4006	Swollen Firm	Treatment Site No.02	.	1	1	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
		4007	Swollen Firm	Treatment Site No.02	.	1	1	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	X	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	X
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.
		4008	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	2	2	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.
			Warm to Touch		.	X	X	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.
			Skin, Scab	Pinna, Left	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.
			Pinna Partly Missing	Left	.	X	X	X	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 PreRx	30	30 DE	31	32
4	m	4005	Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	2	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
		4006	Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	2	.	.
			Swollen Firm	Inguinal, Left	.	.	1	.	.
			Skin, Scab	Treatment Site No.01	X	.	X	.	.
		4007	Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	3	2	.	.
			Swollen Firm	Inguinal, Left	.	.	1	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	X	.	.	.
			Skin, Scab	Treatment Site No.01	.	X	X	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.
		4008	Swollen Soft	Treatment Site No.01	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	3	2	.	.
			Swollen Firm	Inguinal, Left	.	.	1	.	.
			Warm to Touch		.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.
			Skin, Scab	Pinna, Left	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.
			Pinna Partly Missing	Left	X	X	X	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-48 Vet Aid	-37 DE	-23 DE	-9 DE	-1 DE	1
4	m	4009	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	X	X	.	.	.
			Fur, Thin Cover	Cranium	.	X	X	.	.	.
			Pinna Partly Missing	Right	.	.	.	.	X	X
		4010	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Black	Tail	.	X	X	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	X	X	.
			Skin, Scab	Dorsal Cervical	.	X	.	.	.	.
			Skin, Scab	Tip of Tail	X	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	X	X	X	.	.
			Tail, Missing		X	X	X	X	X	X
		4011	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Cranium	.	X	.	.	.	.
			Fur, Thin Cover	Cranium	.	X	X	.	.	.
		4012	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Scapular, Right	.	.	X	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	X	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	X	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	3	4	7 DE	14 DE	15
4	m	4009	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	2	2	.	.	.
			Skin, Red	Treatment Site No.01	.	X	X	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	X	X	X
		4010	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	1	2	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Black	Tail	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	X	X	.	.	.
			Skin, Scab	Tail	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.
			Skin, Scab	Tip of Tail	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.
			Tail, Missing		X	X	X	X	X	X
		4011	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	2	2	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	X	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
		4012	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	1	1	.	.	.
			Skin, Scab	Scapular, Right	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	15 Unsc	16	17	18	21 DE	28 DE
4	m	4009	Swollen Firm	Treatment Site No.02	.	2	1	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
			Pinna Partly Missing	Right	.	X	X	X	X	X
		4010	Swollen Firm	Treatment Site No.02	.	1	1	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		.	X	.	.	.	.
			Skin, Black	Tail	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.
			Skin, Scab	Tip of Tail	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	X
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.
			Tail, Missing		.	X	X	X	X	X
		4011	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	2	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		X	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	X	X	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
		4012	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	2	2	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Skin, Scab	Scapular, Right	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 PreRx	30	30 DE	31	32
4	m	4009	Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	2	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	X	X	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.
			Pinna Partly Missing	Right	X	X	X	.	.
		4010	Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	3	1	.	.
			Warm to Touch		.	.	.	.	.
			Skin, Black	Tail	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.
			Skin, Scab	Tip of Tail	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	X	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.
			Tail, Missing		X	X	X	.	.
		4011	Swollen Soft	Treatment Site No.01	.	2	.	2	2
			Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.
			Warm to Touch		.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.
		4012	Swollen Soft	Treatment Site No.01	.	1	.	2	2
			Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Scapular, Right	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-48 Vet Aid	-37 DE	-23 DE	-9 DE	-1 DE	1
4	m	4013	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	X	.	.
		4014	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.
			Skin, Scab	Cranium	.	X	.	.	.	.
			Fur, Thin Cover	Cranium	.	X	.	.	.	.
		4015	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	3	4	7 DE	14 DE	15
4	m	4013	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	1	2	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	X	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	X	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
		4014	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	1	2	2	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
		4015	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	1	1	1	.	.	.
			Warm to Touch		.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	15 Unsc	16	17	18	21 DE	28 DE
4	m	4013	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	2	2	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		X	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.
			Skin, Red	Pinna, Right	X	.	.	.	.	.
			Skin, Red	Pinna, Left	X	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.
		4014	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	1	2	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		X	.	.	.	.	.
			Skin, Red	Pinna, Right	X	.	.	.	.	.
			Skin, Red	Pinna, Left	X	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.
		4015	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	2	2	1	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.
			Warm to Touch		X	.	.	.	.	.
			Skin, Red	Pinna, Right	X	.	.	.	.	.
			Skin, Red	Pinna, Left	X	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	29 PreRx	30	30 DE	31	32
4	m	4013	Swollen Soft	Treatment Site No.01	.	.	.	.	2
			Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.
			Warm to Touch		.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.
		4014	Swollen Soft	Treatment Site No.01	.	2	.	2	2
			Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.
			Warm to Touch		.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.
		4015	Swollen Soft	Treatment Site No.01	.	1	.	2	2
			Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.
			Warm to Touch		.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	7 DE	14 DE	18	21 DE
1	f	1502	Skin, Scab	Cranium	.	.	.	X	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Interscapular	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	X
			Fur, Thin Cover	Periorbital, Right	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	X	.	.	.	.
		1504	Skin, Red	Pinna, Right	X	X	.	.	.	.	.	.
			Skin, Scab	Pinna, Right	X	X	.	.	.	.	.	.
		1508	Teeth, Clear		.	X	X	.	.	.	.	.
		1509	Skin, Scab	Cranium	.	.	.	.	X	X	.	X
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	X	X	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	X	X	.	X
			Fur, Staining, Red	Cranium	.	.	.	.	X	X	.	X
			Fur, Thin Cover	Cranium	.	.	.	.	X	X	.	X
			Teeth, Clear		.	X	X	.	.	.	.	.
		1510	Skin, Red	Periorbital, Left	.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Periorbital, Left	.	.	.	.	X	X	.	.
			Fur, Thin Cover	Periorbital, Left	.	.	.	.	.	.	.	.
		1512	Fur, Thin Cover	Forepaw, Right	.	.	.	.	X	.	.	.
		1513	Skin, Red	Treatment Site No.02	.	.	.	.	.	.	X	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	X	.	.
			Fur, Staining, Red	Forelimb, Right	.	.	.	.	.	.	.	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	X	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	X	X	X	X	.	X

Severity Codes: X = Present

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	28 DE	29 PreRx	30	30 DE	35 DE	42 DE	43 DE
1	f	1502	Skin, Scab	Cranium	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	X	.	.	.
			Fur, Staining, Red	Interscapular	.	.	.	X	.	.	.
			Fur, Staining, Red	Dorsal Cervical	X	.	.	.	.	.	.
			Fur, Thin Cover	Periorbital, Right	X	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	X	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	X	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	X	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	.	.	.
		1504	Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Right	.	.	.	.	.	.	.
		1508	Teeth, Clear		.	.	.	.	.	.	.
		1509	Skin, Scab	Cranium	X	.	.	X	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	X	.	.	.
			Fur, Staining, Red	Scapular, Right	X	.	.	X	.	.	.
			Fur, Staining, Red	Scapular, Left	X	.	.	X	.	.	.
			Fur, Staining, Red	Dorsal Cervical	X	.	.	X	.	.	.
			Fur, Staining, Red	Cranium	X	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	X	.	.	.
			Teeth, Clear		.	.	.	.	.	.	.
		1510	Skin, Red	Periorbital, Left	X	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	X	X	X	X	.	.	.
			Fur, Staining, Red	Periorbital, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Periorbital, Left	X	.	.	.	.	.	.
		1512	Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	.
		1513	Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	X	X	X
			Fur, Staining, Red	Forelimb, Right	X	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	X	X	X
			Fur, Thin Cover	Forelimb, Right	X	.	.	.	X	X	X

Severity Codes: X = Present

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	7 DE	14 DE	18	21 DE
1	f	1514	Skin, Scab	Pinna, Right	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	X	X	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	X	.	X
			Fur, Thin Cover	Ventral Cervical	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Left	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	X	.	.	X
			Fur, Thin Cover	Interscapular	.	.	.	.	X	X	.	X
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.	X	X	.	X
			Fur, Thin Cover	Dorsal Cervical	.	.	.	X	X	X	.	.
			Fur, Thin Cover	Cranium	.	.	.	X	X	X	.	X
			Fur, Thin Cover	Axillary, Right	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Abdominal	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Aspect Generalized	.	.	.	.	.	.	.	.
		1515	Skin, Scab	Ventral Cervical	.	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Right	.	.	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	X
			Fur, Thin Cover	Ventral Thoracic	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	28 DE	29 PreRx	30	30 DE	35 DE	42 DE	43 DE
1	f	1514	Skin, Scab	Pinna, Right	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	X	X	X
			Fur, Staining, Red	Dorsal Cervical	X	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	.	.	.	.	.	X
			Fur, Thin Cover	Scapular, Right	X	.	.	.	X	.	.
			Fur, Thin Cover	Scapular, Left	X	.	.	.	X	.	.
			Fur, Thin Cover	Lumbar	X	.	.	.	X	.	.
			Fur, Thin Cover	Interscapular	X	.	.	.	X	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	X	X	X
			Fur, Thin Cover	Dorsal Thoracic	X	.	.	.	X	.	.
			Fur, Thin Cover	Dorsal Cervical	X	.	.	.	X	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	X	.	.
			Fur, Thin Cover	Axillary, Right	.	.	.	.	X	X	X
			Fur, Thin Cover	Abdominal	.	.	.	.	X	X	X
			Fur, Thin Cover	Dorsal Aspect Generalized	.	.	.	.	.	X	X
		1515	Skin, Scab	Ventral Cervical	.	.	.	.	X	X	X
			Skin, Scab	Pinna, Right	.	.	.	.	.	X	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	X	X	.
			Skin, Scab	Cranium	X	.	.	.	X	X	X
			Fur, Staining, Red	Dorsal Cervical	X	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Thoracic	.	.	.	.	X	X	X
			Fur, Thin Cover	Ventral Cervical	X	.	.	.	X	X	X
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	X	X	X
			Fur, Thin Cover	Dorsal Cervical	X	.	.	.	X	X	X
			Fur, Thin Cover	Cranium	X	.	.	.	X	X	X

Severity Codes: X = Present

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-23 DE	-9 DE	-1 DE	2	3	4	7 DE	14 DE	16
2	f	2501	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	1	1	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	X	.
			Fur, Thin Cover	Cranium	.	.	X	.	.	.	X	.	.
		2502	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	1	1	.	.	.
			Fur, Staining, Red	Dorsal Thoracic	.	.	.	.	.	.	.	.	.
		2503	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.	.	.
		2504	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Teeth, Clear		X	X	X	.	.	.	.	.	.
		2505	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	1	.	.	.	.
			Skin, Scab	Pinna, Left	.	.	.	.	.	.	X	.	.
		2506	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
		2507	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	.	.	.	.	.
			Skin, Dry	Forepaw, Left	.	.	.	.	.	.	.	.	.
			Skin, Dry	Forelimb, Left	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	X	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	X	.
			Fur, Thin Cover	Hindlimb, Left	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	X	X	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	17	18	21 DE	28 DE	29 PreRx	30	30 DE
2	f	2501	Swollen Soft	Treatment Site No.02	1	2	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	X	X	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	X	.	.	X
		2502	Swollen Soft	Treatment Site No.02	1	1	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Thoracic	.	.	.	X	.	.	.
		2503	Swollen Soft	Treatment Site No.02	1	1	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	X	X	.	.
		2504	Swollen Soft	Treatment Site No.02	1	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	X	.
			Teeth, Clear		.	.	.	.	.	.	.
		2505	Swollen Soft	Treatment Site No.02	1	1	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Left	.	.	.	.	.	.	.
		2506	Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
		2507	Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Dry	Forepaw, Left	.	.	.	.	.	.	X
			Skin, Dry	Forelimb, Left	.	.	.	X	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	X	.	.	X
			Fur, Thin Cover	Hindlimb, Left	.	.	.	.	.	.	X
			Fur, Thin Cover	Forelimb, Right	.	.	X	X	.	.	X
			Fur, Thin Cover	Forelimb, Left	.	.	X	X	.	.	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-23 DE	-9 DE	-1 DE	2	3	4	7 DE	14 DE	16
2	f	2508	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	1	.	.	.	.
			Fur, Staining, Red	Interscapular	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	X	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	X	.
			Fur, Thin Cover	Ventral Cervical	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Left	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	.	.	.
		2509	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.	X	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Interscapular	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	X	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.	.
		2510	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	X	.	.
			Skin, Dry	Tail	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	X	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	17	18	21 DE	28 DE	29 PreRx	30	30 DE
2	f	2508	Swollen Soft	Treatment Site No.02	1	1	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	2
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Fur, Staining, Red	Interscapular	.	.	.	.	.	.	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	X
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	X
			Fur, Thin Cover	Ventral Cervical	.	.	.	X	.	.	X
			Fur, Thin Cover	Scapular, Left	.	.	.	.	.	.	X
			Fur, Thin Cover	Forepaw, Right	.	.	.	X	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	X	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	X
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	.	X
		2509	Swollen Soft	Treatment Site No.02	1	1	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Skin, Red	Treatment Site No.02	.	X	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	X
			Fur, Staining, Red	Scapular, Left	.	.	.	.	.	.	X
			Fur, Staining, Red	Interscapular	.	.	.	.	.	.	X
			Fur, Staining, Red	Dorsal Cervical	.	.	X	X	.	.	X
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	X
		2510	Swollen Soft	Treatment Site No.02	1	1	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.
			Skin, Dry	Tail	.	.	.	X	.	.	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	X	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	2	3	4	7 DE	14 DE	16	17	18
3	f	3501	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	2	2	1
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	2	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	X	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	X	.
			Skin, Scab	Tail	.	.	.	.	X	.	.	.	.
			Skin, Scab	Scapular, Right	.	.	.	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Left	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	X	X	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	X	X	.	.	.
		3502	Limited Usage	Treatment Site No.01	.	1	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	2	2	1
			Swollen Firm	Treatment Site No.01	.	2	2	1	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	X	X	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	X	.
			Skin, Red	Treatment Site No.01	.	.	.	X	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.	.	.
		3503	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	2	2	2
			Swollen Firm	Treatment Site No.01	.	1	2	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	X	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	X	X	X
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Right	.	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	X	.	.	.	.
			Fur, Thin Cover	Interscapular	X	.	.	.	X	X	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.	X	X	.	.	.
			Fur, Thin Cover	Dorsal Cervical	X	.	.	.	X	X	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	X	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	21 DE	28 DE	29 PreRx	30	30 DE
3	f	3501	Swollen Soft	Treatment Site No.02	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	2	1
			Swollen Firm	Treatment Site No.01	.	.	.	.	.
			Warm to Touch		.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.
			Skin, Scab	Scapular, Right	.	.	.	.	X
			Skin, Scab	Dorsal Cervical	.	X	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	.	.	X
			Fur, Thin Cover	Scapular, Left	.	X	.	.	X
			Fur, Thin Cover	Dorsal Cervical	X	X	.	.	X
			Fur, Thin Cover	Cranium	X	X	.	.	X
		3502	Limited Usage	Treatment Site No.01	.	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	1
			Warm to Touch		.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	X
		3503	Swollen Soft	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	2
			Warm to Touch		.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	X	.
			Skin, Scab	Pinna, Right	.	.	.	.	X
			Skin, Scab	Cranium	.	.	.	.	.
			Fur, Thin Cover	Interscapular	X	X	.	.	X
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	X
			Fur, Thin Cover	Dorsal Thoracic	X	X	.	.	X
			Fur, Thin Cover	Dorsal Cervical	.	X	.	.	X
			Fur, Thin Cover	Cranium	X	X	.	.	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	2	3	4	7 DE	14 DE	16	17	18
3	f	3504	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	2	2	2
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	2	2	1	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	X	.	.
			Skin, Red	Treatment Site No.01	.	.	.	X	.	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	.	.	.	.	.	.	.
		3505	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	2	2	1
			Swollen Firm	Treatment Site No.01	.	2	1	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.	.	.
		3506	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	3	2	2
			Swollen Firm	Treatment Site No.01	.	1	2	1	.	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.	X	.	.	.	.
		3507	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	2	2	2
			Swollen Firm	Treatment Site No.01	.	2	2	2	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	X	.	.
			Skin, Red	Treatment Site No.01	.	.	.	X	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	X	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.	.	.
		3508	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	1	1	.
			Swollen Firm	Treatment Site No.01	.	2	1	1	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	X	.	.	.	.	.	.
			Skin, Scab	Forepaw, Left	.	.	.	.	.	X	.	.	.
			Fur, Thin Cover	Forelimb, Right	X	.	.	.	X	X	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	.	.	.	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	21 DE	28 DE	29 PreRx	30	30 DE
3	f	3504	Swollen Soft	Treatment Site No.02	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	1	1
			Swollen Firm	Treatment Site No.01	.	.	.	.	.
			Warm to Touch		.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X
			Fur, Staining, Red	Scapular, Right	.	X	.	.	X
			Fur, Staining, Red	Scapular, Left	.	X	.	.	.
		3505	Swollen Soft	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	2
			Skin, Scab	Treatment Site No.01	.	X	X	.	.
		3506	Swollen Soft	Treatment Site No.01	.	.	.	.	1
			Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.	.
		3507	Swollen Soft	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	1	1
			Warm to Touch		.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	X	.	.	X
			Fur, Thin Cover	Forepaw, Left	.	X	.	.	X
		3508	Swollen Soft	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	2	1
			Swollen Firm	Inguinal, Left	.	.	.	.	1
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Scab	Forepaw, Left	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	X	.	.	X
			Fur, Thin Cover	Forelimb, Left	.	X	.	.	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	2	3	4	7 DE	14 DE	16	17	18
3	f	3509	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	2	2	1
			Swollen Firm	Treatment Site No.01	.	2	2	2	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	X	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.	X	.
			Skin, Red	Treatment Site No.01	.	.	X	X	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.	.	.
			Skin, Scab	Ventral Cervical	.	.	.	.	.	.	.	.	.
			Skin, Scab	Cranium	X	.	.	.	X	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	.	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	X	.	.	.	X	.	.	.	.
		3510	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	3	2	2
			Swollen Firm	Treatment Site No.01	.	.	1	1	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	X	X	.
			Fur, Thin Cover	Forepaw, Left	X	.	.	.	X	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	21 DE	28 DE	29 PreRx	30	30 DE
3	f	3509	Swollen Soft	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	2	1
			Warm to Touch		.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	X
			Skin, Scab	Ventral Cervical	.	X	.	.	.
			Skin, Scab	Cranium	.	X	.	.	X
			Fur, Staining, Red	Cranium	.	.	.	.	X
			Fur, Thin Cover	Ventral Cervical	.	X	.	.	.
			Fur, Thin Cover	Cranium	.	X	.	.	X
		3510	Swollen Soft	Treatment Site No.01	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	2 Unsc
4	f	4501	Dehydrated Suspected		.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
		4502	Dehydrated Suspected		.	.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	.
			Warm to Touch		.	.	.	.	.	X	.
		4503	Backbone Prominent		.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	2	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.	.
			Thin		.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	X	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.
		4504	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	2	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	3	4	7 DE	14 DE	15 Unsc PostRx	16	17
4	f	4501	Dehydrated Suspected		.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.02	.	.	.	.	.	2	2
			Swollen Firm	Treatment Site No.01	2	3	.	.	.	.	.
			Skin, Red	Treatment Site No.01	X	X	.	.	.	.	.
		4502	Dehydrated Suspected		.	.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	2	2	.	.	.	.	.
			Warm to Touch		X	.	.	.	.	X	X
		4503	Backbone Prominent		.	.	X	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	2	3	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.	.
			Thin		.	.	X	.	.	.	.
			Warm to Touch		X	X	.	.	.	X	X
			Skin, Red	Treatment Site No.02	.	.	.	.	.	X	X
			Skin, Red	Treatment Site No.01	X	X	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	X	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	X	.	.	.	.
		4504	Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	2	3	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	X	X
			Skin, Red	Treatment Site No.02	.	.	.	.	.	X	X
			Skin, Red	Treatment Site No.01	.	X	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	18	21 DE	28 DE	29 PreRx	30	30 DE	31
4	f	4501	Dehydrated Suspected		.	.	.	.	.	1	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	1	1	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
		4502	Dehydrated Suspected		.	.	.	.	.	1	.
			Hunched Posture		.	.	.	.	.	X	.
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	1	1	.
			Warm to Touch		.	.	.	.	.	.	.
		4503	Backbone Prominent		.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	2	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	1	.
			Thin		.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	X	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.
		4504	Swollen Soft	Treatment Site No.01	.	.	.	.	1	2	.
			Swollen Firm	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	32	35 DE	42 DE	43 DE
4	f	4501	Dehydrated Suspected		.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.
		4502	Dehydrated Suspected		.	.	.	.
			Hunched Posture		.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Warm to Touch		.	.	.	.
		4503	Backbone Prominent		.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.
			Thin		.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.
		4504	Swollen Soft	Treatment Site No.01	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	2 Unsc
4	f	4505	Dehydrated Suspected		.	.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	X	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	X	.
			Skin, Scab	Dorsal Thoracic	.	.	.	.	.	.	.
			Fur, Erected		.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.
			Tail, Bent		X	X	X	X	X	X	.
		4506	Dehydrated Suspected		.	.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	2	.
			Warm to Touch		.	.	.	.	.	X	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	3	4	7 DE	14 DE	15 Unsc PostRx	16	17
4	f	4505	Dehydrated Suspected		.	.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.02	.	.	.	.	.	2	3
			Swollen Firm	Treatment Site No.01	2	3	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.	.
			Warm to Touch		X	X	.	.	.	X	.
			Skin, Red	Pinna, Right	.	.	X	.	.	.	.
			Skin, Scab	Treatment Site No.01	X	X	.	.	.	.	.
			Skin, Scab	Dorsal Thoracic	.	.	X	X	.	.	.
			Fur, Erected		.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	X	X	.	.	.
			Fur, Thin Cover	Cranium	.	.	X	.	.	.	.
			Tail, Bent		X	.	.	.	.	.	.
		4506	Dehydrated Suspected		.	.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	2	3	.	.	.	.	.
			Warm to Touch		X	X	.	.	.	X	X
			Skin, Red	Treatment Site No.02	.	.	.	.	.	X	X
			Skin, Red	Treatment Site No.01	X	X	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	18	21 DE	28 DE	29 PreRx	30	30 DE	31
4	f	4505	Dehydrated Suspected		.	.	.	.	.	1	.
			Hunched Posture		.	.	.	.	.	X	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.02	1	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	1	2	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	1	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Scab	Dorsal Thoracic	.	.	.	.	.	.	.
			Fur, Erected		.	.	.	.	.	X	.
			Fur, Staining, Red	Cranium	.	X	.	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.
			Tail, Bent		.	.	.	.	.	.	.
		4506	Dehydrated Suspected		.	.	.	.	.	1	.
			Hunched Posture		.	.	.	.	.	X	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	2	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	X	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	X	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	32	35 DE	42 DE	43 DE
4	f	4505	Dehydrated Suspected		.	.	.	.
			Hunched Posture		.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.
			Skin, Scab	Treatment Site No.01	.	.	.	.
			Skin, Scab	Dorsal Thoracic	.	.	.	.
			Fur, Erected		.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.
			Tail, Bent		.	.	.	.
		4506	Dehydrated Suspected		.	.	.	.
			Hunched Posture		.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	2 Unsc
4	f	4507	Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	.
			Warm to Touch		.	.	.	.	.	X	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.
			Fur, Staining, Red	Interscapular	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.
		4508	Limited Usage	Treatment Site No.01	.	.	.	.	.	1	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	2	.
			Warm to Touch		.	.	.	.	.	X	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
		4509	Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	2	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Pinna Partly Missing	Left	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	3	4	7 DE	14 DE	15 Unsc PostRx	16	17
4	f	4507	Limited Usage	Hindlimb, Right	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	2	2	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	X	X
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.
			Fur, Staining, Red	Interscapular	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.
		4508	Limited Usage	Treatment Site No.01	1	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	1
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	2	3	.	.	.	.	.
			Warm to Touch		X	X	.	.	.	X	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	X	X
			Skin, Red	Treatment Site No.01	X	X	.	.	.	.	.
		4509	Limited Usage	Hindlimb, Right	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	3	3	.	.	.	.	.
			Warm to Touch		.	X	.	.	.	X	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	X	X
			Skin, Red	Treatment Site No.01	.	X	.	.	.	.	.
			Pinna Partly Missing	Left	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	18	21 DE	28 DE	29 PreRx	30	30 DE	31
4	f	4507	Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	1	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	2	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	X	.
			Fur, Staining, Red	Interscapular	.	.	.	.	.	X	.
			Fur, Staining, Red	Dorsal Cervical	.	X	X	.	.	X	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	X	.
			Fur, Thin Cover	Lumbar	.	.	X	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	X	.	.	.	.	.
		4508	Limited Usage	Treatment Site No.01	.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	2	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
		4509	Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	2	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Pinna Partly Missing	Left	.	X	X	X	X	X	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	32	35 DE	42 DE	43 DE
4	f	4507	Limited Usage	Hindlimb, Right	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.
			Fur, Staining, Red	Interscapular	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.
		4508	Limited Usage	Treatment Site No.01	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.
		4509	Limited Usage	Hindlimb, Right	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.
			Pinna Partly Missing	Left	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	2 Unsc
4	f	4510	Backbone Prominent		.	.	.	.	.	.	.
			Dehydrated Suspected		.	.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Limited Usage	Treatment Site No.01	.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.	.
			Thin		.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	.	.	.	.	.
			Fur, Staining, Red	Lumbar	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	3	4	7 DE	14 DE	15 Unsc PostRx	16	17
4	f	4510	Backbone Prominent		.	.	.	.	.	.	.
			Dehydrated Suspected		.	.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Limited Usage	Treatment Site No.01	1	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	2	2	.	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	.	.
			Thin		.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	X	X
			Skin, Red	Treatment Site No.02	.	.	.	.	.	X	X
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	X	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	.	.	.	.	.
			Fur, Staining, Red	Lumbar	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	18	21 DE	28 DE	29 PreRx	30	30 DE	31
4	f	4510	Backbone Prominent		.	.	.	.	.	X	.
			Dehydrated Suspected		.	.	.	.	.	1	.
			Hunched Posture		.	.	.	.	.	X	.
			Limited Usage	Treatment Site No.01	.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	1	1	.
			Swollen Firm	Inguinal, Left	.	.	.	.	.	1	.
			Thin		.	.	.	.	.	X	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	X	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	X	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	X	.	.	.	.
			Fur, Staining, Red	Lumbar	.	.	X	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	X	X	.	.	.	.
			Fur, Staining, Red	Cranium	.	X	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	32	35 DE	42 DE	43 DE
4	f	4510	Backbone Prominent		.	.	.	.
			Dehydrated Suspected		.	.	.	.
			Hunched Posture		.	.	.	.
			Limited Usage	Treatment Site No.01	.	.	.	.
			Limited Usage	Hindlimb, Right	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Swollen Firm	Inguinal, Left	.	.	.	.
			Thin		.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	.	.
			Fur, Staining, Red	Lumbar	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	2 Unsc
4	f	4511	Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.
			Skin, Red	Muzzle	.	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Thoracic	X	X	X	X	.	.	.
			Fur, Thin Cover	Ventral Cervical	X	X	X	X	.	.	.
			Fur, Thin Cover	Urogenital	.	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	.	X	.	.	.
			Fur, Thin Cover	Scapular, Left	.	.	.	X	.	.	.
			Fur, Thin Cover	Lumbar	X	X	X	X	.	.	.
			Fur, Thin Cover	Inguinal, Right	.	.	.	.	.	.	.
			Fur, Thin Cover	Inguinal, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Hindlimb, Right	X	X	X	X	.	.	.
			Fur, Thin Cover	Hindlimb, Left	X	X	X	X	.	.	.
			Fur, Thin Cover	Forelimb, Right	X	X	X	X	.	.	.
			Fur, Thin Cover	Forelimb, Left	X	X	X	X	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	X	X	X	X	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	X	X	X	X	.	.	.
			Fur, Thin Cover	Axillary, Right	X	X	X	X	.	.	.
			Fur, Thin Cover	Axillary, Left	X	X	X	X	.	.	.
			Fur, Thin Cover	Abdominal	X	X	X	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	3	4	7 DE	14 DE	15 Unsc PostRx	16	17
4	f	4511	Limited Usage	Hindlimb, Right	.	.	.	.	.	1	1
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	3	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	3	2	.	.	.	.	.
			Warm to Touch		.	.	.	.	X	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	X	.	.
			Skin, Red	Pinna, Left	.	.	.	.	X	.	.
			Skin, Red	Muzzle	.	.	.	.	X	.	.
			Fur, Thin Cover	Ventral Thoracic	.	.	X	X	X	.	.
			Fur, Thin Cover	Ventral Cervical	.	.	X	X	.	.	.
			Fur, Thin Cover	Urogenital	.	.	X	X	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	X	X	X	.	.
			Fur, Thin Cover	Scapular, Left	.	.	X	X	X	.	.
			Fur, Thin Cover	Lumbar	.	.	X	X	X	.	.
			Fur, Thin Cover	Inguinal, Right	.	.	X	X	.	.	.
			Fur, Thin Cover	Inguinal, Left	.	.	X	X	.	.	.
			Fur, Thin Cover	Hindlimb, Right	.	.	X	X	.	.	.
			Fur, Thin Cover	Hindlimb, Left	.	.	X	X	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	X	X	X	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	X	X	X	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	X	X	X	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	X	.	.
			Fur, Thin Cover	Cranium	.	.	X	.	.	.	.
			Fur, Thin Cover	Axillary, Right	.	.	X	X	.	.	.
			Fur, Thin Cover	Axillary, Left	.	.	X	X	.	.	.
			Fur, Thin Cover	Abdominal	.	.	X	X	X	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	18	21 DE	28 DE	29 PreRx	30	30 DE	31
4	f	4511	Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	.	3
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	X	.	X
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	X
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.
			Skin, Red	Muzzle	.	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Thoracic	.	X	X	.	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	X	X	.	.	.	.
			Fur, Thin Cover	Urogenital	.	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	X	X	.	.	.	.
			Fur, Thin Cover	Scapular, Left	.	X	X	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	X	.	.	.	.
			Fur, Thin Cover	Inguinal, Right	.	.	.	.	.	.	.
			Fur, Thin Cover	Inguinal, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Hindlimb, Right	.	.	.	.	.	.	.
			Fur, Thin Cover	Hindlimb, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	X	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	X	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	X	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	X	X	.	.	.	.
			Fur, Thin Cover	Cranium	.	X	X	.	.	.	.
			Fur, Thin Cover	Axillary, Right	.	.	.	.	.	.	.
			Fur, Thin Cover	Axillary, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Abdominal	.	X	X	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	32	35 DE	42 DE	43 DE
4	f	4511	Limited Usage	Hindlimb, Right	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.01	X	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.
			Skin, Red	Muzzle	.	.	.	.
			Fur, Thin Cover	Ventral Thoracic	.	X	X	X
			Fur, Thin Cover	Ventral Cervical	.	X	X	X
			Fur, Thin Cover	Urogenital	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	X	X	X
			Fur, Thin Cover	Scapular, Left	.	X	X	X
			Fur, Thin Cover	Lumbar	.	X	X	X
			Fur, Thin Cover	Inguinal, Right	.	.	.	.
			Fur, Thin Cover	Inguinal, Left	.	.	.	.
			Fur, Thin Cover	Hindlimb, Right	.	.	.	.
			Fur, Thin Cover	Hindlimb, Left	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	X	X	X
			Fur, Thin Cover	Forelimb, Left	.	X	X	X
			Fur, Thin Cover	Dorsal Thoracic	.	X	X	X
			Fur, Thin Cover	Dorsal Cervical	.	X	X	X
			Fur, Thin Cover	Cranium	.	X	X	X
			Fur, Thin Cover	Axillary, Right	.	X	X	X
			Fur, Thin Cover	Axillary, Left	.	X	X	X
			Fur, Thin Cover	Abdominal	.	X	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	2 Unsc
4	f	4512	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	2	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	3	4	7 DE	14 DE	15 Unsc PostRx	16	17
4	f	4512	Swollen Soft	Treatment Site No.02	.	.	.	.	1	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	2
			Swollen Firm	Treatment Site No.01	3	2	.	.	.	.	.
			Warm to Touch		.	.	.	.	X	X	X
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	X	.	.
			Skin, Red	Pinna, Left	.	.	.	.	X	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	18	21 DE	28 DE	29 PreRx	30	30 DE	31
4	f	4512	Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	.	3
			Warm to Touch		.	.	.	.	X	.	X
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	32	35 DE	42 DE	43 DE
4	f	4512	Swollen Soft	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.01	X	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	2 Unsc
4	f	4513	Backbone Prominent		.	.	.	.	.	.	X
			Dehydrated Suspected		.	.	.	.	.	.	2
			Hunched Posture		.	.	.	.	.	.	X
			Limited Usage	Treatment Site No.01	.	.	.	.	.	1	.
			Limited Usage	Hindlimb, Left	.	.	.	.	.	.	1
			Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	3	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	3
			Thin		.	.	.	.	.	.	X
			Warm to Touch		.	.	.	.	.	X	X
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	X	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	X	.	.	.
			Fur, Erected		.	.	.	.	.	.	X
			Fur, Thin Cover	Ventral Thoracic	X	X	X	X	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	.	X	.	.	X
			Fur, Thin Cover	Scapular, Left	.	.	.	X	.	.	X
			Fur, Thin Cover	Lumbar	X	X	X	X	.	.	X
			Fur, Thin Cover	Hindlimb, Right	X	X	X	X	.	.	.
			Fur, Thin Cover	Hindlimb, Left	X	X	X	X	.	.	.
			Fur, Thin Cover	Forelimb, Right	X	X	X	X	.	.	X
			Fur, Thin Cover	Forelimb, Left	X	X	X	X	.	.	X
			Fur, Thin Cover	Dorsal Thoracic	X	X	X	X	.	.	X
			Fur, Thin Cover	Dorsal Cervical	X	X	X	X	.	.	.
			Fur, Thin Cover	Cranium	X	X	X	X	.	.	.
			Fur, Thin Cover	Axillary, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Abdominal	X	X	X	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	3	4	7 DE	14 DE	15 Unsc PostRx	16	17
4	f	4513	Backbone Prominent		.	.	.	.	.	.	.
			Dehydrated Suspected		.	.	1	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Limited Usage	Treatment Site No.01	.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Left	1	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	3	3	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Swollen Firm	Hindlimb, Left	2	3	.	.	.	.	.
			Thin		.	.	.	.	.	.	.
			Warm to Touch		X	X	.	.	.	X	X
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	X
			Skin, Red	Treatment Site No.01	.	X	.	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.
			Fur, Erected		.	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Thoracic	.	.	X	X	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	.	.	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	.	X	X	.	.	.
			Fur, Thin Cover	Scapular, Left	.	.	X	X	.	.	.
			Fur, Thin Cover	Lumbar	.	.	X	X	.	.	.
			Fur, Thin Cover	Hindlimb, Right	.	.	.	.	.	.	.
			Fur, Thin Cover	Hindlimb, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	.	X	X	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	.	X	X	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	X	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	X	.	.	.
			Fur, Thin Cover	Axillary, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Abdominal	.	.	X	X	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	18	21 DE	28 DE	29 PreRx	30	30 DE	31
4	f	4513	Backbone Prominent		.	.	.	.	.	.	.
			Dehydrated Suspected		.	.	.	.	.	.	.
			Hunched Posture		.	.	.	.	.	.	.
			Limited Usage	Treatment Site No.01	.	.	.	.	.	.	.
			Limited Usage	Hindlimb, Left	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	.	3
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.
			Thin		.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	X	.	X
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	X	X	.	X
			Skin, Red	Hindpaw, Right	.	.	.	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	.	.
			Fur, Erected		.	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Thoracic	.	X	X	.	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	.	X	.	.	.	.
			Fur, Thin Cover	Scapular, Right	.	X	X	.	.	.	.
			Fur, Thin Cover	Scapular, Left	.	X	X	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	X	.	.	.	.
			Fur, Thin Cover	Hindlimb, Right	.	.	.	.	.	.	.
			Fur, Thin Cover	Hindlimb, Left	.	.	.	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	X	X	.	.	.	.
			Fur, Thin Cover	Forelimb, Left	.	X	X	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	X	X	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	X	X	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Axillary, Left	.	.	X	.	.	.	.
			Fur, Thin Cover	Abdominal	.	X	X	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	32	35 DE	42 DE	43 DE
4	f	4513	Backbone Prominent		.	.	.	.
			Dehydrated Suspected		.	.	.	.
			Hunched Posture		.	.	.	.
			Limited Usage	Treatment Site No.01	.	.	.	.
			Limited Usage	Hindlimb, Left	.	.	.	.
			Swollen Soft	Treatment Site No.02	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.
			Thin		.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.
			Skin, Red	Treatment Site No.01	X	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.
			Fur, Erected		.	.	.	.
			Fur, Thin Cover	Ventral Thoracic	.	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	X	X	X
			Fur, Thin Cover	Scapular, Right	.	X	X	X
			Fur, Thin Cover	Scapular, Left	.	X	X	X
			Fur, Thin Cover	Lumbar	.	X	X	X
			Fur, Thin Cover	Hindlimb, Right	.	.	.	.
			Fur, Thin Cover	Hindlimb, Left	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	X	X	X
			Fur, Thin Cover	Forelimb, Left	.	X	X	X
			Fur, Thin Cover	Dorsal Thoracic	.	X	X	X
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	X	X
			Fur, Thin Cover	Axillary, Left	.	X	X	X
			Fur, Thin Cover	Abdominal	.	X	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-37 DE	-23 DE	-9 DE	-1 DE	1	2	2 Unsc
4	f	4514	Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	1	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.
			Skin, Red	Muzzle	.	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	X	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.
		4515	Swollen Firm	Treatment Site No.02	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	2	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.
			Skin, Red	Muzzle	.	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	3	4	7 DE	14 DE	15 Unsc PostRx	16	17
4	f	4514	Limited Usage	Hindlimb, Right	.	.	.	.	.	1	1
			Swollen Soft	Treatment Site No.01	.	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	3
			Swollen Firm	Treatment Site No.01	2	2	.	.	.	.	.
			Warm to Touch		.	.	.	.	X	X	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	X
			Skin, Red	Pinna, Right	.	.	.	.	X	.	.
			Skin, Red	Pinna, Left	.	.	.	.	X	.	.
			Skin, Red	Muzzle	.	.	.	.	X	.	.
			Skin, Scab	Tail	.	.	X	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	X	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.
		4515	Swollen Firm	Treatment Site No.02	.	.	.	.	.	3	2
			Swollen Firm	Treatment Site No.01	3	3	.	.	.	.	.
			Warm to Touch		.	.	.	.	X	X	.
			Skin, Red	Treatment Site No.01	X	X	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	X	.	.
			Skin, Red	Pinna, Left	.	.	.	.	X	.	.
			Skin, Red	Muzzle	.	.	.	.	X	.	.
			Skin, Scab	Tail	.	.	X	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	X	X	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	X	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.
			Fur, Thin Cover	Lumbar	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	18	21 DE	28 DE	29 PreRx	30	30 DE	31
4	f	4514	Limited Usage	Hindlimb, Right	.	.	.	.	.	.	.
			Swollen Soft	Treatment Site No.01	.	.	.	.	1	.	1
			Swollen Firm	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	.
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.
			Skin, Red	Muzzle	.	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.	.	.
			Skin, Scab	Cranium	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	X	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	X	.	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	X	.	.	.	.
		4515	Swollen Firm	Treatment Site No.02	2	.	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	.	3
			Warm to Touch		.	.	.	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.	.	.	.
			Skin, Red	Muzzle	.	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	.	.	.	.	.	.
			Fur, Staining, Red	Scapular, Right	.	.	X	.	.	.	.
			Fur, Staining, Red	Scapular, Left	.	.	X	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	X	.	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	X	.	.	.	.
			Fur, Thin Cover	Lumbar	.	X	X	.	.	.	.
			Fur, Thin Cover	Cranium	.	X	.	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 5

Individual Clinical Observations

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	32	35 DE	42 DE	43 DE
4	f	4514	Limited Usage	Hindlimb, Right	.	.	.	.
			Swollen Soft	Treatment Site No.01	1	.	.	.
			Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.02	.	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.
			Skin, Red	Muzzle	.	.	.	.
			Skin, Scab	Tail	.	.	.	.
			Skin, Scab	Cranium	.	.	X	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.	X
			Fur, Staining, Red	Cranium	.	.	.	.
			Fur, Thin Cover	Dorsal Thoracic	.	.	.	.
			Fur, Thin Cover	Cranium	.	X	X	X
		4515	Swollen Firm	Treatment Site No.02	.	.	.	.
			Swollen Firm	Treatment Site No.01	2	1	.	.
			Warm to Touch		.	.	.	.
			Skin, Red	Treatment Site No.01	X	.	.	.
			Skin, Red	Pinna, Right	.	.	.	.
			Skin, Red	Pinna, Left	.	.	.	.
			Skin, Red	Muzzle	.	.	.	.
			Skin, Scab	Tail	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	X	X	X
			Fur, Staining, Red	Scapular, Right	.	X	X	X
			Fur, Staining, Red	Scapular, Left	.	X	X	X
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.
			Fur, Staining, Red	Cranium	.	X	X	X
			Fur, Thin Cover	Lumbar	.	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 100 ug/dose

Appendix 6

Individual Body Weights Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	TERR	Technical error
AVS	Suspected aberrant value	UPTD	Unable to perform due to technical difficulty
OA	Omitted activity	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day -44	-30	-16	-1	7	14	21	28
1M	1001	169	266	325	375	405	427	448	461
	1002	183	270	339	387	399	407	424	431
	1003	163	260	334	376	385	400	421	435
	1004	165	278	381	451	475	495	510	526
	1005	172	274	356	421	442	456	481	501
	1006	190	309	397	456	480	507	529	551
	1007	181	287	375	433	457	471	490	505
	1008	189	312	397	456	477	480	497	520
	1009	161	262	341	402	418	445	470	483
	1010	172	298	412	496	516	539	569	596
	1011	179	291	373	428	449	465	486	510
	1012	176	281	342	393	410	430	450	461
	1013	161	266	338	397	419	439	463	470
	1014	167	268	351	409	430	450	480	500
	1015	186	295	372	428	445	466	490	510

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day 35	Day 42
1M	1001	--	--
	1002	--	--
	1003	--	--
	1004	--	--
	1005	--	--
	1006	--	--
	1007	--	--
	1008	--	--
	1009	--	--
	1010	--	--
	1011	518	541
	1012	479	494
	1013	486	508
	1014	518	537
	1015	531	551

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day -44	-30	-16	-1	7	14	21	28
2M	2001	187	295	383	444	459	478	498	518
	2002	174	270	344	401	408	422	434	451
	2003	179	291	377	435	439	463	480	495
	2004	166	277	341	393	405	429	444	454
	2005	165	263	339	397	408	429	446	460
	2006	171	273	345	399	412	430	443	465
	2007	177	279	357	411	428	447	465	479
	2008	168	282	364	416	431	463	479	509
	2009	182	305	401	461	474	500	520	536
	2010	183	288	353	389	396	417	434	454

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day 35	Day 42
2M	2001	--	--
	2002	--	--
	2003	--	--
	2004	--	--
	2005	--	--
	2006	--	--
	2007	--	--
	2008	--	--
	2009	--	--
	2010	--	--

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day -44	-30	-16	-1	7	14	21	28
3M	3001	174	306	423	520	527	560	576	605
	3002	165	270	359	422	418	449	457	489
	3003	185	295	390	460	469	497	505	536
	3004	179	280	359	407	402	427	432	458
	3005	177	292	386	458	458	492	494	533
	3006	182	283	360	422	424	451	456	491
	3007	167	275	365	427	432	462	459	485
	3008	166	265	339	382	384	412	414	433
	3009	179	301	379	447	440	468	468	496
	3010	170	275	356	408	402	436	437	466

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day 35	Day 42
3M	3001	--	--
	3002	--	--
	3003	--	--
	3004	--	--
	3005	--	--
	3006	--	--
	3007	--	--
	3008	--	--
	3009	--	--
	3010	--	--

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day -44	-30	-16	-1	7	14	21	28
4M	4001	180	284	370	428	415	444	448	478
	4002	188	300	386	438	435	467	480	501
	4003	164	266	342	395	393	413	413	434
	4004	184	281	358	411	402	427	428	452
	4005	178	275	336	388	379	409	408	434
	4006	165	257	330	386	367	399	397	425
	4007	191	304	384	445	426	455	453	482
	4008	188	301	388	459	451	482	485	513
	4009	169	270	336	391	382	411	414	434
	4010	166	268	341	395	388	415	414	439
	4011	179	277	350	393	380	409	405	438
	4012	172	267	341	405	393	422	417	458
	4013	174	276	356	407	399	430	431	468
	4014	158	261	345	407	383	416	408	443
	4015	161	251	332	386	368	398	401	431

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day 35	Day 42
4M	4001	--	--
	4002	--	--
	4003	--	--
	4004	--	--
	4005	--	--
	4006	--	--
	4007	--	--
	4008	--	--
	4009	--	--
	4010	--	--
	4011	446	473
	4012	457	492
	4013	473	508
	4014	433	462
	4015	436	466

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day -45	-30	-16	-1	7	14	21	28
1F	1501	160	190	213	240	247	249	251	261
	1502	158	212	239	253	251	263	279	276
	1503	167	197	220	226	222	230	238	240
	1504	156	198	230	239	237	244	265	260
	1505	155	227	242	256	258	265	274	276
	1506	152	212	248	249	262	274	287	284
	1507	147	193	211	221	222	230	231	245
	1508	169	221	242	264	265	277	276	290
	1509	172	209	228	233	252	250	251	264
	1510	162	223	245	264	281	283	288	296
	1511	161	206	231	238	239	257	250	259
	1512	151	200	233	244	246	255	266	267
	1513	163	205	232	244	234	244	254	259
	1514	174	211	236	254	255	257	268	268
	1515	169	233	255	271	275	286	294	290

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day 35	Day 42
1F	1501	--	--
	1502	--	--
	1503	--	--
	1504	--	--
	1505	--	--
	1506	--	--
	1507	--	--
	1508	--	--
	1509	--	--
	1510	--	--
	1511	260	271
	1512	258	274
	1513	260	277
	1514	269	282
	1515	294	304

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day -45	-30	-16	-1	7	14	21	28
2F	2501	165	227	243	266	258	259	262	273
	2502	154	203	220	237	240	241	250	255
	2503	163	206	224	242	237	249	259	259
	2504	159	195	228	243	247	278	279	275
	2505	155	194	231	243	241	256	257	271
	2506	162	206	236	255	254	270	270	276
	2507	168	229	254	264	270	278	279	279
	2508	156	202	230	243	246	254	258	262
	2509	160	210	236	242	247	259	255	264
	2510	161	203	231	243	244	246	257	259

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day 35	Day 42
2F	2501	--	--
	2502	--	--
	2503	--	--
	2504	--	--
	2505	--	--
	2506	--	--
	2507	--	--
	2508	--	--
	2509	--	--
	2510	--	--

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day -45	-30	-16	-1	7	14	21	28
3F	3501	153	209	235	246	252	261	259	275
	3502	168	212	229	255	250	254	260	276
	3503	156	207	223	235	237	236	248	261
	3504	155	216	244	254	263	265	259	276
	3505	158	219	249	266	260	270	264	277
	3506	165	218	246	273	262	278	272	291
	3507	159	208	245	257	253	260	265	272
	3508	162	226	264	283	280	292	292	300
	3509	165	230	270	295	292	299	315	319
	3510	161	207	239	254	243	256	262	268

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day 35	Day 42
3F	3501	--	--
	3502	--	--
	3503	--	--
	3504	--	--
	3505	--	--
	3506	--	--
	3507	--	--
	3508	--	--
	3509	--	--
	3510	--	--

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day -45	-30	-16	-1	7	14	21	28
4F	4501	150	193	212	224	213	216	216	230
	4502	162	202	223	235	236	246	238	247
	4503	156	194	220	234	229	244	248	251
	4504	168	224	252	276	283	298	293	301
	4505	148	200	222	249	257	259	250	251
	4506	161	204	228	238	248	254	248	260
	4507	163	213	229	249	257	264	271	280
	4508	167	214	241	257	262	275	274	288
	4509	171	211	250	265	263	277	277	287
	4510	160	196	220	235	236	249	247	257
	4511	172	210	228	250	241	241	251	264
	4512	172	220	242	261	254	269	259	268
	4513	155	209	238	251	248	262	272	290
	4514	156	219	251	275	264	275	271	277
	4515	157	197	223	240	237	246	241	253

Appendix 6

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day 35	Day 42
4F	4501	--	--
	4502	--	--
	4503	--	--
	4504	--	--
	4505	--	--
	4506	--	--
	4507	--	--
	4508	--	--
	4509	--	--
	4510	--	--
	4511	263	280
	4512	274	285
	4513	279	292
	4514	270	285
	4515	249	257

Appendix 7

Individual Body Weight Gains Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	TERR	Technical error
AVS	Suspected aberrant value	UPTD	Unable to perform due to technical difficulty
NC	Not calculable	X	Excluded from mean
OA	Omitted activity		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day							
		Change -44 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35
1M	1001	97	59	50	30	22	21	13	--
	1002	87	69	48	12	8	17	7	--
	1003	97	74	42	9	15	21	14	--
	1004	113	103	70	24	20	15	16	--
	1005	102	82	65	21	14	25	20	--
	1006	119	88	59	24	27	22	22	--
	1007	106	88	58	24	14	19	15	--
	1008	123	85	59	21	3	17	23	--
	1009	101	79	61	16	27	25	13	--
	1010	126	114	84	20	23	30	27	--
	1011	112	82	55	21	16	21	24	8
	1012	105	61	51	17	20	20	11	18
	1013	105	72	59	22	20	24	7	16
	1014	101	83	58	21	20	30	20	18
	1015	109	77	56	17	21	24	20	21

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day Change 35 - 42
1M	1001	--
	1002	--
	1003	--
	1004	--
	1005	--
	1006	--
	1007	--
	1008	--
	1009	--
	1010	--
	1011	23
	1012	15
	1013	22
	1014	19
	1015	20

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day Change -44 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35
2M	2001	108	88	61	15	19	20	20	--
	2002	96	74	57	7	14	12	17	--
	2003	112	86	58	4	24	17	15	--
	2004	111	64	52	12	24	15	10	--
	2005	98	76	58	11	21	17	14	--
	2006	102	72	54	13	18	13	22	--
	2007	102	78	54	17	19	18	14	--
	2008	114	82	52	15	32	16	30	--
	2009	123	96	60	13	26	20	16	--
	2010	105	65	36	7	21	17	20	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day Change 35 - 42
2M	2001	--
	2002	--
	2003	--
	2004	--
	2005	--
	2006	--
	2007	--
	2008	--
	2009	--
	2010	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day							
		Change -44 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35
3M	3001	132	117	97	7	33	16	29	--
	3002	105	89	63	-4	31	8	32	--
	3003	110	95	70	9	28	8	31	--
	3004	101	79	48	-5	25	5	26	--
	3005	115	94	72	0	34	2	39	--
	3006	101	77	62	2	27	5	35	--
	3007	108	90	62	5	30	-3	26	--
	3008	99	74	43	2	28	2	19	--
	3009	122	78	68	-7	28	0	28	--
	3010	105	81	52	-6	34	1	29	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day Change 35 - 42
3M	3001	--
	3002	--
	3003	--
	3004	--
	3005	--
	3006	--
	3007	--
	3008	--
	3009	--
	3010	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day							
		Change -44 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35
4M	4001	104	86	58	-13	29	4	30	--
	4002	112	86	52	-3	32	13	21	--
	4003	102	76	53	-2	20	0	21	--
	4004	97	77	53	-9	25	1	24	--
	4005	97	61	52	-9	30	-1	26	--
	4006	92	73	56	-19	32	-2	28	--
	4007	113	80	61	-19	29	-2	29	--
	4008	113	87	71	-8	31	3	28	--
	4009	101	66	55	-9	29	3	20	--
	4010	102	73	54	-7	27	-1	25	--
	4011	98	73	43	-13	29	-4	33	8
	4012	95	74	64	-12	29	-5	41	-1
	4013	102	80	51	-8	31	1	37	5
	4014	103	84	62	-24	33	-8	35	-10
	4015	90	81	54	-18	30	3	30	5

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day Change 35 - 42
4M	4001	--
	4002	--
	4003	--
	4004	--
	4005	--
	4006	--
	4007	--
	4008	--
	4009	--
	4010	--
	4011	27
	4012	35
	4013	35
	4014	29
	4015	30

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day							
		Change -45 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35
1F	1501	30	23	27	7	2	2	10	--
	1502	54	27	14	-2	12	16	-3	--
	1503	30	23	6	-4	8	8	2	--
	1504	42	32	9	-2	7	21	-5	--
	1505	72	15	14	2	7	9	2	--
	1506	60	36	1	13	12	13	-3	--
	1507	46	18	10	1	8	1	14	--
	1508	52	21	22	1	12	-1	14	--
	1509	37	19	5	19	-2	1	13	--
	1510	61	22	19	17	2	5	8	--
	1511	45	25	7	1	18	-7	9	1
	1512	49	33	11	2	9	11	1	-9
	1513	42	27	12	-10	10	10	5	1
	1514	37	25	18	1	2	11	0	1
	1515	64	22	16	4	11	8	-4	4

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day Change 35 - 42
1F	1501	--
	1502	--
	1503	--
	1504	--
	1505	--
	1506	--
	1507	--
	1508	--
	1509	--
	1510	--
	1511	11
	1512	16
	1513	17
	1514	13
	1515	10

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day							
		Change -45 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35
2F	2501	62	16	23	-8	1	3	11	--
	2502	49	17	17	3	1	9	5	--
	2503	43	18	18	-5	12	10	0	--
	2504	36	33	15	4	31	1	-4	--
	2505	39	37	12	-2	15	1	14	--
	2506	44	30	19	-1	16	0	6	--
	2507	61	25	10	6	8	1	0	--
	2508	46	28	13	3	8	4	4	--
	2509	50	26	6	5	12	-4	9	--
	2510	42	28	12	1	2	11	2	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day Change 35 - 42
2F	2501	--
	2502	--
	2503	--
	2504	--
	2505	--
	2506	--
	2507	--
	2508	--
	2509	--
	2510	--

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Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day							
		Change -45 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35
3F	3501	56	26	11	6	9	-2	16	--
	3502	44	17	26	-5	4	6	16	--
	3503	51	16	12	2	-1	12	13	--
	3504	61	28	10	9	2	-6	17	--
	3505	61	30	17	-6	10	-6	13	--
	3506	53	28	27	-11	16	-6	19	--
	3507	49	37	12	-4	7	5	7	--
	3508	64	38	19	-3	12	0	8	--
	3509	65	40	25	-3	7	16	4	--
	3510	46	32	15	-11	13	6	6	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day Change 35 - 42
3F	3501	--
	3502	--
	3503	--
	3504	--
	3505	--
	3506	--
	3507	--
	3508	--
	3509	--
	3510	--

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day							
		Change -45 - -30	Change -30 - -16	Change -16 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35
4F	4501	43	19	12	-11	3	0	14	--
	4502	40	21	12	1	10	-8	9	--
	4503	38	26	14	-5	15	4	3	--
	4504	56	28	24	7	15	-5	8	--
	4505	52	22	27	8	2	-9	1	--
	4506	43	24	10	10	6	-6	12	--
	4507	50	16	20	8	7	7	9	--
	4508	47	27	16	5	13	-1	14	--
	4509	40	39	15	-2	14	0	10	--
	4510	36	24	15	1	13	-2	10	--
	4511	38	18	22	-9	0	10	13	-1
	4512	48	22	19	-7	15	-10	9	6
	4513	54	29	13	-3	14	10	18	-11
	4514	63	32	24	-11	11	-4	6	-7
	4515	40	26	17	-3	9	-5	12	-4

Appendix 7

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day Change 35 - 42
4F	4501	--
	4502	--
	4503	--
	4504	--
	4505	--
	4506	--
	4507	--
	4508	--
	4509	--
	4510	--
	4511	17
	4512	11
	4513	13
	4514	15
	4515	8

Appendix 8

Individual Food Consumption Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	OA	Omitted activity
AFE	Animal found with no food during measurement interval-Exclude	ONEG	Original value negative, animal did not eat
AFNF	Animal found with no food during measurement interval	POWF	Powdered food
ANH	Animal found with no hopper during measurement interval	REHO	Animal rehoused during measurement interval
ANIC	Animal not in cage or in incorrect cage during measurement	REPL	Animal replaced during measurement interval
ANW	Animal found with no water access during measurement intervals	SPIL	Spilled food (by animal)
ANWB	Animal found with no water bottle during measurement interval	TERR	Technical error
AVS	Suspected aberrant value	UPTD	Unable to perform due to technical difficulty
AWE	Animal found with no water in bottle during measurement interval-Exclude	WAFE	Water added to food during measurement interval
FSG	Food supplementation given during interval, included in feed weight	WAFI	Water added to food during measurement interval, included
FSNC	Food supplementation given during interval, value not calculable	WETF	Wet or contaminated food (in container)
NC	Not calculable	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day (From/To) -7/1	1/8	8/15	15/22	22/29	29/36	36/42
1M	1001	28.1	27.1	29.3	29.0	28.0	--	--
	1002	28.1	27.1	29.3	29.0	28.0	--	--
	1003	28.1	27.1	29.3	29.0	28.0	--	--
	1004	31.8	30.5	32.6	32.2	31.2	--	--
	1005	31.8	30.5	32.6	32.2	31.2	--	--
	1006	31.8	30.5	32.6	32.2	31.2	--	--
	1007	31.9	30.4	32.4	30.6	31.1	--	--
	1008	31.9	30.4	32.4	30.6	31.1	--	--
	1009	31.1	31.1	33.5	33.1	33.2	--	--
	1010	31.1	31.1	33.5	33.1	33.2	--	--
	1011	29.1	28.4	29.4	28.4	29.0	27.2	29.4
	1012	29.1	28.4	29.4	28.4	29.0	27.2	29.4
	1013	29.1	28.4	29.4	28.4	29.0	27.2	29.4
	1014	27.5	25.8	29.1	27.8	28.3	27.5	29.1
	1015	27.5	25.8	29.1	27.8	28.3	27.5	29.1

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day (From/To) -7/1	1/8	8/15	15/22	22/29	29/36	36/42
2M	2001	29.8	27.3	30.0	28.0	29.1	--	--
	2002	29.8	27.3	30.0	28.0	29.1	--	--
	2003	29.8	27.3	30.0	28.0	29.1	--	--
	2004	27.2	25.0	27.7	26.0	27.0	--	--
	2005	27.2	25.0	27.7	26.0	27.0	--	--
	2006	27.2	25.0	27.7	26.0	27.0	--	--
	2007	25.9	25.0	28.7	26.7	27.9	--	--
	2008	25.9	25.0	28.7	26.7	27.9	--	--
	2009	29.4	27.1	30.1	28.9	29.8	--	--
	2010	29.4	27.1	30.1	28.9	29.8	--	--

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day (From/To) -7/1	1/8	8/15	15/22	22/29	29/36	36/42
3M	3001	33.1	28.4	32.9	28.5	32.9	--	--
	3002	33.1	28.4	32.9	28.5	32.9	--	--
	3003	33.1	28.4	32.9	28.5	32.9	--	--
	3004	28.3	23.6	28.3	23.7	29.3	--	--
	3005	28.3	23.6	28.3	23.7	29.3	--	--
	3006	28.3	23.6	28.3	23.7	29.3	--	--
	3007	27.6	23.6	28.4	24.1	27.6	--	--
	3008	27.6	23.6	28.4	24.1	27.6	--	--
	3009	30.2	25.6	30.1	25.2	30.6	--	--
	3010	30.2	25.6	30.1	25.2	30.6	--	--

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day (From/To) -7/1	1/8	8/15	15/22	22/29	29/36	36/42
4M	4001	29.1	23.3	34.2	31.8	34.5	--	--
	4002	29.1	23.3	34.2	31.8	34.5	--	--
	4003	29.1	23.3	34.2	31.8	34.5	--	--
	4004	27.4	21.0	33.4	28.8	32.0	--	--
	4005	27.4	21.0	33.4	28.8	32.0	--	--
	4006	27.4	21.0	33.4	28.8	32.0	--	--
	4007	31.4	25.1	36.9	32.1	35.4	--	--
	4008	31.4	25.1	36.9	32.1	35.4	--	--
	4009	27.6	22.6	30.9	26.5	30.6	--	--
	4010	27.6	22.6	30.9	26.5	30.6	--	--
	4011	29.9	22.4	34.5	29.3	34.7	29.0	35.8
	4012	29.9	22.4	34.5	29.3	34.7	29.0	35.8
	4013	29.9	22.4	34.5	29.3	34.7	29.0	35.8
	4014	26.6	20.4	30.7	25.1	31.6	25.8	33.3
	4015	26.6	20.4	30.7	25.1	31.6	25.8	33.3

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day (From/To) -7/1	1/8	8/15	15/22	22/29	29/36	36/42
1F	1501	18.4	18.0	17.9	19.2	18.4	--	--
	1502	18.4	18.0	17.9	19.2	18.4	--	--
	1503	18.4	18.0	17.9	19.2	18.4	--	--
	1504	19.2	19.4	19.9	21.2	20.4	--	--
	1505	19.2	19.4	19.9	21.2	20.4	--	--
	1506	19.2	19.4	19.9	21.2	20.4	--	--
	1507	17.6	16.7	17.6	17.2	17.9	--	--
	1508	17.6	16.7	17.6	17.2	17.9	--	--
	1509	19.9	21.4	20.5	20.2	21.2	--	--
	1510	19.9	21.4	20.5	20.2	21.2	--	--
	1511	17.9	16.8	18.7	18.4	18.2	16.9	19.2
	1512	17.9	16.8	18.7	18.4	18.2	16.9	19.2
	1513	17.9	16.8	18.7	18.4	18.2	16.9	19.2
	1514	19.9	17.5	19.8	18.9	19.5	17.3	20.8
	1515	19.9	17.5	19.8	18.9	19.5	17.3	20.8

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day (From/To) -7/1	1/8	8/15	15/22	22/29	29/36	36/42
2F	2501	19.1	16.8	17.7	17.7	17.8	--	--
	2502	19.1	16.8	17.7	17.7	17.8	--	--
	2503	19.1	16.8	17.7	17.7	17.8	--	--
	2504	19.6	17.7	21.0	18.7	19.5	--	--
	2505	19.6	17.7	21.0	18.7	19.5	--	--
	2506	19.6	17.7	21.0	18.7	19.5	--	--
	2507	19.5	18.0	19.8	17.4	19.3	--	--
	2508	19.5	18.0	19.8	17.4	19.3	--	--
	2509	17.9	16.3	17.3	16.9	17.6	--	--
	2510	17.9	16.3	17.3	16.9	17.6	--	--

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day (From/To) -7/1	1/8	8/15	15/22	22/29	29/36	36/42
3F	3501	18.4	17.0	18.4	17.4	19.0	--	--
	3502	18.4	17.0	18.4	17.4	19.0	--	--
	3503	18.4	17.0	18.4	17.4	19.0	--	--
	3504	19.0	16.6	18.9	16.7	19.3	--	--
	3505	19.0	16.6	18.9	16.7	19.3	--	--
	3506	19.0	16.6	18.9	16.7	19.3	--	--
	3507	21.1	18.5	21.6	18.9	20.5	--	--
	3508	21.1	18.5	21.6	18.9	20.5	--	--
	3509	19.6	15.8	19.1	17.4	19.4	--	--
	3510	19.6	15.8	19.1	17.4	19.4	--	--

Appendix 8

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Day (From/To) -7/1	1/8	8/15	15/22	22/29	29/36	36/42
4F	4501	17.0	15.0	22.6	20.4	22.6	--	--
	4502	17.0	15.0	22.6	20.4	22.6	--	--
	4503	17.0	15.0	22.6	20.4	22.6	--	--
	4504	20.5	19.7	27.4	23.9	27.4	--	--
	4505	20.5	19.7	27.4	23.9	27.4	--	--
	4506	20.5	19.7	27.4	23.9	27.4	--	--
	4507	19.4	18.1	24.0	24.0	22.7	--	--
	4508	19.4	18.1	24.0	24.0	22.7	--	--
	4509	19.8	17.3	24.0	24.6	23.6	--	--
	4510	19.8	17.3	24.0	24.6	23.6	--	--
	4511	20.5	22.5	27.0	18.9	26.1	22.0	26.2
	4512	20.5	22.5	27.0	18.9	26.1	22.0	26.2
	4513	20.5	22.5	27.0	18.9	26.1	22.0	26.2
	4514	21.9	17.1	25.1	20.2	25.1	21.4	26.3
	4515	21.9	17.1	25.1	20.2	25.1	21.4	26.3

Appendix 9

Individual Body Temperature Values Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	TERR	Technical error
AVS	Suspected aberrant value	X	Excluded from mean
NR	Not recorded	p	6 hours post dosing
pr	Predosing		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 (pr)	Day 1 (p)	Day 2	Day 29 (pr)	Day 29 (p)	Day 30
1M	1001	37.2	36.9	36.5	34.8	36.9	36.9
	1002	37.1	37.3	36.6	36.3	36.7	36.1
	1003	37.8	37.1	36.6	36.8	37.1	36.8
	1004	37.4	38.3	36.5	35.3	36.8	36.8
	1005	37.8	37.3	36.6	36.0	36.8	36.2
	1006	37.4	37.9	36.6	36.2	37.3	36.4
	1007	37.4	38.5	36.4	38.2	38.4	37.5
	1008	37.1	37.6	36.6	37.3	36.7	36.2
	1009	37.5	38.1	36.3	36.3	36.5	36.1
	1010	37.8	37.0	36.6	36.2	37.0	36.4
	1011	37.6	37.6	36.4	36.0	37.1	37.0
	1012	37.7	36.6	36.7	36.4	37.0	36.9
	1013	36.4	37.6	36.5	36.1	37.3	36.7
	1014	37.1	37.4	36.4	36.0	37.0	36.9
	1015	37.1	37.3	36.5	36.3	37.3	36.9

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 (pr)	Day 1 (p)	Day 2	Day 29 (pr)	Day 29 (p)	Day 30
2M	2001	36.6	37.8	36.6	38.2	37.8	38.4
	2002	37.0	38.3	37.2	36.7	38.6	37.3
	2003	37.0	37.5	37.8	36.6	37.7	38.0
	2004	36.9	37.7	37.4	37.7	38.3	38.6
	2005	36.5	38.6	37.2	37.9	38.4	38.3
	2006	36.4	38.3	37.6	37.7	38.0	37.0
	2007	37.8	37.6	35.3	35.7	37.6	37.4
	2008	36.7	38.7	36.1	36.1	37.7	37.0
	2009	37.8	37.8	36.3	36.6	37.5	36.8
	2010	37.0	37.4	36.0	36.2	37.6	37.2

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 (pr)	Day 1 (p)	Day 2	Day 29 (pr)	Day 29 (p)	Day 30
3M	3001	36.6	38.1	37.9	36.1	38.2	38.3
	3002	37.1	36.8	37.2	37.6	38.6	39.1
	3003	37.4	38.3	37.3	37.0	37.9	38.7
	3004	36.9	39.1	38.4	36.4	39.0	39.6
	3005	36.7	38.1	37.4	35.5	38.5	38.1
	3006	36.9	38.5	37.5	36.3	38.5	38.8
	3007	37.4	38.8	38.2	36.6	38.9	38.0
	3008	37.3	38.6	37.1	36.6	38.8	39.2
	3009	37.0	38.4	37.1	36.1	38.6	38.9
	3010	36.4	38.3	37.3	35.8	38.4	38.3

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 (pr)	Day 1 (p)	Day 2	Day 29 (pr)	Day 29 (p)	Day 30
4M	4001	37.7	38.9	37.4	37.6	38.5	38.8
	4002	36.8	38.3	38.3	36.5	38.1	38.9
	4003	36.8	38.7	37.6	37.9	38.6	39.3
	4004	36.5	38.8	37.2	37.4	38.8	39.2
	4005	36.7	38.9	38.0	36.7	39.1	39.0
	4006	37.1	38.9	37.5	36.2	38.4	38.3
	4007	37.7	38.5	37.7	36.7	38.5	38.5
	4008	36.7	39.2	37.8	36.7	38.2	39.4
	4009	36.7	38.6	36.2	36.3	38.2	38.7
	4010	36.4	38.6	36.9	36.3	38.2	38.8
	4011	37.5	38.8	39.0	37.3	39.4	39.0
	4012	36.9	39.1	38.2	36.4	39.1	38.2
	4013	37.4	38.4	38.5	36.6	38.9	39.0
	4014	38.0	38.7	38.3	36.7	38.7	39.1
	4015	37.5	38.6	38.0	36.8	39.2	38.7

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 (pr)	Day 1 (p)	Day 2	Day 3	Day 29 (pr)	Day 29 (p)	Day 30
1F	1501	38.6	37.0	36.6	--	38.7	36.4	37.2
	1502	37.9	37.2	36.5	--	36.7	36.6	36.6
	1503	39.0	37.2	37.8	--	36.6	35.9	36.2
	1504	38.4	36.7	36.5	--	38.9	36.5	37.6
	1505	38.3	37.3	37.2	--	38.3	37.6	37.6
	1506	38.3	36.7	36.8	--	38.3	35.4	36.8
	1507	38.7	38.2	36.4	--	38.1	36.4	37.4
	1508	38.9	38.3	37.0	--	38.7	36.9	38.2
	1509	39.3	39.3	38.0	--	39.6	38.6	38.8
	1510	39.2	38.6	36.8	--	38.2	37.4	37.5
	1511	37.9	38.1	37.0	--	37.4	36.6	37.1
	1512	38.4	38.3	37.4	--	38.1	37.7	36.8
	1513	38.1	38.2	36.7	--	37.8	37.4	37.4
	1514	38.8	38.4	37.6	--	38.7	38.1	37.9
	1515	38.9	37.9	37.1	--	38.7	37.7	37.7

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 31
1F	1501	--
	1502	--
	1503	--
	1504	--
	1505	--
	1506	--
	1507	--
	1508	--
	1509	--
	1510	--
	1511	--
	1512	--
	1513	--
	1514	--
	1515	--

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 (pr)	Day 1 (p)	Day 2	Day 3	Day 29 (pr)	Day 29 (p)	Day 30
2F	2501	38.8	37.3	37.2	--	38.7	38.0	38.4
	2502	38.7	37.5	36.5	--	39.1	37.1	37.6
	2503	38.3	39.0	37.7	--	38.9	39.0	39.1
	2504	38.2	38.5	37.2	--	39.0	36.8	37.6
	2505	38.9	38.4	38.2	--	39.2	38.1	38.4
	2506	38.2	38.2	38.0	--	36.7	37.0	38.3
	2507	39.1	39.5	38.4	--	38.9	39.0	38.3
	2508	38.4	38.4	38.2	--	38.3	38.7	38.4
	2509	38.3	38.7	37.9	--	39.5	39.2	38.4
	2510	38.2	38.1	37.9	--	37.2	37.7	38.0

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 31
2F	2501	--
	2502	--
	2503	--
	2504	--
	2505	--
	2506	--
	2507	--
	2508	--
	2509	--
	2510	--

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 (pr)	Day 1 (p)	Day 2	Day 3	Day 29 (pr)	Day 29 (p)	Day 30
3F	3501	38.6	38.5	38.4	--	38.0	37.6	38.2
	3502	37.8	38.9	39.0	--	36.8	38.8	39.5
	3503	37.6	39.2	39.2	--	37.2	38.0	39.0
	3504	38.0	38.6	38.1	--	38.9	38.3	38.9
	3505	37.3	38.3	38.6	--	39.0	38.1	39.5
	3506	38.0	39.4	38.2	--	38.7	38.6	38.9
	3507	37.3	38.0	38.2	--	38.9	37.7	38.7
	3508	37.3	37.2	38.5	--	38.1	37.7	38.7
	3509	38.5	38.6	38.9	--	36.6	38.2	39.2
	3510	38.4	38.9	38.3	--	36.3	38.6	39.1

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 31
3F	3501	--
	3502	--
	3503	--
	3504	--
	3505	--
	3506	--
	3507	--
	3508	--
	3509	--
	3510	--

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Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 1 (pr)	Day 1 (p)	Day 2	Day 3	Day 29 (pr)	Day 29 (p)	Day 30
4F	4501	37.3	38.9	39.2	38.1	37.1	38.6	39.7
	4502	38.2	39.3	40.0	38.4	37.5	37.8	39.6
	4503	37.5	38.5	39.5	37.8	37.5	38.8	39.1
	4504	38.6	40.1	39.4	38.1	39.4	39.6	39.5
	4505	38.4	39.2	39.1	38.7	39.0	38.8	38.9
	4506	38.9	39.6	39.9	37.8	39.2	39.5	39.5
	4507	38.5	38.9	39.3	37.7	37.6	38.8	39.2
	4508	37.2	39.1	39.6	37.8	37.3	38.1	39.7
	4509	37.6	39.3	38.1	38.2	38.8	39.1	38.5
	4510	38.8	39.4	38.3	37.3	38.2	38.9	39.2
	4511	37.7	38.9	39.0	37.9	38.0	38.1	39.0
	4512	37.0	39.1	39.4	37.5	36.6	38.6	39.7
	4513	37.9	38.9	39.8	36.9	37.1	38.5	39.3
	4514	38.8	39.1	39.7	38.1	39.1	38.8	38.6
	4515	38.5	39.0	39.2	37.5	38.2	38.3	38.7

Appendix 9

Individual Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Parameter: Body Temp
°C

Group / Sex	Animal No.	Day 31
4F	4501	--
	4502	--
	4503	--
	4504	--
	4505	--
	4506	--
	4507	--
	4508	--
	4509	--
	4510	--
	4511	37.6
	4512	36.9
	4513	37.7
	4514	--
	4515	--

Appendix 10

Individual Hematology Values Explanation Page

ADVIA 120 Analyzer
Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Hematocrit	HCT	%	Calculated
Hemoglobin	HGB	g/dL	Colorimetric
Mean Corpuscular Hemoglobin	MCH	pg	Calculated
Mean Corpuscular Hemoglobin Concentration	MCHC	g/dL	Calculated
Mean Corpuscular Volume	MCV	fL(μm^3)	Calculated
Mean Platelet Volume	MPV	fL(μm^3)	Calculated
Platelet Count	PLT	$x10^3/\mu L$	Light scatter
Red Blood Cell Count	RBC	$x10^6/\mu L$	Light scatter
Red Blood Cell Distribution Width	RDW	%	Calculated
Reticulocytes	RETIC	$x10^9/L$	Calculated
Reticulocytes Percent	RETIC	%	Light scatter
White Blood Cell Count	WBC	$x10^3/\mu L$	Light scatter
White Blood Cell Differential Count			
Neutrophils Percent	NEUT	%	Light scatter
Lymphocytes Percent	LYMPH	%	Light scatter
Monocytes Percent	MONO	%	Light scatter
Eosinophils Percent	EOS	%	Light scatter
Basophils Percent	BASO	%	Light scatter
Large Unstained Cells Percent	LUC	%	Light scatter
Neutrophils	NEUT	$x10^3/\mu L$	Calculated
Lymphocytes	LYMPH	$x10^3/\mu L$	Calculated
Monocytes	MONO	$x10^3/\mu L$	Calculated
Eosinophils	EOS	$x10^3/\mu L$	Calculated
Basophils	BASO	$x10^3/\mu L$	Calculated
Large Unstained Cells	LUC	$x10^3/\mu L$	Calculated

Manual and Visual

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Count		% and/or $x10^3/\mu L$	Microscopic enumeration (100 white cells)
- Immature Neutrophils Count	IMM NEUT		
- Immature Neutrophils Percent	IMM NEUT		
- Immature Cells Percent	IMM CELL		
- Immature Cells Count	IMM CELL		
- Large Platelets	LPLT		
- Neutrophils Band Form	NEUT BAND		
- Neutrophils Band Form Percent	NEUT BAND		
- Packed Cell Volume	PCV		
- Neutrophils	NEUT		
- Lymphocytes	LYMPH		

Appendix 10

- 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		
- Burr Cells	BURR		

Appendix 10

- 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
OA	Omitted activity	Vet	Bleed for veterinary monitoring
OOS	Sample analysed outside of established stability, results for	VNC	Value not calculable

Appendix 10

information only

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: 4004, 4008, 4508

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	7.54	1.19	6.07	0.17	0.08	0.01	0.03
	1002	9.90	1.25	8.41	0.11	0.06	0.01	0.06
	1003	4.79	0.69	3.89	0.13	0.05	0.00	0.03
	1004	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	1005	6.02	1.02	4.68	0.21	0.07	0.00	0.03
	1006	8.77	1.29	7.05	0.18	0.16	0.02	0.08
	1007	4.98	0.84	3.96	0.09	0.07	0.00	0.02
	1008	7.67	1.15	6.22	0.16	0.10	0.01	0.04
	1009	4.41	0.75	3.48	0.11	0.05	0.01	0.02
	1010	9.68	0.74	8.57	0.18	0.12	0.01	0.06
2M	2001	15.01	10.04	4.51	0.16	0.19	0.01	0.10
	2002	13.73	9.98	3.26	0.16	0.24	0.01	0.07
	2003	16.90	11.91	4.31	0.21	0.31	0.01	0.14
	2004	15.09	10.06	4.24	0.41	0.22	0.01	0.14
	2005	19.45	13.79	4.77	0.36	0.25	0.03	0.25
	2006	14.04	9.14	4.26	0.24	0.18	0.02	0.21
	2007	13.63	8.63	4.21	0.39	0.21	0.01	0.17
	2008	15.62	9.56	4.90	0.46	0.23	0.02	0.45
	2009	13.61	7.31	5.27	0.33	0.41	0.03	0.26
	2010	14.78	8.48	5.55	0.33	0.24	0.02	0.15

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	8.64	14.4	42.3	49.0	16.7	34.1	13.8
	1002	8.40	14.8	43.3	51.5	17.6	34.1	13.5
	1003	8.83	14.5	42.7	48.4	16.4	34.0	12.2
	1004	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	1005	8.50	14.0	41.5	48.9	16.5	33.7	12.9
	1006	7.87	13.6	41.0	52.1	17.2	33.0	14.0
	1007	8.34	13.5	40.7	48.8	16.2	33.1	13.7
	1008	8.89	14.6	43.7	49.1	16.4	33.4	12.8
	1009	8.86	15.4	46.7	52.8	17.4	33.0	12.5
	1010	8.06	13.7	40.7	50.6	17.0	33.7	14.3
2M	2001	8.35	14.5	43.4	51.9	17.4	33.4	13.9
	2002	8.26	14.2	41.8	50.6	17.2	34.0	14.6
	2003	8.71	14.9	42.6	48.9	17.1	34.9	13.8
	2004	8.10	14.7	42.3	52.2	18.2	34.9	14.3
	2005	8.56	14.2	42.5	49.7	16.6	33.5	13.6
	2006	8.57	14.3	43.1	50.3	16.6	33.1	13.5
	2007	6.98	11.9	36.0	51.6	17.1	33.1	13.7
	2008	7.75	14.0	41.7	53.8	18.1	33.6	13.5
	2009	8.81	15.0	45.5	51.7	17.1	33.1	13.4
	2010	9.20	15.2	46.8	50.9	16.6	32.5	14.6

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLATELET CLUMPS	WBC MORPH
1M	1001	1234	244.8	--	--	--	--
	1002	1054	222.2	--	--	--	--
	1003	1171	220.3	--	--	--	--
	1004	--CLOT	--CLOT	--	--	--	--
	1005	1107	281.6	--	--	--	--
	1006	1394	237.0	--	--	--	--
	1007	1080	192.2	--	--	--	--
	1008	1175	241.6	--	--	--	--
	1009	1088	210.1	--	--	--	--
	1010	1209	265.3	--	--	--	--
2M	2001	1195	273.5	--	--	--	--
	2002	1422	228.5	--	--	--	--
	2003	1123	185.4	--	--	--	--
	2004	767	190.8	--	--	--	--
	2005	1176	152.8	--	--	--	--
	2006	1221	222.1	--	--	--	--
	2007	1239	172.7	--	--	--	--
	2008	1166	179.0	--	--	--	--
	2009	865	203.4	--	--	--	--
	2010	1052	238.9	--	--	--	--

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	19.05	14.33	3.70	0.28	0.48	0.01	0.25
	3002	13.60	11.03	1.89	0.25	0.20	0.01	0.22
	3003	18.74	15.74	2.23	0.31	0.30	0.03	0.12
	3004	12.51	10.86	1.26	0.25	0.07	0.00	0.08
	3005	15.10	12.02	2.47	0.19	0.14	0.01	0.27
	3006	17.45	13.76	3.14	0.22	0.08	0.01	0.22
	3007	16.40	12.17	3.10	0.74	0.09	0.02	0.27
	3008	17.41	13.14	3.53	0.31	0.12	0.02	0.28
	3009	17.33	12.51	4.14	0.25	0.20	0.02	0.20
	3010	17.05	13.23	2.98	0.40	0.24	0.03	0.17
4M	4001	15.69	14.02	1.08	0.31	0.10	0.01	0.17
	4002	13.98	12.10	1.42	0.27	0.08	0.01	0.11
	4003	9.81	8.58	0.95	0.13	0.03	0.01	0.11
	4004	11.67	10.32	1.07	0.13	0.10	0.00	0.06
	4005	14.28	12.04	1.80	0.17	0.10	0.01	0.16
	4006	10.31	9.09	0.93	0.19	0.02	0.01	0.08
	4007	16.87	13.96	2.51	0.18	0.06	0.01	0.15
	4008	13.34	11.87	1.07	0.40	0.00	0.00	--MDIFF
	4009	9.44	6.81	2.00	0.20	0.28	0.01	0.14
	4010	15.66	12.80	2.40	0.19	0.15	0.01	0.12

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	8.84	14.4	42.8	48.5	16.3	33.6	15.3
	3002	8.18	14.4	42.5	52.0	17.6	33.9	15.0
	3003	8.84	15.4	44.8	50.7	17.5	34.4	14.8
	3004	8.88	15.1	44.2	49.8	17.0	34.1	13.6
	3005	8.39	14.6	43.1	51.4	17.4	33.8	15.2
	3006	8.68	14.7	43.3	49.9	16.9	33.9	14.9
	3007	10.61	17.3	54.9	51.8	16.4	31.6	13.6
	3008	8.11	14.8	44.3	54.6	18.3	33.5	13.3
	3009	6.91	12.0	35.6	51.5	17.3	33.7	14.5
	3010	8.94	15.3	46.3	51.8	17.1	33.0	15.4
4M	4001	8.51	15.6	45.5	53.4	18.3	34.3	14.1
	4002	8.37	14.5	43.6	52.0	17.4	33.3	15.1
	4003	8.29	14.6	42.4	51.2	17.6	34.3	15.1
	4004	8.47	15.1	44.1	52.1	17.8	34.2	13.8
	4005	8.38	15.1	44.9	53.6	18.0	33.6	14.3
	4006	8.92	15.8	46.8	52.5	17.7	33.8	13.5
	4007	8.66	15.0	44.6	51.5	17.3	33.6	14.6
	4008	9.14	15.2	46.2	50.5	16.6	32.8	14.1
	4009	8.91	15.1	45.2	50.7	16.9	33.3	15.2
	4010	8.35	14.6	44.1	52.8	17.4	33.0	14.6

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLATELET CLUMPS	WBC MORPH
3M	3001	1468	270.5	--	--	--	--
	3002	1160	194.3	--	--	--	--
	3003	895	237.6	--	--	--	--
	3004	1122	156.8	--	--	--	--
	3005	1160	191.7	--	--	--	--
	3006	1113	184.5	--	--	--	--
	3007	1038	181.5	--	--	--	--
	3008	645	148.2	--	--	--	--
	3009	1081	140.2	--	--	--	--
	3010	650	180.1	--	--	--	--
4M	4001	1115	199.7	--	--	--	--
	4002	1112	200.1	--	--	--	--
	4003	1162	168.5	--	--	--	--
	4004	1117	191.4	1+	1+	3+	NAF
	4005	1135	167.1	--	--	--	--
	4006	996	141.8	--	--	--	--
	4007	1143	154.5	--	--	--	--
	4008	887	141.3	1+	1+	2+	NAF
	4009	907	158.8	--	--	--	--
	4010	1432	172.3	--	--	--	--

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	5.56	0.80	4.46	0.18	0.06	0.01	0.05
	1502	4.79	0.76	3.82	0.11	0.06	0.01	0.03
	1503	2.89	0.47	2.33	0.04	0.04	0.00	0.01
	1504	4.00	0.59	3.25	0.08	0.06	0.00	0.03
	1505	2.71	0.39	2.20	0.04	0.05	0.00	0.03
	1506	4.30	0.80	3.33	0.09	0.05	0.00	0.03
	1507	7.09	2.03	4.73	0.16	0.05	0.01	0.11
	1508	3.56	0.46	3.02	0.03	0.04	0.00	0.01
	1509	2.94	0.43	2.43	0.04	0.04	0.00	0.02
	1510	4.73	0.42	4.16	0.07	0.04	0.01	0.03
2F	2501	8.04	5.75	1.87	0.12	0.22	0.00	0.08
	2502	9.67	5.28	3.83	0.10	0.38	0.01	0.07
	2503	7.07	5.78	1.00	0.04	0.20	0.00	0.04
	2504	15.03	9.83	4.45	0.17	0.45	0.02	0.11
	2505	9.74	6.70	2.44	0.13	0.37	0.01	0.08
	2506	10.94	7.14	2.87	0.20	0.61	0.01	0.10
	2507	11.18	6.35	4.31	0.12	0.25	0.01	0.13
	2508	14.83	9.32	4.84	0.24	0.22	0.02	0.20
	2509	9.76	5.52	3.69	0.15	0.27	0.00	0.12
	2510	11.49	7.37	3.58	0.20	0.21	0.02	0.11

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	7.79	14.4	40.2	51.6	18.4	35.7	10.9
	1502	7.46	13.8	39.3	52.6	18.5	35.1	11.7
	1503	7.62	13.1	38.3	50.2	17.1	34.1	12.4
	1504	8.00	13.6	40.3	50.3	16.9	33.7	11.8
	1505	7.70	13.4	38.9	50.5	17.4	34.4	11.3
	1506	7.32	13.2	38.5	52.6	18.1	34.4	11.7
	1507	7.43	12.9	37.5	50.5	17.3	34.3	12.0
	1508	7.12	13.1	38.2	53.6	18.4	34.4	10.9
	1509	7.72	13.7	40.1	52.0	17.7	34.1	11.2
	1510	7.20	13.2	38.5	53.4	18.3	34.3	11.2
2F	2501	8.13	13.8	40.1	49.4	17.0	34.4	12.3
	2502	7.64	13.9	40.3	52.8	18.2	34.4	12.1
	2503	6.94	12.8	37.6	54.2	18.4	33.9	12.6
	2504	8.04	14.3	40.9	50.9	17.8	35.0	12.0
	2505	7.56	13.5	39.1	51.7	17.9	34.5	12.1
	2506	8.11	14.2	41.1	50.6	17.4	34.5	12.5
	2507	7.55	13.2	38.5	51.0	17.5	34.3	11.6
	2508	7.24	12.9	37.5	51.8	17.8	34.4	11.9
	2509	7.76	13.8	40.2	51.8	17.8	34.4	12.1
	2510	8.05	14.0	40.8	50.7	17.4	34.4	12.4

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLATELET CLUMPS	WBC MORPH
1F	1501	1079	97.0	--	--	--	--
	1502	1150	170.1	--	--	--	--
	1503	989	250.7	--	--	--	--
	1504	1159	200.9	--	--	--	--
	1505	1239	191.2	--	--	--	--
	1506	1112	155.4	--	--	--	--
	1507	1035	142.8	--	--	--	--
	1508	1080	190.4	--	--	--	--
	1509	1258	157.4	--	--	--	--
	1510	1133	147.6	--	--	--	--
2F	2501	1272	158.4	--	--	--	--
	2502	1123	124.2	--	--	--	--
	2503	1073	181.0	--	--	--	--
	2504	1131	106.7	--	--	--	--
	2505	903	135.3	--	--	--	--
	2506	1221	151.9	--	--	--	--
	2507	967	152.0	--	--	--	--
	2508	1632	169.8	--	--	--	--
	2509	941	153.1	--	--	--	--
	2510	1064	196.1	--	--	--	--

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	3.40	1.93	1.26	0.04	0.14	0.00	0.02
	3502	11.59	9.91	1.32	0.16	0.05	0.00	0.14
	3503	8.60	7.63	0.75	0.11	0.07	0.00	0.05
	3504	4.96	3.71	0.95	0.06	0.14	0.00	0.09
	3505	4.84	3.39	1.18	0.06	0.16	0.00	0.04
	3506	7.69	4.83	2.63	0.06	0.14	0.01	0.03
	3507	7.09	4.87	1.62	0.14	0.33	0.01	0.13
	3508	11.73	7.53	3.45	0.15	0.40	0.01	0.18
	3509	7.19	5.27	1.47	0.10	0.29	0.01	0.06
	3510	9.23	7.33	1.48	0.19	0.13	0.01	0.09
4F	4501	1.70	1.07	0.56	0.03	0.02	0.00	0.02
	4502	4.09	3.24	0.73	0.05	0.04	0.00	0.03
	4503	2.36	1.39	0.84	0.02	0.08	0.00	0.03
	4504	2.55	1.85	0.59	0.04	0.05	0.00	0.01
	4505	3.67	2.59	0.79	0.07	0.14	0.00	0.07
	4506	3.57	2.50	0.84	0.05	0.17	0.00	0.02
	4507	8.67	6.96	1.44	0.17	0.06	0.00	0.04
	4508	1.17	0.50	0.49	0.13	0.05	0.00	--MDIFF
	4509	5.12	3.54	1.37	0.04	0.11	0.00	0.05
	4510	5.54	4.65	0.55	0.11	0.08	0.00	0.14

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	8.05	13.8	40.9	50.8	17.1	33.7	13.1
	3502	8.46	14.9	43.5	51.4	17.6	34.3	12.2
	3503	8.34	14.3	41.9	50.2	17.1	34.1	12.5
	3504	8.15	15.1	44.2	54.2	18.6	34.3	12.4
	3505	8.05	14.5	41.5	51.6	18.0	35.0	12.5
	3506	8.06	14.4	42.3	52.4	17.8	34.0	13.4
	3507	8.10	13.9	40.5	49.9	17.2	34.4	12.5
	3508	7.80	14.2	41.0	52.6	18.3	34.8	12.8
	3509	7.12	13.1	38.3	53.8	18.4	34.2	13.3
	3510	8.94	15.6	44.9	50.3	17.4	34.6	13.0
4F	4501	8.56	15.5	45.2	52.8	18.1	34.3	12.0
	4502	8.49	15.0	44.2	52.1	17.7	33.9	12.4
	4503	8.14	14.4	41.8	51.4	17.7	34.3	14.2
	4504	8.54	15.5	45.7	53.5	18.1	33.9	13.1
	4505	8.36	14.7	43.0	51.5	17.6	34.1	13.3
	4506	8.33	14.8	44.3	53.2	17.7	33.3	13.0
	4507	7.85	14.4	42.3	53.9	18.4	34.1	12.6
	4508	8.43	15.2	43.8	52.0	18.1	34.8	12.9
	4509	7.35	13.3	38.1	51.9	18.2	35.0	14.0
	4510	8.89	15.9	46.6	52.4	17.9	34.1	12.6

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLATELET CLUMPS	WBC MORPH
3F	3501	956	143.2	--	--	--	--
	3502	1041	209.0	--	--	--	--
	3503	1207	169.5	--	--	--	--
	3504	1020	144.6	--	--	--	--
	3505	1181	148.0	--	--	--	--
	3506	1483	158.4	--	--	--	--
	3507	886	174.3	--	--	--	--
	3508	1061	197.2	--	--	--	--
	3509	885	143.1	--	--	--	--
	3510	1091	178.1	--	--	--	--
4F	4501	862	101.9	--	--	--	--
	4502	902	108.4	--	--	--	--
	4503	872	150.9	--	--	--	--
	4504	817	139.8	--	--	--	--
	4505	915	164.6	--	--	--	--
	4506	1006	125.0	--	--	--	--
	4507	951	167.4	--	--	--	--
	4508	848	142.9	1+	--	2+	NAF
	4509	949	181.1	--	--	--	--
	4510	903	115.3	--	--	--	--

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	10.63	0.99	9.20	0.23	0.11	0.02	0.07
	1012	7.45	1.59	5.57	0.17	0.06	0.01	0.05
	1013	5.69	0.81	4.59	0.12	0.07	0.01	0.08
	1014	8.80	1.63	6.81	0.19	0.10	0.01	0.06
	1015	5.79	0.90	4.63	0.10	0.09	0.01	0.06
4M	4011	8.26	2.51	5.42	0.18	0.07	0.01	0.06
	4012	8.20	1.47	6.29	0.23	0.10	0.01	0.11
	4013	10.22	3.37	6.39	0.32	0.06	0.01	0.07
	4014	7.82	1.18	6.16	0.26	0.06	0.01	0.14
	4015	8.79	1.30	7.12	0.20	0.08	0.00	0.09

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	8.10	13.7	41.6	51.4	16.9	33.0	13.2
	1012	8.00	13.9	41.6	51.9	17.4	33.5	12.5
	1013	8.19	14.0	42.6	52.1	17.1	32.8	13.7
	1014	8.12	14.0	41.9	51.6	17.2	33.4	12.4
	1015	7.94	13.9	42.2	53.1	17.5	32.9	13.0
4M	4011	7.28	13.1	39.2	53.9	18.0	33.3	14.1
	4012	8.29	13.8	42.3	51.0	16.6	32.5	15.0
	4013	7.93	13.8	41.7	52.6	17.4	33.0	15.5
	4014	7.93	14.3	43.5	54.9	18.0	32.9	14.5
	4015	7.48	13.3	40.7	54.4	17.8	32.7	16.1

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLATELET CLUMPS	WBC MORPH
1M	1011	1150	277.0	--	--	--	--
	1012	1360	209.9	--	--	--	--
	1013	1238	237.7	--	--	--	--
	1014	1269	197.7	--	--	--	--
	1015	1091	199.1	--	--	--	--
4M	4011	1445	249.4	--	--	--	--
	4012	1172	289.2	--	--	--	--
	4013	1101	274.5	--	--	--	--
	4014	1232	250.2	--	--	--	--
	4015	1308	298.5	--	--	--	--

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	3.87	0.63	3.08	0.10	0.04	0.00	0.03
	1512	5.29	0.90	4.11	0.13	0.05	0.00	0.10
	1513	2.72	0.48	2.06	0.10	0.04	0.00	0.04
	1514	5.67	0.72	4.77	0.07	0.06	0.00	0.06
	1515	6.31	1.04	4.91	0.25	0.06	0.01	0.04
4F	4511	3.11	0.89	2.12	0.05	0.03	0.00	0.02
	4512	6.90	1.53	5.00	0.21	0.07	0.01	0.09
	4513	5.60	0.79	4.60	0.09	0.05	0.01	0.05
	4514	7.52	1.99	5.14	0.25	0.05	0.01	0.08
	4515	4.08	0.73	3.08	0.16	0.04	0.00	0.08

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	1511	6.98	12.7	36.6	52.4	18.2	34.8	11.4
	1512	6.87	12.4	36.4	53.0	18.0	34.0	11.8
	1513	6.95	12.2	36.5	52.5	17.6	33.5	11.6
	1514	7.52	13.1	40.0	53.2	17.4	32.7	11.3
	1515	7.54	13.7	39.6	52.6	18.1	34.5	11.5
4F	4511	6.43	11.8	35.6	55.4	18.3	33.1	13.5
	4512	6.70	12.1	36.1	53.9	18.1	33.6	13.4
	4513	6.76	12.0	35.9	53.0	17.7	33.5	12.9
	4514	6.69	12.5	37.5	56.1	18.6	33.2	12.8
	4515	7.23	12.8	37.9	52.5	17.7	33.8	13.0

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLATELET CLUMPS	WBC MORPH
1F	1511	1000	133.8	--	--	--	--
	1512	1045	182.9	--	--	--	--
	1513	1252	177.2	--	--	--	--
	1514	1080	172.8	--	--	--	--
	1515	1178	186.4	--	--	--	--
4F	4511	1037	214.4	--	--	--	--
	4512	1291	180.1	--	--	--	--
	4513	1067	152.6	--	--	--	--
	4514	1212	214.9	--	--	--	--
	4515	1267	229.4	--	--	--	--

Appendix 11

Individual Coagulation Values Explanation Page

START 4 Compact Stago Analyzer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Activated Partial Thromboplastin Time	APTT	sec	Viscosity
Fibrinogen	FIB	mg/dL	Viscosity
Prothrombin Time	PT	sec	Viscosity

STA Compact Stago Analyser

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Prothrombin Time	PT	sec	Viscosity
Activated Partial Thromboplastin Time	APTT	sec	Viscosity
Fibrinogen	FIB	mg/dL	Viscosity

Plasma Appearance (Reported as SAMQ PLASMA)

Analyzed Parameter Descriptions

Parameter	Abbreviation	Degree is graded as	Methodology
Normal sample	N	Normal	Manual and visual
Hemolyzed sample	H	+ = slight (pale/light red) ++ = moderate (red) +++ = severe (dark red)	Manual and visual
Lipemic sample	L	+ = slight (cloudy) ++ = moderate (turbid) +++ = severe (lactescent)	Manual and visual
Icterus sample	I	+ = slight (dark yellow) ++ = moderate (very dark yellow) +++ = severe (dark yellow-green)	Manual and visual

Appendix 11

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
--	Not required for veterinary monitoring / Not scheduled to be performed / Dead	RSV	Refer to source data
AVS	Suspected aberrant value	SND	Stability not documented
CLOT	Sample clotted	SNR	Sample not received
COMM	Comment added	Unsc	Unscheduled bleed
NCD	No clot detected	UPTD	Unable to perform due to technical difficulty
NSCH	Not scheduled to be performed	UTD	Unable to determine
OA	Omitted activity	UTDR	Unable to determine, results not reproducible
OOS	Sample analysed outside of established stability, results for information only	Vet	Bleed for veterinary monitoring
QNS	Quantity not sufficient	VNC	Value not calculable
		X	Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 11

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1001	17.1	14.0	276	N
	1002	19.1	15.4	298	N
	1003	16.9	14.7	236	N
	1004	16.9	15.5	292	N
	1005	17.7	14.4	301	N
	1006	17.5	15.0	279	N
	1007	16.9	15.2	308	N
	1008	16.3	15.8	255	N
	1009	17.1	15.4	273	N
	1010	16.5	15.3	284	N
2M	2001	15.8	17.4	538	N
	2002	16.7	17.1	609	N
	2003	15.8	18.2	879	N
	2004	15.9	17.0	617	N
	2005	15.2	18.8	699	N
	2006	16.3	17.3	662	N
	2007	17.7	17.7	719	N
	2008	16.2	18.2	581	N
	2009	15.8	16.2	645	N
	2010	15.2	16.5	613	N

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Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3M	3001	15.7	18.9	641	N
	3002	17.5	18.0	595	N
	3003	16.8	18.0	645	N
	3004	15.2	15.1	641	N
	3005	15.8	18.8	741	N
	3006	17.0	16.5	758	N
	3007	16.3	19.1	714	N
	3008	17.5	19.2	653	N
	3009	16.7	18.6	879	N
	3010	15.9	19.3	598	N
4M	4001	16.9	18.6	609	N
	4002	17.1	18.9	714	N
	4003	18.0	19.0	649	N
	4004	15.4	19.3	666	N
	4005	15.4	18.8	675	N
	4006	16.5	21.1	568	N
	4007	16.0	17.4	662	N
	4008	17.0	19.8	578	N
	4009	15.7	19.3	666	N
	4010	17.3	18.4	741	N

Appendix 11

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1501	17.7	14.5	187	N
	1502	17.4	13.8	207	N
	1503	19.2	16.0	168	N
	1504	17.6	15.4	180	N
	1505	17.6	15.7	198	N
	1506	18.4	15.1	189	N
	1507	18.0	14.4	213	N
	1508	17.3	15.0	161	N
	1509	18.1	14.9	192	N
	1510	17.3	14.6	186	N
2F	2501	17.9	19.1	438	N
	2502	17.0	17.6	422	N
	2503	17.3	19.2	452	N
	2504	16.4	17.6	438	N
	2505	--CLOT	--CLOT	--CLOT	--CLOT
	2506	17.1	18.6	511	N
	2507	18.0	19.0	408	L+
	2508	17.1	18.3	524	N
	2509	16.6	18.1	454	N
	2510	17.6	20.3	440	N

Appendix 11

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3F	3501	19.6	23.3	422	N
	3502	17.7	19.5	477	N
	3503	16.8	18.4	493	N
	3504	18.0	19.8	454	N
	3505	18.7	21.1	464	L+
	3506	19.2	20.2	498	N
	3507	15.8	21.7	552	N
	3508	19.3	21.6	452	N
	3509	18.5	17.4	511	N
	3510	17.5	20.1	513	N
4F	4501	22.9	24.0	286	N
	4502	18.6	21.5	405	N
	4503	19.7	20.3	452	N
	4504	23.5	22.0	308	N
	4505	18.1	20.1	568	N
	4506	18.6	20.1	503	N
	4507	20.0	18.2	493	N
	4508	17.7	21.7	544	N
	4509	17.3	19.5	454	N
	4510	20.9	20.3	448	N

Appendix 11

Individual Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1011	17.9	14.1	288	N
	1012	17.6	14.1	282	N
	1013	17.6	14.0	252	N
	1014	16.3	14.9	275	N
	1015	16.0	13.6	272	N
4M	4011	18.1	15.2	223	N
	4012	17.9	13.7	262	N
	4013	17.4	14.1	255	N
	4014	18.3	15.0	257	N
	4015	18.1	15.0	252	N

Appendix 11

Individual Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1511	17.4	14.8	160	N
	1512	17.1	16.1	147	N
	1513	17.5	16.2	151	N
	1514	17.6	15.4	190	N
	1515	17.1	14.2	156	N
4F	4511	18.8	15.7	146	N
	4512	18.2	15.2	189	N
	4513	17.2	14.1	155	N
	4514	17.0	13.1	143	N
	4515	17.8	16.0	179	N

Appendix 12

Individual Clinical Chemistry Values Explanation Page

Modular Analytics

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Alanine Aminotransferase	ALT	U/L	ALT IFCC UV
Albumin	ALB	g/dL	Bromcresol green colorimetric
Alkaline Phosphatase	ALP	U/L	ALP IFCC liquid colorimetric
Aspartate Aminotransferase	AST	U/L	AST IFCC UV
Calcium	CA	mg/dL	O-cresolphthalein complexone colorimetric
Cholesterol	CHOL	mg/dL	CHOD-PAP enzymatic colorimetric
Creatinine	CREAT	mg/dL	Jaffe kinetic colorimetric. Rate-blanked and compensated
Creatine Kinase	CK	U/L	NAC activated UV
Direct Bilirubin	DBIL	mg/dL	Jendrassik colorimetric
GAMMA-Glutamyl Transferase	GGT	U/L	Nitro-Anilide, Glycylglycine; enzymatic colorimetric
Glucose	GLUC	mg/dL	Hexokinase UV
Iron	FE	µg/dL	Colorimetric
Lactate	LACT	mg/dL	Enzymatic colorimetric
Magnesium	MG	mg/dL	Colorimetric
Phosphorus	PHOS	mg/dL	Molybdate UV
Sodium, Potassium, Chloride (SI)	NA,K,CL	mmol/L	Indirect measurement (Ion selective electrode)
Total Bilirubin	TBIL	mg/dL	DPD colorimetric
Total Protein	TPROT	g/dL	Biuret colorimetric
Triglycerides	TRIG	mg/dL	GPO-PAP enzymatic colorimetric
Urea Nitrogen	UREAN	mg/dL	Urease kinetic UV

Calculations

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Calculation
Albumin/Globulin ratio	A/G	None	Albumin / Globulin
Globulin	GLOB	g/dL	Total Protein - Albumin
Indirect Bilirubin	IBIL	mg/dL	Total Bilirubin - Direct Bilirubin

Appendix 12

Serum Appearance
(Reported as SAMQ SERUM)

Analyzed Parameter Descriptions

Parameter	Abbreviation	Key to Results (Code)	Methodology
Normal sample	N	Normal	Manual and visual
Hemolyzed sample	H	+ = slight (pale/light red) ++ = moderate (red) +++ = severe (dark red)	Manual and visual
Lipemic sample	L	+ = slight (cloudy) ++ = moderate (turbid) +++ = severe (lactescent)	Manual and visual
Icterus sample	I	+ = slight (dark yellow) ++ = moderate (very dark yellow) +++ = severe (dark yellow-green)	Manual and visual

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
--	Not evaluated/Not required for veterinary monitoring	SNR	Sample not received
AVS	Suspected aberrant value	TNR	Test not reported
COMM	Comment added	Unsc	Unscheduled bleed
CLOT	Sample clotted	UPTD	Unable to perform due to technical difficulty
LLD	Less than lower limit of detection	UTD	Unable to determine
LLOQ/LLQ	Less than lower limit of quantitation	UTDH	Unable to determine due to marked hemolysis
NSCH	Not scheduled to be performed	UTDL	Unable to determine due to marked lipemia
OA	Omitted activity	UTDR	Unable to determine, results not reproducible
OOS	Sample analysed outside of established stability, results for information only	VARR	Assigned value above reportable range
QNS	Quantity not sufficient	VBRR	Assigned value below reportable range
RSV	Refer to source data	Vet	Bleed for veterinary monitoring
SND	Stability not documented	VNC	Value not calculable
		X	Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Appendix 12

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 12

Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	148	48	125	2VBRR	1290XOOS	0.05	17
	1002	80	48	90	2VBRR	463	0.07	14
	1003	88	45	131	2VBRR	97	0.05	18
	1004	80	36	106	2VBRR	363	0.05	20
	1005	103	43	84	2VBRR	657	0.10	17
	1006	70	34	72	2VBRR	148	0.07	13
	1007	72	36	100	2VBRR	225	0.06	23
	1008	94	35	74	2VBRR	600	0.07	15
	1009	64	33	114	2VBRR	122	0.07	14
	1010	89	36	66	2VBRR	529	0.06	14
2M	2001	121	39	66	2VBRR	797	0.07	23
	2002	100	34	103	2VBRR	593	0.10	18
	2003	66	42	82	2VBRR	99	0.08	18
	2004	79	33	71	2VBRR	320	0.07	15
	2005	88	37	95	2VBRR	435	0.04	22
	2006	135	34	121	2VBRR	1066	0.03	22
	2007	94	42	88	2VBRR	538	0.13	15
	2008	87	32	75	2VBRR	328	0.07	17
	2009	68	36	97	2VBRR	130	0.07	17
	2010	122	42	90	2VBRR	687	0.11	19

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	184	84	73	6.5	3.9	2.6
	1002	0.4	202	57	82	6.6	3.6	3.0
	1003	0.4	204	86	118	6.0	3.8	2.2
	1004	0.4	187	65	48	6.3	3.8	2.5
	1005	0.3	166	74	56	6.0	3.9	2.1
	1006	0.4	181	53	37	5.9	3.6	2.3
	1007	0.4	216	62	96	6.2	4.0	2.2
	1008	0.3	247	68	94	6.1	3.9	2.2
	1009	0.4	224	72	44	6.0	3.9	2.1
	1010	0.4	228	55	76	6.1	3.6	2.5
2M	2001	0.5	132	73	55	6.2	3.6	2.6
	2002	0.5	152	78	72	6.4	3.4	3.0
	2003	0.4	151	78	48	6.8	3.7	3.1
	2004	0.4	156	70	45	6.4	3.5	2.9
	2005	0.4	164	85	39	6.1	3.4	2.7
	2006	0.4	173	77	63	5.9	3.4	2.5
	2007	0.4	203	45	32	6.0	3.5	2.5
	2008	0.4	201	66	58	6.1	3.4	2.7
	2009	0.4	157	117	42	6.4	3.5	2.9
	2010	0.4	211	106	37	6.3	3.4	2.9

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	1.5	10.6	7.2	142	5.6	100	N
	1002	1.2	11.1	5.8	141	5.0	101	N
	1003	1.7	10.9	6.6	141	5.0	100	L+
	1004	1.5	10.0	6.4	143	5.5	102	N
	1005	1.9	10.0	7.1	140	5.0	100	N
	1006	1.6	10.0	6.4	143	4.7	104	N
	1007	1.8	10.7	6.1	140	5.2	100	L+
	1008	1.8	11.1	6.5	140	5.2	101	N
	1009	1.9	10.8	6.7	142	4.8	99	N
	1010	1.4	10.6	7.1	140	5.3	101	N
2M	2001	1.4	10.5	7.7	141	5.2	98	N
	2002	1.1	11.0	8.0	139	5.6	99	N
	2003	1.2	11.2	7.9	141	4.7	100	N
	2004	1.2	10.8	7.1	141	5.0	102	N
	2005	1.3	10.7	7.3	140	5.3	98	N
	2006	1.4	10.2	7.4	141	5.8	100	N
	2007	1.4	10.5	7.2	139	5.2	100	N
	2008	1.3	10.8	6.8	141	5.3	100	N
	2009	1.2	11.1	6.2	141	5.0	100	N
	2010	1.2	10.5	7.1	140	5.2	99	N

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	109	32	104	2VBRR	681	0.09	17
	3002	107	49	111	2VBRR	575	0.10	18
	3003	131	33	88	2VBRR	1060	0.09	17
	3004	149	52	144	2VBRR	1141	0.09	16
	3005	69	37	110	2VBRR	111	0.12	13
	3006	104	59	138	2VBRR	430	0.08	17
	3007	76	37	101	2VBRR	243	0.08	15
	3008	86	38	183	2VBRR	110	0.06	25
	3009	73	48	99	2VBRR	122	0.08	15
	3010	167	43	128	2VBRR	1206	0.10	16
4M	4001	140	42	106	2VBRR	1057XOOS	0.12	15
	4002	104	41	133	2VBRR	537	0.07	14
	4003	172	40	141	2VBRR	1502	0.07	19
	4004	161	37	163	2VBRR	1503	0.06	13
	4005	95	45	170	2VBRR	330	0.08	19
	4006	136	60	137	2VBRR	639	0.06	18
	4007	84	37	118	2VBRR	149	0.10	14
	4008	90	42	94	2VBRR	194	0.05	19
	4009	103	35	123	2VBRR	493	0.09	13
	4010	82	45	116	2VBRR	221	0.08	15

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	147	107	75	6.5	3.6	2.9
	3002	0.5	134	61	49	6.0	3.5	2.5
	3003	0.4	139	109	71	6.7	3.6	3.1
	3004	0.5	149	70	44	6.3	3.7	2.6
	3005	0.4	167	85	64	6.7	3.6	3.1
	3006	0.5	174	71	55	6.3	3.5	2.8
	3007	0.4	190	64	45	5.9	3.1	2.8
	3008	0.5	181	68	81	5.8	3.4	2.4
	3009	0.4	188	106	164	6.6	3.3	3.3
	3010	0.5	164	84	46	6.2	3.4	2.8
4M	4001	0.5	119	93	50	6.2	3.5	2.7
	4002	0.5	162	81	61	6.1	3.3	2.8
	4003	0.5	135	64	59	6.0	3.5	2.5
	4004	0.4	144	88	72	6.2	3.4	2.8
	4005	0.5	157	120	98	6.2	3.6	2.6
	4006	0.4	135	59	36	6.1	3.4	2.7
	4007	0.4	151	76	55	6.0	3.4	2.6
	4008	0.4	146	45	35	5.9	3.4	2.5
	4009	0.5	150	67	64	6.4	3.4	3.0
	4010	0.4	181	96	52	6.7	3.4	3.3

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	1.2	10.4	7.8	141	5.6	98	N
	3002	1.4	10.3	6.9	140	5.1	101	N
	3003	1.2	10.5	8.5	139	5.5	97	N
	3004	1.4	10.3	7.0	141	5.8	102	N
	3005	1.2	11.2	7.8	142	5.4	100	N
	3006	1.3	10.8	6.9	141	6.1	100	N
	3007	1.1	10.7	8.3	143	5.5	100	N
	3008	1.4	10.7	7.1	140	5.6	102	N
	3009	1.0	11.5	7.4	136	5.7	95	N
	3010	1.2	10.1	8.4	140	5.8	102	N
4M	4001	1.3	10.0	7.2	139	5.6	98	N
	4002	1.2	10.3	8.3	139	5.4	100	N
	4003	1.4	9.9	7.1	141	5.5	100	N
	4004	1.2	9.9	8.6	140	5.4	101	N
	4005	1.4	10.6	6.3	141	5.2	99	N
	4006	1.3	9.9	7.4	141	5.5	103	N
	4007	1.3	10.6	7.9	144	5.2	105	N
	4008	1.4	10.5	8.3	140	6.1	100	N
	4009	1.1	11.1	6.7	140	5.9	100	N
	4010	1.0	10.9	7.4	144	5.9	102	N

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	96	32	42	2VBRR	592	0.09	16
	1502	73	29	60	2VBRR	319	0.06	10
	1503	77	43	72	2VBRR	96	0.05	17
	1504	67	28	39	2VBRR	113	0.06	13
	1505	176	64	43	2VBRR	172	0.06	13
	1506	66	38	45	2VBRR	165	0.05	15
	1507	577	281	49	2VBRR	566	0.06	12
	1508	72	25	61	2VBRR	252	0.08	13
	1509	111	28	63	2VBRR	814	0.00VBRR	18
	1510	69	28	71	2VBRR	242	0.05	15
2F	2501	81	30	85	2VBRR	416	0.05	19
	2502	111	37	70	2VBRR	800	0.04	18
	2503	103	33	51	2VBRR	604	0.06	16
	2504	73	35	56	2VBRR	90	0.08	18
	2505	84	35	52	2VBRR	130	0.08	29
	2506	103	35	60	2VBRR	412	0.07	22
	2507	71	39	83	2VBRR	102	0.06	23
	2508	108	25	55	2VBRR	673	0.06	19
	2509	119	52	82	2VBRR	505	0.11	21
	2510	99	49	81	2VBRR	242	0.04	18

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	1501	0.5	139	94	30	7.0	4.6	2.4
	1502	0.4	210	61	33	6.6	4.4	2.2
	1503	0.5	202	82	53	6.5	4.2	2.3
	1504	0.5	167	55	48	6.9	4.8	2.1
	1505	0.4	188	73	56	7.1	4.7	2.4
	1506	0.4	225	60	37	6.6	4.6	2.0
	1507	0.4	180	99	39	6.5	4.3	2.2
	1508	0.4	149	59	31	6.0	4.4	1.6
	1509	0.4	201	71	61	6.2	4.0	2.2
	1510	0.4	220	87	76	6.7	4.8	1.9
2F	2501	0.4	170	80	35	6.6	4.1	2.5
	2502	0.5	142	105	56	6.6	4.0	2.6
	2503	0.5	180	82	41	6.5	4.1	2.4
	2504	0.4	202	63	65	6.6	4.0	2.6
	2505	0.5	170	77	37	6.3	4.0	2.3
	2506	0.5	150	79	32	6.7	4.1	2.6
	2507	0.4	147	76	89	6.4	4.0	2.4
	2508	0.5	186	83	37	6.6	4.1	2.5
	2509	0.4	181	66	39	6.1	4.0	2.1
	2510	0.4	204	78	53	6.1	4.1	2.0

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	1.9	11.0	5.1	142	4.4	104	N
	1502	2.0	10.5	4.6	142	4.1	101	N
	1503	1.8	10.5	6.4	143	4.2	106	N
	1504	2.3	10.2	5.6	145	4.3	105	N
	1505	2.0	10.7	7.2	141	4.9	103	N
	1506	2.3	11.4	6.8	142	4.5	104	N
	1507	2.0	11.1	6.4	140	4.6	100	N
	1508	2.8	10.7	7.2	144	4.6	106	N
	1509	1.8	10.5	7.1	142	4.7	102	N
	1510	2.5	11.1	6.7	144	4.6	104	N
2F	2501	1.6	11.0	7.2	141	4.8	102	N
	2502	1.5	11.0	5.4	141	4.5	102	N
	2503	1.7	10.6	7.4	141	4.7	101	N
	2504	1.5	11.0	6.2	140	4.5	100	N
	2505	1.7	10.7	6.3	139	5.0	102	N
	2506	1.6	10.9	6.7	142	5.3	101	N
	2507	1.7	11.0	4.9	141	4.9	104	L+
	2508	1.6	10.7	6.7	141	5.4	98	N
	2509	1.9	10.8	6.6	142	5.1	103	N
	2510	2.0	10.9	6.3	142	4.8	101	N

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	509	107	61	2VBRR	678	0.15	18
	3502	127	57	93	2VBRR	328	0.06	15
	3503	106	65	72	2VBRR	219	0.05	15
	3504	87	39	68	2VBRR	209	0.07	13
	3505	111	42	66	2VBRR	364	0.10	15
	3506	178	42	71	2VBRR	1531	0.10	16
	3507	147	43	49	2VBRR	705	0.10	12
	3508	77	38	67	2VBRR	135	0.07	22
	3509	79	32	77	2VBRR	78	0.09	13
	3510	105	44	106	2VBRR	410	0.06	16
4F	4501	735	89	95	2VBRR	194	0.12	16
	4502	392	132	116	2VBRR	140	0.08	16
	4503	201	65	67	2VBRR	289	0.09	13
	4504	220	83	84	2VBRR	554	0.05	13
	4505	107	41	78	2VBRR	78	0.09	13
	4506	98	41	79	2VBRR	280	0.06	19
	4507	84	41	98	2VBRR	117	0.06	13
	4508	108	37	79	2VBRR	444	0.10	12
	4509	89	37	89	2VBRR	347	0.09	25
	4510	106	48	101	2VBRR	142	0.08	17

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	132	102	100	7.0	4.6	2.4
	3502	0.5	135	73	40	6.4	4.2	2.2
	3503	0.4	148	105	46	6.7	4.3	2.4
	3504	0.5	164	74	45	6.7	4.2	2.5
	3505	0.4	139	82	54	6.3	4.1	2.2
	3506	0.5	104	50	38	6.5	4.0	2.5
	3507	0.4	135	114	59	7.4	4.7	2.7
	3508	0.4	170	64	53	6.1	3.9	2.2
	3509	0.5	169	61	71	5.4	3.4	2.0
	3510	0.4	158	74	53	6.4	4.0	2.4
4F	4501	0.4	133	46	28	6.1	4.1	2.0
	4502	0.5	152	61	36	6.0	4.1	1.9
	4503	0.4	113	87	79	6.4	4.2	2.2
	4504	0.4	111	42	40	5.6	3.6	2.0
	4505	0.4	151	76	74	6.0	3.7	2.3
	4506	0.5	149	62	32	5.9	3.4	2.5
	4507	0.4	128	30	27	5.2	3.3	1.9
	4508	0.5	124	100	99	6.7	4.3	2.4
	4509	0.5	159	96	52	6.4	4.0	2.4
	4510	0.4	133	46	28	5.7	3.5	2.2

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	11.4	8.0	143	4.5	100	N
	3502	1.9	10.7	7.2	142	4.8	100	N
	3503	1.8	11.0	7.8	141	4.5	102	N
	3504	1.7	10.9	8.2	143	5.2	101	N
	3505	1.9	10.3	8.3	142	4.5	103	N
	3506	1.6	10.4	8.0	141	5.5	100	N
	3507	1.7	11.4	7.7	142	4.9	102	N
	3508	1.8	10.5	6.1	141	4.6	100	N
	3509	1.7	10.6	9.5	144	4.1	105	N
	3510	1.7	10.8	6.8	140	5.6	99	N
4F	4501	2.0	10.2	8.9	140	4.6	103	N
	4502	2.2	10.0	6.7	138	4.2	99	N
	4503	1.9	10.6	8.2	140	4.3	101	N
	4504	1.8	9.9	7.6	141	4.5	104	N
	4505	1.6	10.6	7.6	139	4.6	102	N
	4506	1.4	10.5	7.8	139	5.3	99	N
	4507	1.7	10.0	7.4	142	4.5	106	N
	4508	1.8	10.4	6.7	140	4.9	100	N
	4509	1.7	10.8	6.7	140	4.7	100	N
	4510	1.6	10.2	7.1	141	4.8	105	N

Appendix 12

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	108	41	93	2VBRR	716	0.07	16
	1012	102	54	107	2VBRR	474	0.07	13
	1013	111	40	102	2VBRR	754	0.05	17
	1014	70	37	70	2VBRR	169	0.06	13
	1015	64	45	70	2VBRR	115	0.04	13
4M	4011	105	41	97	2VBRR	631	0.05	17
	4012	64	38	87	2VBRR	134	0.06	13
	4013	84	45	95	2VBRR	138	0.06	13
	4014	109	29	85	2VBRR	729	0.06	13
	4015	60	34	89	2VBRR	144	0.06	13

Appendix 12

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	181	112	63	6.4	3.9	2.5
	1012	0.3	235	97	95	5.9	3.7	2.2
	1013	0.3	269	76	73	6.3	3.9	2.4
	1014	0.3	169	68	76	5.9	3.5	2.4
	1015	0.3	241	106	58	6.1	3.6	2.5
4M	4011	0.4	149	50	55	6.1	3.9	2.2
	4012	0.3	258	86	71	6.2	3.8	2.4
	4013	0.3	154	59	60	6.1	3.7	2.4
	4014	0.4	231	66	51	5.8	3.6	2.2
	4015	0.4	313	66	60	5.7	3.8	1.9

Appendix 12

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1M	1011	1.6	10.8	7.4	141	4.7	102	N
	1012	1.7	10.5	7.2	137	5.1	101	N
	1013	1.6	10.8	8.1	138	5.5	99	N
	1014	1.5	10.6	6.8	140	5.0	103	N
	1015	1.4	10.6	6.7	140	4.9	101	N
4M	4011	1.8	10.4	7.5	140	4.9	102	N
	4012	1.6	10.8	7.8	138	5.2	100	N
	4013	1.5	10.4	7.7	142	4.8	104	N
	4014	1.6	10.5	7.9	139	5.9	100	N
	4015	2.0	10.1	7.7	137	5.6	102	N

Appendix 12

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	120	43	67	2VBRR	662	0.05	15
	1512	134	49	70	2VBRR	694	0.05	18
	1513	108	55	86	2VBRR	588	0.04	15
	1514	137	49	104	2VBRR	1165	0.04	18
	1515	102	43	41	2VBRR	436	0.07	20
4F	4511	75	42	81	2VBRR	230	0.03	15
	4512	113	54	70	2VBRR	395	0.03	14
	4513	82	46	68	2VBRR	218	0.00VBRR	16
	4514	80	31	79	2VBRR	143	0.07	14
	4515	69	40	57	2VBRR	98	0.05	15

Appendix 12

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	1511	0.5	174	60	47	6.4	4.6	1.8
	1512	0.6	165	50	41	6.9	4.7	2.2
	1513	0.4	202	104	75	6.8	4.8	2.0
	1514	0.4	191	78	63	6.0	4.1	1.9
	1515	0.4	133	72	45	6.4	4.3	2.1
4F	4511	0.4	259	55	65	6.0	4.1	1.9
	4512	0.4	206	99	59	6.7	4.5	2.2
	4513	0.4	214	60	90	6.1	4.0	2.1
	4514	0.3	202	60	41	6.1	4.4	1.7
	4515	0.3	204	92	42	6.6	4.5	2.1

Appendix 12

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 100 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	2.6	10.0	5.5	140	4.2	103	N
	1512	2.1	10.0	5.7	139	4.8	104	N
	1513	2.4	10.3	7.7	140	4.6	101	N
	1514	2.2	10.2	7.4	141	4.8	104	N
	1515	2.0	10.4	7.5	140	4.3	100	N
4F	4511	2.2	10.0	8.2	140	4.7	103	N
	4512	2.0	10.5	7.0	139	5.2	102	N
	4513	1.9	10.4	6.5	139	4.7	104	L+
	4514	2.6	10.6	7.9	141	4.8	102	N
	4515	2.1	10.4	6.2	138	4.4	104	N

Appendix 13

FINAL REPORT

Study Phase: Ophthalmology Evaluation

Test Facility Study No. 5002231

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

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Appendix 13

LIST OF APPENDICES

Appendix 13

1. INTRODUCTION

This report presents the ophthalmology evaluations for the study entitled *A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With a 2-Week Recovery Period* (Study No. 5002231).

For the work detailed in this report, the ophthalmology phase start date was 19 Mar 2017, and the ophthalmology phase completion date was 25 May 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)	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-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

2.1. Ophthalmic Examinations

Frequency: Examinations were performed once prestudy and again at the end of the dosing period.

Procedure: All animals were subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used was 1% tropicamide.

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 13

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 the Dosing Period 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. CONCLUSION

Administration of mRNA-1706 by intramuscular injection vaccine on Days 1, 15, and 29 (3 doses) to Sprague-Dawley rats at doses of 10, 50, and 100 µg/dose did not result in any test item-related ophthalmic changes.

Appendix 13

5. REPORT APPROVAL

(b) (6) Date: 27 NOV 2017

Appendix 13

Appendix 1
Individual Ophthalmic Findings

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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 13

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

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Appendix 1

Individual Ophthalmic Findings

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-46	-45	22	23
1	m	1002	Lens,Op ,Nucleus	Right	.	.	.	1
			Retina, Fold	Left	.	.	.	X
		1003	Ret/Chor, Atrophy,Linear,Focal	Left	.	.	.	3
		1006	Lens Op, Cortex, Ant, Focal	Right Inferior	.	.	.	1
		1007	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		1009	Lens Nucleus Prominent	Right	.	X	.	X
			Lens Nucleus Prominent	Left	.	X	.	X
		1010	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		1012	Cornea, Op, Multi, Pinpoint	Right	.	.	.	2
		1013	Lens Nucleus Prominent	Right	.	X	.	X
			Lens Nucleus Prominent	Left	.	X	.	X

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight; 3 = 3 Moderate

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-46	-45	22	23
2	m	2001	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		2002	Lens Op, Cortex, Ant, Focal	Right Nasal	.	.	.	1
		2004	Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		2005	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	1

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight; 3 = 3 Moderate

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-46	-45	22	23
3	m	3001	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		3006	Lens Nucleus Prominent	Right	.	X	.	.
			Lens Nucleus Prominent	Left	.	X	.	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight; 3 = 3 Moderate

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-46	-45	22	23
4	m	4005	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
		4009	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4013	Lens Op, Cortex, Ant, Focal	Right	.	.	.	1
			Lens Op, Cortex, Ant, Focal	Left Supero-Temporal	.	1	.	1
		4014	Cornea, Loss of Luster	Left	.	.	.	X
			Cornea, Op, Multi, Pinpoint	Left	.	.	.	2
			Lens Nucleus Prominent	Right	.	X	.	X
			Lens Nucleus Prominent	Left	.	X	.	X
		4015	Lens Nucleus Prominent	Right	.	X	.	X
			Lens Nucleus Prominent	Left	.	X	.	X
			Lens,Op ,Nucleus	Right	.	2	.	1
			Lens,Op ,Nucleus	Left	.	2	.	1

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight; 3 = 3 Moderate

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-46	-45	22	23
1	f	1502	Lens Op, Cortex, Ant, Focal	Left Superior	.	.	2	.
		1504	Lens,Op ,Nucleus	Right	1	.	2	.
			Lens,Op ,Nucleus	Left	1	.	2	.
		1506	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1507	Lens Op, Cortex, Ant, Focal	Left Inferior	1	.	1	.
		1508	Lens Op, Cortex, Ant, Focal	Right Superior	1	.	1	.
		1509	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1510	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		1512	Lens,Op ,Nucleus	Right	1	.	1	.
		1514	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		1515	Lens Op, Cortex, Ant, Focal	Left Superior	.	.	1	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight; 3 = 3 Moderate

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-46	-45	22	23
2	f	2503	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		2505	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		2506	Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		2508	Lens Op, Cortex, Ant, Focal	Right	.	.	1	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight; 3 = 3 Moderate

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-46	-45	22	23
3	f	3501	Lens Op, Cortex, Ant, Focal	Right Superior	.	.	1	.
			Lens Op, Cortex, Ant, Multi	Left	.	.	1	.
		3502	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3503	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3505	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3507	Lens Op, Cortex, Ant, Focal	Right Superior	1	.	.	.
			Lens Op, Cortex, Ant, Multi	Right	.	.	1	.
		3508	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3510	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight; 3 = 3 Moderate

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002231

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-46	-45	22	23
4	f	4502	Cornea, Op, Multi, Pinpoint	Left	.	.	1	.
			Lens,Op ,Nucleus	Right	1	.	1	.
			Lens,Op ,Nucleus	Left	1	.	1	.
		4503	Vitreous, Hemorrhage	Right	1	.	.	.
		4504	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4508	Lens,Op ,Nucleus	Right Superior	1	.	1	.
		4511	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4512	Lens Op, Cortex, Ant, Focal	Left Nasal	.	.	1	.

Severity Codes: X = Present; 1 = 1 Very slight; 2 = 2 Slight; 3 = 3 Moderate

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 14

NON-GLP FINAL REPORT

Study Phase: Biomarker (Cytokines) Interpretative Report

Test Facility Study No. 5002231

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

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Appendix 14

1. INTRODUCTION

This report describes the biomarker evaluation of Cytokines/Chemokines (IL-1b, IL-6, TNF-α, IP-10, MIP-1α, and MCP-1) in rat plasma (EDTA) samples from Study No. 5002231 entitled "A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With a 2-Week Recovery Period".

For the work detailed in this report, the Cytokines/Chemokines phase experimental start and end dates were 22 Jun 2017 and 12 Jul 2017, respectively.

2. EXPERIMENTAL PROCEDURES

2.1. Materials and Methods

The methodology and materials used for the biomarker analyses were detailed in the analytical procedure and listed in the table below:

Biomarkers	Analytical Procedure No.	Validation study number(s)
IL-1b, IL-6, TNF-α, IP-10, MIP-1α, and MCP-1α	AP.5002231.CYT.01	Qualified method only

2.2. 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
Bio Plex Manager (Bio-Rad)	Version 6.1	Data collection
Watson LIMS	7.4.2 SP1	Data analysis
Microsoft Excel	2007	Descriptive statistics
Microsoft Word	2007	Reporting of data in the report
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

3. RESULTS AND DISCUSSIONS

The upper limit of the normal range of concentrations was defined as the overall baseline mean (all time points of all Group 1 animals, males and females calculated separately) plus 2 standard deviations. Incidence indicates the number of individual animals per group with Cytokine/Chemokine concentration > upper limit of the normal range of concentrations.
Fold change indicates the ratio of the measured Cytokine/Chemokine concentrations over the upper limit (or below the upper limit) of the normal range of concentration.

Appendix 14

Individual animal data were compared to the upper limit of the normal range for any observed trends (time or dose related changes). For individual animals, if a Cytokine/Chemokine value was above this value, this increase was considered to indicate a potential mRNA-1706 treatment-related effect.

3.1. Cytokines and Chemokines Study Samples

For Cytokines/Chemokines analysis, plasma samples collected from all recovery animals (Groups 1 and 4) on Days 1, 15 and 29, 6 hours after dosing, and at scheduled termination on Day 43 were analyzed.

For all Cytokines/Chemokines, study samples were analyzed diluted 2-fold in assay buffer in duplicate using a qualified method. As the method was only qualified, no stabilities were proven. Study samples will be discarded prior to report finalization.

3.2. Standards and Quality Control Samples for Cytokines/Chemokines

Standard, Quality control (QC) preparation and acceptance criteria are described in the analytical procedure (Appendix 2). Standard curve and quality control specifications are presented in Text Table 2.

Text Table 2
Cytokines/Chemokines Standard Curve and Quality Controls Specifications

Cytokines	Range of the Curve (pg/mL)	LLOQ (pg/mL)	ULOQ (pg/mL)	QC1 (pg/mL)	QC2 (pg/mL)	QC3 (pg/mL)
IL-1ß, IP-10 and MIP-1α	2.93 to 3000.00*	11.72	1500.00	26.02	150.00	1200.00
TNF-α	2.93 to 3000.00**	2.93	375.00	7.81	37.50	300.00
IL-6	87.89 to 90000.00***	351.56	45000.00	780.47	4500.00	36000.00
MCP-1	35.16 to 36000.00****	140.63	18000.00	312.19	1800.00	14400.00

* Standards 2.93, 5.86 and 3000.00 pg/mL are accessory standards used to define the lower and higher portions of the curve.
** Standards 750.00, 1500.00 and 3000.00 pg/mL are accessory standards used to define the higher portion of the curve.
*** Standards 87.89, 175.78, and 90000.00 pg/mL are accessory standards used to define the lower and higher portions of the curve.
**** Standards 35.16, 70.31, and 36000.00 pg/mL are accessory standards used to define the lower and higher portions of the curve.

A total of 4 assays were performed for Cytokines/Chemokines, except for IL-1ß, for which a total of 5 assays were performed, and all met the method acceptance criteria. All results are reported from the assays that met the acceptance criteria.

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3.2.1. Cytokines/Chemokines Results

Acceptance criteria are described in the latest version of the Analytical Procedure (Appendix 2). Results are presented in Appendix 3 and Table 1.

The upper limit of normal range specifications are presented in Text Table 3.

Text Table 3
Cytokines/Chemokines Upper Limit of Normal Range Specifications (pg/mL)

	IL-1b	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Males	66.88	351.56	117.95	462.94	11.72	2.93
Females	190.22	351.56	116.23	267.05	11.72	2.93

For IP-10, increases were observed for all animals dosed at 100 µg/dose on Days 1, 15 and 29 (6 hrs post dose), with increases ranging from 2.6-fold to 10.1-fold for males and from 6.4-fold to 18.7-fold for females. At recovery Day 43, the level of IP-10 were back to the normal range values for almost all animals, only one male and one female still had small increases of 2.0-fold and 1.2-fold respectively. These increases were considered mRNA-1706 related due to the high magnitude and incidence observed for the mRNA-1706 dosed group, as well as the reversibility of mRNA-1706 treatment (Day 43).

For MIP-1α and MCP-1, increases above the upper limit of normal range were observed on Days 1, 15 and 26 (6 hrs post dose). These increases were apparent for some males, at a lower magnitude, but were apparent for most of the females dosed at 100 µg/dose. At recovery Day 43, the level of both MIP-1α and MCP-1 were back to the normal range values for all animals. These increases were considered to be mRNA-1706 related due to similar incidence, magnitude and pattern observed in the mRNA-1706 dosed group for both MIP-1α and MCP-1.

For IL-1b, slight increases above the upper limit of normal range were noted for one male and one female dosed at 100 µg/dose, on Day 29 at 6 hrs post dose (1.2-fold and 1.6-fold respectively). These increases we still present at recovery Day 43, at a higher magnitude for the male (8.5-fold). Those changes were not considered to be mRNA-1706 related due to low incidence as well as similar slight increases also observed in control group animals.

For TNF-α and IL-6, all concentrations were below the limit of quantitation, except one female dosed at 100 µg/dose on Day 15 (6 hrs post dose), for which an increase of 2.1-fold for TNF-α and 2.4-fold for IL-6 was observed. Due to the low incidence and magnitude observed, the increase was not considered to be mRNA-1706 treatment-related.

Appendix 14

4. CONCLUSION

All samples collected for the Cytokines/Chemokines were analyzed using a qualified immunoassay method. As the method was only qualified, no stabilities were proven. Based on the acceptable performance of the standards and QCs during sample analysis, it is concluded that the values reported for the study samples are valid. The sample results are presented in Appendix 3 and Table 1.

For IP-10, high incidence and magnitude of change observed for males and females of higher dose group (100 µg/dose) were considered to be mRNA-1706 treatment-related.

Increases observed for MIP-1α and MCP-1 were also considered mRNA-1706 related due to the magnitude and incidence observed in the mRNA-1706 dosed groups.

No mRNA-1706 treatment-related results were observed for IL-1β, TNF-α and IL-6.

All the treatment-related increases observed tend to be reversible.

Appendix 14

5. REPORT APPROVAL

(b) (6) _____ Date: 30-Nov-2017

Appendix 14

Table 1
Summary of Cytokine Values

Appendix 14
Table 1
Summary of Cytokine Values

IL-1β (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	11.720	11.720	11.720	33.906
	SD	0.000	0.000	0.000	49.609
	N	5	5	5	5
4	Mean	15.364	14.994	26.048	122.832
	SD	8.148	7.321	32.038	248.454
	N	5	5	5	5
	% Diff (G1)	31	28	122	262

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)

Appendix 14
Table 1
Summary of Cytokine Values

IL-6 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	351.560	351.560	351.560	351.560
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	351.560	351.560	351.560	351.560
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
	% Diff (G1)	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)

Appendix 14
Table 1
Summary of Cytokine Values

TNF-α (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	2.930	2.930	2.930	2.930
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	2.930	2.930	2.930	2.930
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
	% Diff (G1)	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)

Appendix 14
Table 1
Summary of Cytokine Values

IP-10 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	58.762	62.900	75.906	63.468
	SD	12.127	17.218	35.820	36.954
	N	5	5	5	5
4	Mean	852.920 D	591.852 D	811.432 C	96.796
	SD	187.332	250.658	293.188	80.237
	N	5	5	5	5
	% Diff (G1)	1351	841	969	53

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

Appendix 14
Table 1
Summary of Cytokine Values

MIP-1-α (pg/mL)
Males

Group 1 - Reference Item Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	11.720	11.720	11.720	11.720
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	20.682	14.536	14.684	11.720
	SD	8.370	6.297	6.628	0.000
	N	5	5	5	5
	% Diff (G1)	76	24	25	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)

Appendix 14
Table 1
Summary of Cytokine Values

MCP-1 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	292.366	203.094	321.152	140.630
	SD	92.530	85.989	133.153	0.000
	N	5	5	5	5
4	Mean	500.112 A	411.536 B	473.198	140.630
	SD	161.181	89.399	126.766	0.000
	N	5	5	5	5
	% Diff (G1)	71	103	47	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)

Appendix 14
Table 1
Summary of Cytokine Values

IL-1β (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	47.678	44.500	56.302	42.144
	SD	80.405	73.298	86.745	68.030
	N	5	5	5	5
4	Mean	29.710	11.720	71.994	78.038
	SD	35.980	0.000	134.777	129.660
	N	4	4	5	5
	% Diff (G1)	-38	-74	28	85

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)

Appendix 14
Table 1
Summary of Cytokine Values

IL-6 (pg/mL)
Females

Group 1 - Reference Item Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	351.560	351.560	351.560	351.560
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	451.910	351.560	351.560	351.560
	SD	224.389	0.000	0.000	0.000
	N	5	4	5	5
	% Diff (G1)	29	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)

Appendix 14
Table 1
Summary of Cytokine Values

TNF-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	2.930	2.930	2.930	2.930
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	3.578	2.930	2.930	2.930
	SD	1.449	0.000	0.000	0.000
	N	5	4	5	5
	% Diff (G1)	22	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)

Appendix 14
Table 1
Summary of Cytokine Values

IP-10 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	70.984	62.736	68.774	62.326
	SD	23.122	20.764	30.829	31.393
	N	5	5	5	5
4	Mean	1401.728 D	862.310 D	1283.416 D	83.114
	SD	353.901	88.904	601.658	42.654
	N	5	4	5	5
	% Diff (G1)	1875	1275	1766	33

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)

Appendix 14
Table 1
Summary of Cytokine Values

MIP-1-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	11.720	11.720	11.720	11.720
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	67.320 E	21.990	37.930 D	11.720
	SD	35.291	13.457	32.122	0.000
	N	5	4	5	5
	% Diff (G1)	474	88	224	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)

Appendix 14
Table 1
Summary of Cytokine Values

MCP-1 (pg/mL)
Females

Group 1 - Reference Item Group 4 - mRNA-1706 100 µg/dose

Group	Summary Information	Day 1 - 6 h PD	15 - 6 h PD	29 - 6 h PD	43
1	Mean	178.856	172.824	140.630	140.630
	SD	85.476	71.988	0.000	0.000
	N	5	5	5	5
4	Mean	671.020 B	500.678 B	666.018 E	140.630
	SD	248.446	138.871	372.086	0.000
	N	5	4	5	5
	% Diff (G1)	275	190	374	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)

Appendix 14

Appendix 1
Deviations

Appendix 14

DEVIATIONS

No deviation occurred during this study phase.

Appendix 14

Appendix 2
AP.5002231.CYT.01

Appendix 14

charles river | every step of the way.

Title: **LUMINEX METHOD FOR THE QUANTITATIVE DETECTION OF IL-1β, IL-6, IP-10, TNF-α, MCP-1, MIP-1α, IN RAT PLASMA USING THE MAGNETIC BEADS**	AP Number: AP.5002231.CYT.01	Effective Date: Signature of AP
	CR MTL	Supersedes: N/Ap
Prepared by: (b) (6) (b) (6)		Date: 19-Jun-2017
Verified by: (b) (6) (b) (6)		Date: 19 Jun 2017
Management Approval: (b) (6) (b) (6)		Date: 19 Jun 2017

1.0 Purpose

To describe a method to determine the concentration of IL-1β, IL-6, IP-10, TNF-α, MCP-1, MIP-1a in rat plasma by Luminex.

2.0 Scope

This procedure applies to Luminex assays undertaken in the Biomarkers department.

3.0 Responsibilities

All staff performing this assay are responsible for compliance with this analytical procedure.

4.0 Required forms

Appendix 1	Cytokine Multiplex Spiking Sheet (Example of spreadsheet)
Appendix 2	Cytokine Multiplex Assay Sheet (Example of document)
Appendix 3	Daily Solution preparation Sheet (Example of spreadsheet) **Note: Appendix # 2 of CACI-001 can be used as well.**
Appendix 4	Solution preparation Sheet (Example of spreadsheet) **Note: Appendix # 1 of CACI-001 can be used as well.**
Appendix 5	Assay Instructions Sheet (Example of spreadsheet)

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Appendix 14

AP Number: AP. 5002231.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

5.0 Materials/Equipment/Reagents

Materials can be substituted provided the same specifications are met.

The procedure may require other general laboratory supplies commonly used in Laboratory Sciences.

5.1 Materials/Equipment

(b) (4)

5.2 Kit Components

(b) (4)

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Appendix 14

AP Number: AP. 5002231.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

Rat cytokine/chemokine magnetic bead panel Kit
(Millipore cat# RECYTMAG-65k-XX, where XX denotes the number of cytokines included in the panel.

(b) (4)

5.3 Other reagents

(b) (4)

6.0 Preparation of Assay Reagents

(b) (4)

6.1

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Appendix 14

AP Number: AP. 5002231.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

6.2 Preparation of the Rat Cytokine Standards and Quality Control (QC) Samples in Assay Buffer

(b) (4)

7.0 **Assay procedure**

(b) (4)

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Appendix 14

AP Number: AP. 5002231.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

8.0 Plate Washing using Handheld magnetic washer

(b) (4)

9.0 Preparation of the Bio-Plex Suspension Array (Luminex) Protocol

(b) (4)

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Appendix 14

AP Number: AP. 5002231.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

Refer to Appendix 5 and appropriate Study plan for the list of cytokines to be analyzed.

(b) (4)

10.0 Exporting data to Watson LIMS

(b) (4)

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Appendix 14

AP Number: AP. 5002231.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

10.1 Export data to Watson LIMS as follows:

(b) (4)

11.0 Preparation of the Bio-Plex Manager printout

(b) (4)

11.0.3 Calculation

(b) (4)

12.0 Assay Acceptance Criteria

12.1 Standard Curve Acceptance Criteria

(b) (4)

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Appendix 14

AP Number: AP. 5002231.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

12.2 Acceptance Criteria for QC samples prepared in Assay Buffer

(b) (4)

12.3 Run Acceptance Criteria

(b) (4)

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Appendix 14

AP Number: AP. 5002231.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

12.4 Acceptance criteria for Study samples

(b) (4)

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AP Number: AP. 5002231.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

12.5 Reporting:

(b) (4)

13.0 **Revision History**

Version	Date	Reason For Revision
1	Signature of AP	New AP

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Appendix 14

Cytokine Multiplex Spiking Sheet

Study/reference number: 5002231 Assay ID _____
Reference material: Rat Cytokine/Chemokine Standard

Reagent ID:	Lot #	Inventory ID:
Rat cytokine/chemokine standard:		
Assay buffer	refer to appendix # 2	

Standard ID	Stock ID	# of vial(s) used	Volume of UPW added to each vial (µL) Vial inverted several times to mix, and vortex for 10 seconds	Left at ambient RT for at least 5 minutes		Transfer to PP* tube	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	Stock performed (√)	Assay buffer volume	Assay buffer 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)	( )	(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					( )		( )				
QC3B	**STD 10**					( )		( )				
QC3A	STD 8					( )		( )				
QC2B	**STD 10**					( )		( )				
QC2A	STD 8					( )		( )				
QC1B	**STD 5**					( )		( )				
QC1A	**STD 5**					( )		( )				

Comments: * PP = Polypropylene

Spiking sheet verified by/ date: _____ Calculations verified by/ date: _____

Spiking performed by/ date: _____ Reviewed by/ date: _____

Appendix 1 (AP.5002231.CYT.01) 1 of 1

Appendix 14

Cytokine Multiplex Assay sheet

Study/Reference No: 5002231 Assay I.D.: _____

Page: 1 of 6

Reagents/ Working Solutions					
Name	*Batch or Lot # (as appropriate)*	*Inventory number* Assay ID:	Assay ID: or ☐ N/Ap	*Expiry Date*	*Entered by /Date*
Rat Cytokine/Chemokine magnetic kit					
Assay Buffer					
Assay Plate					
Bead diluent					
Antibody-Immobilized Beads Working solution	ABWS-	N/Ap	N/Ap		
Streptavidin-Phycoerythrin					
Detection Antibodies		N/Ap	N/Ap		
Wash Buffer Cytokines	rtpCytWB-				
Sheath fluid					
UPW	N/Ap	N/Ap	N/Ap		

PLATE SEQUENCE (Printed from Watson)

In-Process Sample Storage Assay ID: or N/Ap ☐	Performed (√)		Start time	Performed by / Date
Samples transported from Sample Management	Dry Ice	( )	N/Ap	
Samples thawed and diluted	Ambient RT	( )		
Samples placed in temporary storage after use and until returned to Sample Management	Dry Ice	( )		
In-Process Sample Storage **Assay ID:** or N/Ap ☐	**Performed (√)**		**Start time**	**Performed by / Date**
Samples transported from Sample Management	Dry Ice	( )	N/Ap	
Samples thawed and diluted	Ambient RT	( )		
Samples placed in temporary storage after use and until returned to Sample Management	Dry Ice	( )		

Appendix 2 (AP.5002231.CYT.01)

Appendix 14

Cytokine Multiplex Assay sheet

Study/Reference No: 5002231 Assay I.D.: _____

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INSTRUMENTS		
Name	***ID***	***Entered by/ Date***
Day 1		
(b) (4)		
Day 2		
(b) (4)		
	or ( ) N/Ap	

Comments: _____

_____

_____

_____

Appendix 2 (AP.5002231.CYT.01)

Appendix 14

Cytokine Multiplex Assay sheet

Study/Reference No: 5002231 Assay I.D.: _____

Page: 3 of 6

Steps	Incubation times /Performed (√) Assay ID:	Assay ID: or N/Ap ☐	Performed by/ Date
DAY 1			
(b) (4)	( ) ( ) or N/Ap ( )	( ) ( ) or N/Ap ( )	
	( )	( )	
	( )	( )	
	( )	( )	
	( )	( )	
	Start:	Start:	
DAY 2			
(b) (4)	Finish:	Finish:	
	( ) ( ) ( )	( ) ( ) ( )	
	Start:	Start:	
	Finish:	Finish:	
	Start:	Start:	
	Finish:	Finish:	
	( ) ( ) ( )	( ) ( ) ( )	
	Start:	Start:	
	Finish:	Finish:	

Appendix 2 (AP.5002231.CYT.01)

Appendix 14

Cytokine Multiplex Assay sheet

Study/Reference No: 5002231 Assay I.D.: _____

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ASSAY CONT'D					
Steps	Incubation times /Performed (√)				Performed by/ Date
	Assay ID:		Assay ID: or N/Ap ☐		
(b) (4)	Start:		Start:		
	Finish:		Finish:		
	N/Ap ( )		N/Ap ( )		
	Start:		Start:		
	Finish:		Finish:		
	N/Ap ( )		N/Ap ( )		
	Prime ( ) Unclog ( ) or N/Ap( )		Prime ( ) Unclog ( ) or N/Ap ( )		
	Yes ( )	N/Ap ( )	Yes ( )	N/Ap ( )	
	( )		( )		
	( )	N/Ap ( )	( )	N/Ap ( )	
	( )	N/Ap ( )	( )	N/Ap ( )	

Appendix 2 (AP.5002231.CYT.01)

Appendix 14

Cytokine Multiplex Assay sheet

Study/Reference No: 5002231 Assay I.D.:

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SCIENTIFIC DATA REVIEW						
Assay ID:						
	IL-1β or ☐ N/Ap	**IL-6** or ☐ N/Ap	**IP-10** or ☐ N/Ap	**MCP-1** or ☐ N/Ap	**MIP-1a** or ☐ N/Ap	**TNF-a** or ☐ N/Ap
Mean of (FI) Blank < Mean of (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of working standards within ±25% of the theoretical values (±30% for LLOQ and ULOQ):	/	/	/	/	/	/
QC samples						
Number of QC1A within acceptance criteria*:	/	/	/	/	/	/
Number of QC1B within acceptance criteria*:	/	/	/	/	/	/
Number of QC2A within acceptance criteria*:	/	/	/	/	/	/
Number of QC2B within acceptance criteria*:	/	/	/	/	/	/
Number of QC3A within acceptance criteria*:	/	/	/	/	/	/
Number of QC3B within acceptance criteria*:	/	/	/	/	/	/
Number of beads acquired ≥ 30 in all wells:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Samples to repeat:	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap
Performed by / Date:						

*Concentration within 75-125% of theoretical, %CV ≤ 25% between duplicates.

Appendix 2 (AP.5002231.CYT.01)

Appendix 14

Cytokine Multiplex Assay sheet

Study/Reference No: 5002231 Assay I.D.: _____

Page: 6 of 6

SCIENTIFIC DATA REVIEW						
Assay ID: *or N/Ap* ☐						
	IL-1β or ☐ N/Ap	**IL-6** or ☐ N/Ap	**IP-10** or ☐ N/Ap	**MCP-1** or ☐ N/Ap	**MIP-1a** or ☐ N/Ap	**TNF-a** or ☐ N/Ap
Mean of (FI) Blank < Mean of (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of working standards within ±25% of the theoretical values (±30% for LLOQ and ULOQ):	/	/	/	/	/	/
QC samples						
Number of QC1A within acceptance criteria*:	/	/	/	/	/	/
Number of QC1B within acceptance criteria*:	/	/	/	/	/	/
Number of QC2A within acceptance criteria*:	/	/	/	/	/	/
Number of QC2B within acceptance criteria*:	/	/	/	/	/	/
Number of QC3A within acceptance criteria*:	/	/	/	/	/	/
Number of QC3B within acceptance criteria*:	/	/	/	/	/	/
Number of beads acquired ≥ 30 in all wells:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Samples to repeat:	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap
Performed by / Date:						

*Concentration within 75-125% of theoretical, %CV ≤ 25% between duplicates.

Appendix #2 Reviewed by/date: _____

Appendix 2 (AP.5002231.CYT.01)

Appendix 14

Daily Solution Preparation Sheet

Study/Reference no: 5002231 Assay ID: _____

Preparation of: **Antibody-immobilized Beads Working Solution (code: ABWS)**

Note: if not all cytokines are needed to be analyzed, Bead Diluent should be used to replace the missing antibody-bead volume. The total volume of the solution needs to be 3.000 mL. (Dilution 1/50)

Batch #	Reagents	Supplier	Lot/Batch no	Inventory Number	*Calculated Volume units (µL)	Actual Volume units (µL)	Performed by & Date	*Calculations verified by/date:
	Bead Diluent	Millipore						
	Anti-IL-1β beads	Millipore						
	Anti-IL-6 beads	Millipore						
	Anti-IP-10 beads	Millipore						
	Anti-MCP-1 beads	Millipore						
	Anti-MIP-1α beads	Millipore						
	Anti-TNF-α beads	Millipore						
					Total volume:			

* Applicable only when the volumes are scaled up or down.

Reviewed by/date: _____

Appendix 3 (AP.5002231.CYT.01)

Appendix 14

Solution Preparation Sheet

Study/Reference no: 5002231

Preparation **Wash Buffer Cytokines (Code: rtpCytWB)**

Storage: Location / Expiration: _____ or discarded after use ☐

Batch no	Reagents	Supplier	Lot no	Expiry date	Inventory Number	*Calculated Volume units	Actual Volume units	Prepared by & Date	*Calculations verified by/date:
rtpCyt WB/	(b) (4)								
			N/Ap		N/Ap				
					Total volume:				

*Applicable only when the volumes are scaled up or down

Comments _____

Reviewed by/Date: _____

Appendix 4 (AP.5002231.CYT.01)

Appendix 14

Assay instruction sheet

Study/reference number: 5002231

Assay ID: _____

ID	lot# to be used *
Rat cytokine/chemokine magnetic bead panel kit	
Rat cytokine standard	

* Lots qualified in assay(s): _____

Cytokines to be analyzed:

IL-1β	√
IL-6	√
IP-10	√
MCP-1	√
MIP-1α	√
TNF-α	√

• Study samples to be diluted as per dilution sheet.

Standard and QC concentrations:

Standards ID	Concentration (pg/mL)					
	IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Standard stock	(b) (4)					
STD 11						
STD 10						
STD 9						
STD 8						
STD 7						
STD 6						
STD 5						
STD 4						
STD 3						
STD 2						
STD 1						
STD 0						
QC ID	**Concentration (pg/mL)**					
	IL-1β	**IL-6**	**IP-10**	**MCP-1**	**MIP-1α**	**TNF-α**
QC3B	(b) (4)					N/A
QC3A	N/Ap	N/Ap	N/Ap	N/Ap	N/Ap	(b) (4)
QC2B	(b) (4)					N/Ap
QC2A	N/Ap	N/Ap	N/Ap	N/Ap	N/Ap	(b) (4)
QC1B	(b) (4)					N/Ap
QC1A	N/Ap	N/Ap	N/Ap	N/Ap	N/Ap	(b) (4)

Bold concentrations reflect the appropriate levels for each cytokine (LLOQ, ULOQ and QCs)

Threshold value

The threshold value for a replicate to reach a limit of % CV acceptance criteria from LLOQ (pg/mL)*	Concentration (pg/mL)					
	IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Threshold value:	(b) (4)					

*Fold dilution not taken into account.

Verified by/date: _____ Reviewed by/date: _____

Appendix 5 (AP.5002231.CYT.01) 1 of 1

Appendix 14

Appendix 3
Individual Cytokines Values

Appendix 14

Individual Cytokine Values Explanation Page

Abbreviation	Description	Abbreviation	Description
--	No findings / Dead	QNS	Quantity not sufficient
CLOT	Sample clotted	SNR	Sample not received
NA	Not applicable	TNR	Test not reported
NC	Not calculable	X	Excluded from mean
NR	Not reported	SNC	Sample not collected
PD	Post Dose		
a	% CV between singlicate values > acceptance criteria. Mean of original and repeat values reported for information purposes only		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note:

For IL-1β, MIP-1-α

Lower Limit of Quantitation (LLOQ) = 11.72 pg/mL (23.44 pg/mL when taking the dilution factor into account), <23.44 was assigned as 23.44/2 (11.72 pg/mL) for statistical analysis purposes

For IL-6

Lower Limit of Quantitation (LLOQ) = 351.56 pg/mL (703.12 pg/mL when taking the dilution factor into account), <703.12 was assigned as 703.12/2 (351.56 pg/mL) for statistical analysis purposes

For MCP-1

Lower Limit of Quantitation (LLOQ) = 140.63 pg/mL (281.26 pg/mL when taking the dilution factor into account), <281.26 was assigned as 281.26/2 (140.63 pg/mL) for statistical analysis purposes

For TNF-α

Lower Limit of Quantitation (LLOQ) = 2.93 pg/mL (5.86 pg/mL when taking the dilution factor into account), <5.86 was assigned as 5.86/2 (2.93 pg/mL) for statistical analysis purposes

Appendix 14

The upper limit of the normal range of concentration was defined as:
The overall baseline mean (predose/pretreatment values for all animals* in all groups) ** + 2 standard deviations

Incidence of Cytokine elevations was reported as:
The number of individual animals* per group with Cytokine concentrations > upper limit of the normal range of concentrations

Fold Change was reported as:
The ratio of the measured Cytokine concentration / upper limit of the normal range of concentrations

The fold change was calculated for each sample

*Calculations were done separately for females and males

** If predose values were not available, values from all animals of the non-treated group(s) were used to generate the overall baseline mean

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

Appendix 14
Appendix 1
Individual Cytokine Values

Males

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1011	1 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	122.65	1	1.8	<703.12	0	1.0	<5.86	0	1.0
	1012	1 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
	1013	1 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
	1014	1 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0

Appendix 14
Appendix 1
Individual Cytokine Values

Males

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1015	1 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0

Appendix 14
Appendix 1
Individual Cytokine Values

Males

Group 1 - Reference Item

Group	Animal Number	Day	IP-10 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	MCP-1 pg/mL	Incidence	Fold Change
1	1011	1 - 6 h PD	53.13	0	0.5	<23.44	0	1.0	311.30	0	0.7
		15 - 6 h PD	74.30	0	0.6	<23.44	0	1.0	<281.26	0	0.3
		29 - 6 h PD	68.37	0	0.6	<23.44	0	1.0	<281.26	0	0.3
		43	125.31	1	1.1	<23.44	0	1.0	<281.26	0	0.3
	1012	1 - 6 h PD	54.88	0	0.5	<23.44	0	1.0	<281.26	0	0.3
		15 - 6 h PD	42.16	0	0.4	<23.44	0	1.0	<281.26	0	0.3
		29 - 6 h PD	45.86	0	0.4	<23.44	0	1.0	284.47	0	0.6
		43	33.53	0	0.3	<23.44	0	1.0	<281.26	0	0.3
	1013	1 - 6 h PD	68.85	0	0.6	<23.44	0	1.0	393.97	0	0.9
		15 - 6 h PD	76.17	0	0.6	<23.44	0	1.0	309.31	0	0.7
		29 - 6 h PD	76.19	0	0.6	<23.44	0	1.0	340.75	0	0.7
		43	69.19	0	0.6	<23.44	0	1.0	<281.26	0	0.3
	1014	1 - 6 h PD	73.30	0	0.6	<23.44	0	1.0	313.21	0	0.7
		15 - 6 h PD	75.80	0	0.6	<23.44	0	1.0	<281.26	0	0.3
		29 - 6 h PD	52.86	0	0.4	<23.44	0	1.0	327.55	0	0.7
		43	45.41	0	0.4	<23.44	0	1.0	<281.26	0	0.3

Appendix 14
Appendix 1
Individual Cytokine Values

Males

Group 1 - Reference Item

Group	Animal Number	Day	IP-10 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	MCP-1 pg/mL	Incidence	Fold Change
1	1015	1 - 6 h PD	43.65	0	0.4	<23.44	0	1.0	302.72	0	0.7
		15 - 6 h PD	46.07	0	0.4	<23.44	0	1.0	284.27	0	0.6
		29 - 6 h PD	136.25	1	1.2	<23.44	0	1.0	512.36	1	1.1
		43	43.90	0	0.4	<23.44	0	1.0	<281.26	0	0.3

Appendix 14
Appendix 1
Individual Cytokine Values

Males

Group 4 - mRNA-1706 100 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4011	1 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
	4012	1 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
	4013	1 - 6 h PD	29.94	0	0.4	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	28.09	0	0.4	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	83.36	1	1.2	<703.12	0	1.0	<5.86	0	1.0
		43	567.28	1	8.5	<703.12	0	1.0	<5.86	0	1.0
	4014	1 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0

Appendix 14
Appendix 1
Individual Cytokine Values

Males

Group 4 - mRNA-1706 100 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4015	1 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.2	<703.12	0	1.0	<5.86	0	1.0

Appendix 14
Appendix 1
Individual Cytokine Values

Males

Group 4 - mRNA-1706 100 µg/dose

Group	Animal Number	Day	IP-10 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	MCP-1 pg/mL	Incidence	Fold Change
4	4011	1 - 6 h PD	723.47	1	6.1	<23.44	0	1.0	748.95	1	1.6
		15 - 6 h PD	328.50	1	2.8	<23.44	0	1.0	527.58	1	1.1
		29 - 6 h PD	376.50	1	3.2	26.54	1	2.3	663.23	1	1.4
		43	60.29	0	0.5	<23.44	0	1.0	<281.26	0	0.3
	4012	1 - 6 h PD	648.03	1	5.5	<23.44	0	1.0	378.58	0	0.8
		15 - 6 h PD	309.60	1	2.6	<23.44	0	1.0	327.55	0	0.7
		29 - 6 h PD	750.71	1	6.4	<23.44	0	1.0	348.21	0	0.8
		43	53.79	0	0.5	<23.44	0	1.0	<281.26	0	0.3
	4013	1 - 6 h PD	887.69	1	7.5	26.96	1	2.3	563.48	1	1.2
		15 - 6 h PD	812.00	1	6.9	<23.44	0	1.0	376.90	0	0.8
		29 - 6 h PD	1190.18	1	10.1	<23.44	0	1.0	465.45	1	1.0
		43	239.17	1	2.0	<23.44	0	1.0	<281.26	0	0.3
	4014	1 - 6 h PD	869.37	1	7.4	28.99	1	2.5	454.94	0	1.0
		15 - 6 h PD	775.46	1	6.6	25.80	1	2.2	484.40	1	1.0
		29 - 6 h PD	888.61	1	7.5	<23.44	0	1.0	518.18	1	1.1
		43	78.08	0	0.7	<23.44	0	1.0	<281.26	0	0.3

Appendix 14
Appendix 1
Individual Cytokine Values

Males

Group 4 - mRNA-1706 100 µg/dose

Group	Animal Number	Day	IP-10 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	MCP-1 pg/mL	Incidence	Fold Change
4	4015	1 - 6 h PD	1136.04	1	9.6	24.02	1	2.0	354.61	0	0.8
		15 - 6 h PD	733.70	1	6.2	<23.44	0	1.0	341.25	0	0.7
		29 - 6 h PD	851.16	1	7.2	<23.44	0	1.0	370.92	0	0.8
		43	52.65	0	0.4	<23.44	0	1.0	<281.26	0	0.3

Appendix 14
Appendix 1
Individual Cytokine Values

Females

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1511	1 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	36.02	0	0.2	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
	1512	1 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
	1513	1 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
	1514	1 - 6 h PD	191.51	1	1.0	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	175.62	0	0.9	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	210.33	1	1.1	<703.12	0	1.0	<5.86	0	1.0
		43	163.84	0	0.9	<703.12	0	1.0	<5.86	0	1.0

Appendix 14
Appendix 1
Individual Cytokine Values

Females

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1515	1 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0

Appendix 14
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Individual Cytokine Values

Females

Group 1 - Reference Item

Group	Animal Number	Day	IP-10 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	MCP-1 pg/mL	Incidence	Fold Change
1	1511	1 - 6 h PD	50.51	0	0.4	<23.44	0	1.0	<281.26	0	0.5
		15 - 6 h PD	40.51	0	0.3	<23.44	0	1.0	<281.26	0	0.5
		29 - 6 h PD	53.33	0	0.5	<23.44	0	1.0	<281.26	0	0.5
		43	44.45	0	0.4	<23.44	0	1.0	<281.26	0	0.5
	1512	1 - 6 h PD	74.46	0	0.6	<23.44	0	1.0	<281.26	0	0.5
		15 - 6 h PD	42.98	0	0.4	<23.44	0	1.0	<281.26	0	0.5
		29 - 6 h PD	50.45	0	0.4	<23.44	0	1.0	<281.26	0	0.5
		43	42.72	0	0.4	<23.44	0	1.0	<281.26	0	0.5
	1513	1 - 6 h PD	44.43	0	0.4	<23.44	0	1.0	331.76	1	1.2
		15 - 6 h PD	74.64	0	0.6	<23.44	0	1.0	301.60	1	1.1
		29 - 6 h PD	43.29	0	0.4	<23.44	0	1.0	<281.26	0	0.5
		43	37.01	0	0.3	<23.44	0	1.0	<281.26	0	0.5
	1514	1 - 6 h PD	97.94	0	0.8	<23.44	0	1.0	<281.26	0	0.5
		15 - 6 h PD	88.87	0	0.8	<23.44	0	1.0	<281.26	0	0.5
		29 - 6 h PD	118.68	1	1.0	<23.44	0	1.0	<281.26	0	0.5
		43	111.41	0	1.0	<23.44	0	1.0	<281.26	0	0.5

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Appendix 1
Individual Cytokine Values

Females

Group 1 - Reference Item

Group	Animal Number	Day	IP-10 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	MCP-1 pg/mL	Incidence	Fold Change
1	1515	1 - 6 h PD	87.58	0	0.8	<23.44	0	1.0	<281.26	0	0.5
		15 - 6 h PD	66.68	0	0.6	<23.44	0	1.0	<281.26	0	0.5
		29 - 6 h PD	78.12	0	0.7	<23.44	0	1.0	<281.26	0	0.5
		43	76.04	0	0.7	<23.44	0	1.0	<281.26	0	0.5

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Individual Cytokine Values

Females

Group 4 - mRNA-1706 100 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4511	1 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
	4512	1 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
	4513	1 - 6 h PD	78.64 a	NC	NC	853.31	1	2.4	6.17	1	2.1
		15 - 6 h PD	SNR	NC	NC	SNR	NC	NC	SNR	NC	NC
		29 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		43	46.63	0	0.2	<703.12	0	1.0	<5.86	0	1.0
	4514	1 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		43	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0

Appendix 14
Appendix 1
Individual Cytokine Values

Females

Group 4 - mRNA-1706 100 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4515	1 - 6 h PD	83.68	0	0.4	<703.12	0	1.0	<5.86	0	1.0
		15 - 6 h PD	<23.44	0	0.1	<703.12	0	1.0	<5.86	0	1.0
		29 - 6 h PD	313.09	1	1.6	<703.12	0	1.0	<5.86	0	1.0
		43	308.40	1	1.6	<703.12	0	1.0	<5.86	0	1.0

Appendix 14
Appendix 1
Individual Cytokine Values

Females

Group 4 - mRNA-1706 100 µg/dose

Group	Animal Number	Day	IP-10 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	MCP-1 pg/mL	Incidence	Fold Change
4	4511	1 - 6 h PD	967.60	1	8.3	29.91	1	2.6	596.69	1	2.2
		15 - 6 h PD	941.74	1	8.1	24.47	1	2.1	684.96	1	2.6
		29 - 6 h PD	837.22	1	7.2	<23.44	0	1.0	704.32	1	2.6
		43	43.50	0	0.4	<23.44	0	1.0	<281.26	0	0.5
	4512	1 - 6 h PD	1230.67	1	10.6	85.96	1	7.3	527.82	1	2.0
		15 - 6 h PD	841.89	1	7.2	40.05	1	3.4	507.27	1	1.9
		29 - 6 h PD	819.94	1	7.1	24.61	1	2.1	354.30	1	1.3
		43	104.65	0	0.9	<23.44	0	1.0	<281.26	0	0.5
	4513	1 - 6 h PD	1874.92	1	16.1	108.67	1	9.3	1069.73	1	4.0
		15 - 6 h PD	SNR	NC	NC	SNR	NC	NC	SNR	NC	NC
		29 - 6 h PD	947.98	1	8.2	27.77	1	2.4	519.59	1	1.9
		43	81.47	0	0.7	<23.44	0	1.0	<281.26	0	0.5
	4514	1 - 6 h PD	1626.84	1	14.0	81.23	1	6.9	731.24	1	2.7
		15 - 6 h PD	920.11	1	7.9	<23.44	0	1.0	352.16	1	1.3
		29 - 6 h PD	1635.41	1	14.1	93.80	1	8.0	1291.62	1	4.8
		43	42.74	0	0.4	<23.44	0	1.0	<281.26	0	0.5

Appendix 14
Appendix 1
Individual Cytokine Values

Females

Group 4 - mRNA-1706 100 µg/dose

Group	Animal Number	Day	IP-10 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	MCP-1 pg/mL	Incidence	Fold Change
4	4515	1 - 6 h PD	1308.61	1	11.3	30.83	1	2.6	429.62	1	1.6
		15 - 6 h PD	745.50	1	6.4	<23.44	0	1.0	458.32	1	1.7
		29 - 6 h PD	2176.53	1	18.7	31.75	1	2.7	460.26	1	1.7
		43	143.21	1	1.2	<23.44	0	1.0	<281.26	0	0.5

Appendix 15

FINAL REPORT

Study Phase: Molecular Biology – Purity Analysis

Test Facility Study No. 5002231

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

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Appendix 15

TABLE OF CONTENTS

Appendix 15

LIST OF TABLES

LIST OF APPENDICES

Appendix 15

1. SUMMARY

The bulk test item was analyzed using the (b) (4) System for the determination of mRNA-1706 purity.

The bulk test item was collected at the end of the dosing period of Study No. 5002231 entitled "A 1-Month (3 Doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With 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-1706 purity in the bulk test item from Study No. 5002231.

For the work detailed in this report, the analytical experimental phase start date was 13 Jun 2017 and the end date was 19 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:	mRNA-1325*
Physical Description:	Clear, colorless solution, no visible particulates and no turbidity
Batch/Lot No.:	MTDS16004
Concentration:	1.84/2.15** mg/mL
Retest Date:	Apr 2017
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

* mRNA-1325 and mRNA-1706 have the same mRNA construct.
** Concentration based on summary of analysis (SoA) released on 29 Apr 2016 /Concentration based on SoA released on 25 Apr 2017.

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4.1.2. Bulk Test Item

Identification:	mRNA-1706 (in lipid nanoparticles)
Physical Description:	0.5 mL per vial, white to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP17036
Concentration:	2.1 mg/mL
Expiry Date:	The end of use bulk Test Item analysis demonstrated that the Test Item was suitable for use during the study period.
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

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 15

Text Table 1
Computerized Systems

	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 did not occur during this phase of the study. 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 15

7. REPORT APPROVAL

(b) (6)

(b) (6)

Date: 30 Nov 2017

Appendix 15

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 15

Appendix 1

(b) (4)

Appendix 15

charles river

ANALYTICAL PROCEDURE

TITLE: (b) (4)	AP No: AP.5002231.RNA.01	Effective Date: Signature of AP
	Page 1 of 2 pages	Supersedes Date: N/Ap
Prepared by: (b) (6)	(b) (6)	Date: 09 Jun 2017
Reviewed by: (b) (6)	(b) (6)	Date: 09 Jun 2017
Approved by: (b) (6)	(b) (6)	Date: 09 Jun 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 15

AP No: AP.5002231.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 (b) (4)

8.0 **REVISION HISTORY**

Version	Date	Reason for revision
01	Signature of AP	New AP

Appendix 15

(b) (4)

Study/Reference No: 5002231 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.5002231.RNA.01)

Appendix 15

(b) (4)

Study/Reference No: 5002231 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.5002231.RNA.01)

Appendix 15

(b) (4)

Study/Reference No: 5002231 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)		

Comments: _____

_____

All pages reviewed by / Date: _____

Appendix #1 (AP.5002231.RNA.01)

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Appendix 2

(b) (4)

Appendix 15

charles river

ANALYTICAL PROCEDURE

TITLE: (b) (4)	AP No: AP.5002231.RQF.01	Effective Date: Signature of AP
	Page 1 of 4 pages	Supersedes Date: N/Ap
Prepared by: (b) (6)		Date: 09 Jun 2017
Reviewed by: (b) (6)		Date: 09 Jun 2017
Approved by: (b) (6)		Date: 09 Jun 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.5002231.RQF.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 2 of 4 pages

5.2 (b) (4)

5.3 (b) (4)

5.4 Reagents

(b) (4)

6.0 PREPARATION OF REAGENTS

(b) (4)

Appendix 15

AP No: AP.5002231.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 15

AP No: AP.5002231.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 15

(b) (4)

Study/Reference No: 5002231 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.5002231.RQF.01)

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(b) (4)

Study/Reference No: 5002231 Assay I.D.: Pro-xx

Page: 2 of 6

Preparation o (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.5002231.RQF.01)

Appendix 15

(b) (4)

Study/Reference No: 5002231 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.5002231.RQF.01)

Appendix 15

(b) (4)

Study/Reference No: 5002231 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.5002231.RQF.01)

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(b) (4)

Study/Reference No: 5002231 Assay I.D.: Pro-xx

Page: 5 of 6

(b) (4)

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

Clarifications to Prosize, if any: _____

Comments: _____

Appendix #1 (AP.5002231.RQF.01)

Appendix 15

(b) (4)

Study/Reference No: 5002231 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.5002231.RQF.01)

Appendix 15

(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 15

Appendix 3
Certificates of Analysis

Appendix 15

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

eurofins | Advantar

Summary of Analysis ***DATE: 28 April 2017***

Part I Release Testing Results for mRNA-1706 LNP Drug Product Lot MTDP17036

Protocol Number: MRA-C0019-RTP0005.00 **Document Number:** MRA-C0019-RTR0011.00 (CPR15095)	**Date Received at Eurofins Advantar:** March 31, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion (20mM Tris Buffer, 8% Sucrose, pH 7.4)
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17036	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATION (Specifications per protocol)	TEST DATE	RESULTS
RNA Content (mg/mL) (Draft MRA-C0000-GTM0023)	(b) (4)	04/27/2017	(b) (4)
[1]Bacterial Endotoxins (USP <85>)		04/04/2017	
[2]Bioburden (USP <61>)		03/31/2017	

[1] Testing performed at Associates of Cape Cod Incorporated
[2]Testing performed at Nelson Laboratories
[3]Three samples tested and all sample results are (b) (4)

The data generated at Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Advantar has archived the raw data.

(b) (6)

28 APR 2017
Date

Appendix 15

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

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Summary of Analysis *DATE: 6 July 2017*

Part II Release Testing Results for mRNA-1706 LNP Drug Product Lot MTDP17036

Protocol Number: MRA-C0019-RTP0005.00 **Document Number:** MRA-C0019-RTR0012.00 (CPR15101)	**Date Received at Eurofins Advantar:** March 31, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion (20mM Tris Buffer, 8% Sucrose, pH 7.4)
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17036	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Appearance (MRA-C0000-GTM0016.00)	White to off-white dispersion, no visible particulates	04/27/2017	Conforms (CPR15097 Page 10)
Identity (Sanger Sequencing)	Sequence matches 100% description of the coding region	04/28/2017	Conforms (CPR15097 ADR C1)
Purity (MRA-C0000-GTM0019.01)	(b) (4)	05/01/2017	(b) (4)
Related Impurities (MRA-C0000-GTM0019.01)	Report % Pre-main peak and % Post main peak areas	05/01/2017	
Encapsulated RNA (MRA-C0000-GTM0014.00)	(b) (4)	04/24/2017 05/04/2017 05/05/2017	
Lipid Identification		05/22/2017	
SM-102	Matches retention time of standard		Conforms
Cholesterol	Matches retention time of standard		Conforms
DSPC	Matches retention time of standard		Conforms
PEG2000-DMG	Matches retention time of standard		Conforms
(UHPLC-CAD)			(CPR15097 ADR C1)
Lipid Content	Lipid (mg/mL)	05/22/2017	(b) (4)
SM-102	(b) (4)		
Cholesterol			
DSPC			
PEG2000-DMG			
(UHPLC-CAD)			

Appendix 15

Eurofins Advantar Laboratories, Inc.
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Summary of Analysis ***DATE: 6 July 2017***

Part II Release Testing Results for mRNA-1706 LNP Drug Product Lot MTDP17036

Protocol Number: MRA-C0019-RTP0005.00 **Document Number:** MRA-C0019-RTR0012.00 (CPR15101)	**Date Received at Eurofins Advantar:** March 31, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion (20mM Tris Buffer, 8% Sucrose, pH 7.4)
Time point: Release **Storage Condition:** -20°C	**Product Lot #:** MTDP17036	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Lipid Impurities (UHPLC-CAD)	Report total % Area and RRT	05/22/2017	(b) (4)
Mean Particle Size (nm) (MRA-C0000-GTM0015.02)	Report result	04/27/2017	
Polydispersity (MRA-C0000-GTM0015.02)	Report result	04/27/2017	
Particulate Matter[1] (USP <788> method 2)	(b) (4)	04/07/2017	
Residual Solvents from Formulation: Ethanol (MRA-C0000-GTM0018.01)		05/04/2017	
Osmolality (USP <785>)	Report Result	04/27/2017	
pH (MRA-C0000-GTM0017.01)	Report result	04/27/2017	

[1] Testing performed at Nelson Laboratories.
[2] This is a composite mean coming from 3 data sets (below) as requested by the Sponsor (CPR15099, ADR F1-F2):
T=0 (n=1, 84%), CPR15099, ADR D5
Method Qualification-Linearity (n=6 preps, 90%, 90%, 89%, 90%, 90%, 89%), CPR14795, ADR E7
Method Qualification-Stability (n=1, 88%), CPR14796, ADR F5

The data generated at Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Advantar has archived the raw data.

(b) (6)

06JUL 2017
Date

Appendix 15

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SUMMARY OF ANALYSIS

Sample Description:	**mRNA-1325** (mRNA API)
Lot or Batch No:	MTDS16004
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	March 2016
Date of Analysis:	April 2016
Storage:	Shipping Temperature: ≤ 15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	April 2017

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Appearance	(MRA-C0000-GTM0008.00)	Clear, colorless solution, essentially free of visible particulates	Clear, colorless solution, with no visible particulates and no turbidity was observed	CPR10317 ADR C1
Identification	Capillary Electrophoresis (MRA-C0000-GTM0001.02)	Migration time consistent with standard	N/A (First lot)	N/A
	RT/Sanger Sequencing TSOP134.03	Sequence matches 100% description of coding region	(b) (4)	209-TSOP134-073.00
Purity	Capillary Electrophoresis (MRA-C0000-GTM0001.02)	(b) (4)		CPR10314 ADR A16
	RP-HPLC (MRA-C0000-GTM0003.02)	Report % main peak area		CPR10316 ADR B24
Product related impurities	Capillary Electrophoresis (MRA-C0000-GTM0001.02)	Report % Pre-main peak and % Post-main areas		CPR10314 ADR A16
	RP-HPLC (MRA-C0000-GTM0003.02)	Report % peak area for individual impurities		CPR10316 ADR B24

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Residual plasmid DNA	qPCR TSOP344.01	(b) (4)		TSOP344-095.00
Residual solvents	GC (MRA-C0000-GTM0005.01) (MRA-C0000-GTM0007.02) (MRA-C0000-GTM0007.02) (MRA-C0000-GTM0009.02)	Report results	(b) (4)	CPR10318 p16 CPR10319 p27 CPR10319 p15 CPR10320 p11
Cap content	LCMS (MRA-C0000-GTM0002.01)	(b) (4)	(b) (4)	CPR10315 p13
Total RNA content (mg/mL)	UV (MRA-C0000-GTM0010.00)			CPR10317 ADR A5
pH	USP<791> (MRA-C0000-GTM0006.00)			CPR10317 ADR B1
Bacterial Endotoxin	USP<85>			PD Batch Record MTDS16004
Bioburden	USP<61> MTL-1001H/1001AH rev 013		Testing pending	TBD

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

29 APR 2016
Date:

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

29 APR 2016
Date:

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SUMMARY OF ANALYSIS

Sample Description:	**CX-000171 (formerly mRNA-1325)** (mRNA API)
mRNA length:	(b) (4)
SCC:	33.54 µg/mL
Plasmid ID:	PL-007718
Lot or Batch No:	**MTDS16004**
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	March 2016
Date of Analysis:	April 2016
Storage:	Shipping Temperature: ≤ - 15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	April 2017

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Appearance	(MRA-C0000-GTM0008.00)	Clear, colorless solution, essentially free of visible particulates	Clear, colorless solution, with no visible particulates and no turbidity was observed	CPR10317 ADR C1
Identity	RT/Sanger Sequencing TSOP134.03	Sequence matches 100% description of the coding region	(b) (4)	209-TSOP134-073.00
Purity	Capillary Electrophoresis (MRA-C0000-GTM0001.02)	(b) (4)		CPR10314 ADR A16
	RP-HPLC (MRA-C0000-GTM0003.02)	Report % main peak area		CPR10316 ADR B24
Product related impurities	Capillary Electrophoresis (MRA-C0000-GTM0001.02)	Report % Pre-main peak and % Post-main areas		CPR10314 ADR A16
	RP-HPLC (MRA-C0000-GTM0003.02)	Report % peak area for individual impurities		CPR10316 ADR B24
Residual plasmid DNA	qPCR TSOP344.01	(b) (4)		209-TSOP344-095.00

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Residual solvents IPA TEA Ethanol Hexylene glycol	(MRA-C0000-GTM0005.01) (MRA-C0000-GTM0007.02) (MRA-C0000-GTM0007.02) (MRA-C0000-GTM0009.02)	Report results	CPR10319 p15 CPR10318 p16 CPR10319 p27 CPR10320 p11
Cap content	LCMS (MRA-C0000-GTM0002.01)	(b) (4)	CPR10315 p13
Total RNA content	DSAD-TM-0019*		2017_03_23-014-(b) (6)
pH	USP<791> (MRA-C0000-GTM0006.00)		CPR10317 ADR B1
Bacterial Endotoxins	USP<85>		PD Batch Record MTDS16004
Bioburden	USP<61> MTL-1001H/1001AH rev 013		16-03720

(b) (4)

Signatures:

(b) (6)
Generated by: (b) (6) — 25 Apr 17 — Date:

(b) (6)
Reviewed by: (b) (6) — 25 APR 2017 — Date:

Appendix 16

Study Phase: Serology ELISA to detect Anti-Therapeutic Antibody (ATA)

Test Site Reference No. BS-3173
Test Facility Study No. 5002231

A 1-Month Study (3 doses) of mRNA-1706 by Intramuscular Injection in Sprague-Dawley Rats with a 2-Week Recovery Period

TEST SITE:
Integrated BioTherapeutics, Inc.
4 Research Court, Suite 300
Rockville, MD 20850

TEST FACILITY:
Charles River Laboratories Montreal ULC
Sherbrooke Site
1580 Ida-Métivier
Sherbrooke, QC J1E 0B5
Canada

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Correction : Sample occasions listed in Tables 6, 7 and 8 should read « Day -14 » instead of « Day 1 ».

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1. RESPONSIBLE PERSONNEL

Principal Investigator (b) (6)
Integrated BioTherapeutics, Inc.
VP, Manufacturing and Bioanalytics

2. INTRODUCTION

This report describes the detection of anti-ZIKV antibodies in vaccinated Sprague-Dawley rat sera from Charles River Study No. 5002231, entitled "A 1-Month Study (3 doses) of mRNA-1706 by Intramuscular Injection in Sprague-Dawley Rats with a 2-Week Recovery Period." The objectives of this study are to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period

The study was sponsored by Moderna Therapeutics Inc., Cambridge, Massachusetts. (b) (6), ALM served as Sponsor Representative for Moderna Therapeutics Inc.

A total of 221 serum samples (100 samples from Day -14 before initial dosing, 80 samples from Day 30, and 20 samples from Day 43; 21 separate spare pre-bleed samples) were received at Integrated BioTherapeutics, Inc. (IBT) from Charles River Laboratories on June 21, 2017.

Any remaining samples are discarded 30 days upon completion of the signed report. All records will be maintained at IBT Bioservices for a period up to three years.

This study phase was not within the scope of regulations governing the conduct of nonclinical laboratory studies and was not intended to comply with such regulations. However, this non GLP study phase was conducted in accordance with the Standard Operating Procedures of Integrated Biotherapeutics, Inc.

Appendix 16

3. EXPERIMENTAL DESIGN

Table 1: Study Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.50	10	10	5	5
Intramuscular injections for Groups 1-4 on days 1, 15 and 29								

4. MATERIALS AND METHODS

Table 2: Equipment

Equipment	Manufacturer	Model	IBT equipment#
(b) (4)			

Table 3: Materials

Material	Vendor	Cat#	Lot#	Expiry date
(b) (4)				N/A
				N/A

Table 4: Reagents

Reagent	Vendor	Cat#	Lot#	Expiry date
(b) (4)				(b) (4)
				N/A
				N/A
				(b) (4)
				N/A

Appendix 16

4.1. Zika (ZIKV) (sucrose-purified) virus lysate

Identification:	ZIKV lysate from strain FSS 13025
Supplier:	IBT Bioservices
Batch/Lot No.:	08.01.2016
Concentration:	305 µg /mL
Used concentration:	2 µg/mL
Expiry:	Not available
Retest Date:	01AUG2018
Storage conditions:	Kept in a freezer set to maintain -80°C

4.2. Standard

Identification:	Anti-ZIKV pooled rat serum Sprague Dawley rats vaccinated with mRNA-1325 Charles River Study 5001842, Group 4 and 5 (Day 43)
Supplier:	IBT Bioservices
Batch/Lot No.:	N/A
Concentration:	Not applicable
Expected Titer:	5,586 AU/mL
Expiry:	Not available
Retest Date:	N/A
Storage conditions:	Kept in a freezer set to maintain -80°C

4.3. Unknown test samples

Identification:	Sprague-Dawley rat sera (Charles River Study Number 5002231)
Supplier:	Charles River Laboratories
Storage conditions:	Kept in a freezer set to maintain -80°C
Duration:	Test samples will be discarded 30 days from completion of the project unless otherwise instructed

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4.4. Detection Antibody

Identification:	Goat anti-rat IgG (H+L)-HRP, mouse serum-adsorbed
Supplier:	KPL
Batch/Lot No.:	Catalog # 474-1612, lot 150317
Storage conditions:	Kept in a refrigerator set to maintain +4°C
Expiry:	Not available
Retest Date:	01AUG2018
Storage conditions:	Kept in a freezer set to maintain -80°C

4.5. Computerized Systems

Table 5: Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
SoftMax® Pro	5.4.5	• Collection of Absorbance Values at 650 nm • Calculations of Antibody Titers (X) based Absorbance Values (Y) by interpolating from a 4-parameter standard curve
Microsoft Excel	Office 365	Data summary
GraphPad Prism	Version 6	Graphs

4.6. Brief procedure

(b) (4)

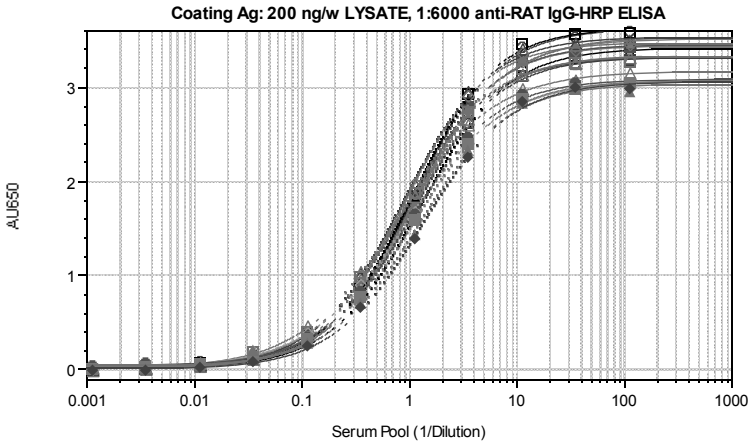
Appendix 16

5. RESULTS AND DISCUSSIONS

5.1. Standard

The standard is a well-characterized anti-ZIKV pooled rat serum whose titer (Antibody Units/mL) and has been re-assigned 5,586 AU/mL based on the average EC50 value of multiple runs during Assay Development. A cumulative graph of the standard curves tested on is shown below in **Figure 1.**

Figure 1: Cumulative Standard curves



4-P Fit: y = (A - D)/(1 + (x/C)^B) + D:	A	B	C	D	R^2
Plot#1 (ZIKA Std #1: Concentration vs MeanValue)	0.00948	1.03	0.862	3.33	0.999
Plot#9 (ZIKA Std #9: Concentration vs MeanValue)	0.0174	1.07	1.23	3.42	1
Plot#10 (ZIKA Std #10: Concentration vs MeanVa...	0.018	1.07	1.04	3.32	1
Plot#11 (ZIKA Std #11: Concentration vs MeanVa...	0.0131	1.08	1.02	3.34	1
Plot#12 (ZIKA Std #12: Concentration vs MeanVa...	0.0274	1.12	1.03	3.44	1
Plot#13 (ZIKA Std #13: Concentration vs MeanVa...	0.0299	1.1	1.04	3.46	1
Plot#14 (ZIKA Std #14: Concentration vs MeanVa...	0.0244	1.1	1.01	3.46	1
Plot#15 (ZIKA Std #15: Concentration vs MeanVa...	0.0193	1.06	1.09	3.52	1
Plot#16 (ZIKA Std #16: Concentration vs MeanVa...	0.0244	1.02	1.11	3.54	1
Plot#17 (ZIKA Std #17: Concentration vs MeanVa...	0.0393	1.08	1.07	3.63	0.999
Plot#18 (ZIKA Std #18: Concentration vs MeanVa...	0.0411	1.12	1.05	3.63	0.999
Plot#19 (ZIKA Std #19: Concentration vs MeanVa...	0.0242	1.08	0.862	3.54	0.999
Plot#20 (ZIKA Std #20: Concentration vs MeanVa...	0.0228	1.13	0.862	3.48	1
Plot#2 (ZIKA Std #2: Concentration vs MeanValue)	0.0305	1.05	0.854	3.33	0.999
Plot#3 (ZIKA Std #3: Concentration vs MeanValue)	0.0156	0.96	0.77	3.17	1
Plot#4 (ZIKA Std #4: Concentration vs MeanValue)	0.0269	0.961	0.919	3.07	0.999
Plot#5 (ZIKA Std #5: Concentration vs MeanValue)	0.0449	1.06	0.979	3.09	1
Plot#6 (ZIKA Std #6: Concentration vs MeanValue)	0.0202	1.03	1.06	3.07	1
Plot#7 (ZIKA Std #7: Concentration vs MeanValue)	0.0384	1.05	1.2	3.04	0.999
Plot#8 (ZIKA Std #8: Concentration vs MeanValue)	0.00652	1.05	1.29	3.06	0.999

Appendix 16

5.2. Study Samples

Antibody titers of Unknown Test Samples tested at 1:100 and 1:10,000 dilutions were calculated from the standard curve tested on each plate.

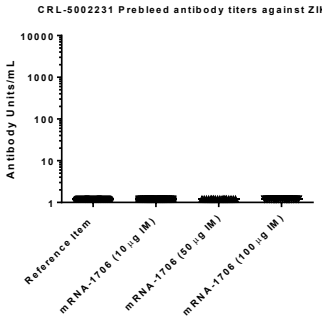
Main study: Day 30 rat sera from animals vaccinated with mRNA-1706 at 10 µg/dose, 50 µg/dose, 100 µg/dose on days 1, 15, and 29 intramuscularly showed detectable antibody responses against ZIKV lysate.

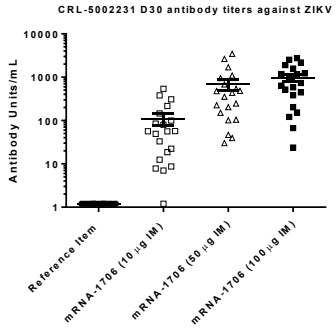
Recovery study: Day 43 rat sera from animals vaccinated with mRNA-1706 on days 1, 15 and 29, showed higher antibody titers than Day 30 rats.

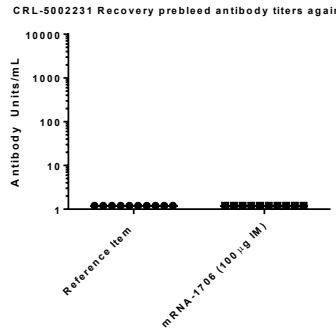
Individual Antibody Titers are shown in **Table 6, Table 7, and Table 8**. Graphs are shown in **Figure 2**.

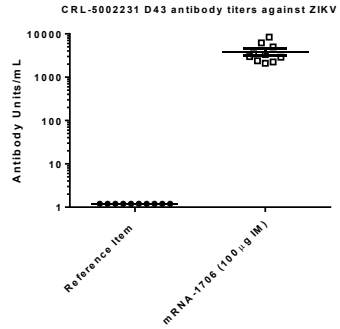
Figure 2: Graphs of Antibody Titers against ZIKV

Main Study		Recovery Study	
Day -14	Day 30	Day -14	Day 43









Appendix 16

Table 6: Antibody Titers (Antibody Units/mL) against ZIKV lysate for Groups 1 & 2

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animal ID	Day 1	Day 1 Average	Day 30	Day 30 Average	Animal ID	Day 1	Day 1 Average	Day 30	Day 30 Average	Animal ID	Day 1	Day 1 Average	Day 43	Day 43 Average
1	Reference Item	0	200	0	1001	1.2	1.2	1.2	1.2	1501	1.2	1.2	1.2	1.2	1011	1.2	1.2	1.2	1.2
					1002	1.2		1.2		1502	1.2		1.2		1012	1.2		1.2	
					1003	1.2		1.2		1503	1.2		1.2		1013	1.2		1.2	
					1004	1.2		1.2		1504	1.2		1.2		1014	1.2		1.2	
					1005	1.2		1.2		1505	1.2		1.2		1015	1.2		1.2	
					1006	1.2		1.2		1506	1.2		1.2		1511	1.2		1.2	
					1007	1.2		1.2		1507	1.2		1.2		1512	1.2		1.2	
					1008	1.2		1.2		1508	1.2		1.2		1513	1.2		1.2	
					1009	1.2		1.2		1509	1.2		1.2		1514	1.2		1.2	
					1010	1.2		1.2		1510	1.2		1.2		1515	1.2		1.2	

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animal ID	Day 1	Day 1 Average	Day 30	Day 30 Average	Animal ID	Day 1	Day 1 Average	Day 30	Day 30 Average
2	mRNA-1706	10	200	0.05	2001	1.2	1.2	1.2	52.83	2501	1.2	1.2	540.5	165.11
					2002	1.2		12.4		2502	1.2		56.9	
					2003	1.2		22.3		2503	1.2		99.7	
					2004	1.2		7		2504	1.2		56.6	
					2005	1.2		33.1		2505	1.2		377.5	
					2006	1.2		49.3		2506	1.2		145	
					2007	1.2		7.8		2507	1.2		56.1	
					2008	1.2		79.5		2508	1.2		215.5	
					2009	1.2		8.7		2509	1.2		84.7	
					2010	1.2		307		2510	1.2		18.6	

Note: Values below the level of quantitation were assigned a value of 1.2 AU/mL for plotting purposes

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Table 7: Antibody Titers (Antibody Units/mL) against ZIKV lysate for Groups 3 & 4

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animal ID	Day 1	Day 1 Average	Day 30	Day 30 Average	Animal ID	Day 1	Day 1 Average	Day 30	Day 30 Average					
3	mRNA-1706	50	200	0.25	3001	1.2	1.2	538.5	365.95	3501	1.2	1.2	46.7	1028.26					
					3002	1.2		484.5		3502	1.2		681						
					3003	1.2		1095		3503	1.2		39.4						
					3004	1.2		30		3504	1.2		2647						
					3005	1.2		101		3505	1.2		245.5						
					3006	1.2		477		3506	1.2		950						
					3007	1.2		354.5		3507	1.2		1691						
					3008	1.2		203		3508	1.2		104						
					3009	1.2		151		3509	1.2		3443						
					3010	1.2		225		3510	1.2		435						
Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animal ID	Day 1	Day 1 Average	Day 30	Day 30 Average	Animal ID	Day 1	Day 1 Average	Day 30	Day 30 Average	Animal ID	Day 1	Day 1 Average	Day 43	Day 43 Average
4	mRNA-1706	100	200	0.5	4001	1.2	1.2	731	538.73	4501	1.2	1.2	446	1387.4	4011	1.2	1.2	3459	2707.2
					4002	1.2		202		4502	1.2		1180		4012	1.2		2391	
					4003	1.2		583		4503	1.2		904		4013	1.2		2249	
					4004	1.2		1897		4504	1.2		518		4014	1.2		3335	
					4005	1.2		1227		4505	1.2		636		4015	1.2		2102	
					4006	1.2		382.5		4506	1.2		2524		4511	1.2		6196	5099.2
					4007	1.2		23.8		4507	1.2		1158		4512	1.2		2887	
					4008	1.2		67		4508	1.2		1579		4513	1.2		2980	
					4009	1.2		121		4509	1.2		2748		4514	1.2		8424	
					4010	1.2		153		4510	1.2		2181		4515	1.2		5009	

Note: Values below the level of quantitation were assigned a value of 1.2 AU/mL for plotting purposes

Table 8: Antibody Titers (Antibody Units/mL) against ZIKV lysate for Spare Animals

Group No.	Animal ID	Day 1	Animal ID	Day 1	Animal ID	Day 1
Spare	100	1.2	19	1.2	90	1.2
	106	1.2	4	1.2		
	111	1.2	45	1.2		
	112	1.2	48	1.2		
	12	1.2	49	1.2		
	120	1.2	52	1.2		
	13	1.2	64	1.2		
	14	1.2	65	1.2		
	16	1.2	75	1.2		
	17	1.2	80	1.2		

Note: Values below the level of quantitation were assigned a value of 1.2 AU/mL for plotting purposes

Appendix 16

6. CONCLUSION

A total of 221 rat serum samples was successfully tested to detect anti-ZIKV antibodies against ZIKV virus lysate.

7. REPORT APPROVAL

(b) (6) Date: November 20, 2017

Integrated BioTherapeutics, Inc.

8. REFERENCES:

N/A

Appendix 17

charles river

FINAL REPORT

Study Phase: Pathology

Test Facility Study No. 5002231

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

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1. SUMMARY

This report presents the pathology findings in rats assigned to Study No. 5002231. The objectives of this study were to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

The intramuscular injection of mRNA-1706 to rats for 1 month (3 doses) at all dose levels resulted in inflammation and hemorrhage at the injection site (correlating with abnormal consistency; firm and material accumulation; clot, respectively) with mixed cell infiltration in the draining lymph nodes (inguinal, popliteal and iliac, correlating with enlargement), increased myeloid cellularity in the bone marrow, decreased lymphoid cellularity in the periarteriolar sheath of the spleen and paracortex of the mesenteric lymph node and Kupffer cell hypertrophy in the liver (with occasional centrilobular degeneration). At ≥ 50 µg/dose, additional microscopic findings attributed to the administration of mRNA-1706 were cortical hypertrophy in the adrenal glands (correlating with higher adrenal weights) and single cell necrosis in the thymus. Microscopic changes observed only at 100 µg/dose, were single cell necrosis of lymphocyte in the spleen and decreased lymphoid cellularity in the thymus.

All macroscopic and microscopic findings as well as difference in organ weights were completely recovered at the end of the 2-week recovery period except at the injection site where mononuclear cell infiltration was observed and considered as the healing process from previous inflammation.

2. INTRODUCTION

This report presents the pathology findings in rats assigned to Study No. 5002231. The objectives of this study were to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

3. MATERIALS AND METHODS

Experimental procedures applicable to pathology investigations are summarized in Text Table 1.

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

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A complete gross pathological examination was performed on all animals and organ weights were recorded, as specified in the Study Plan. A detailed microscopic evaluation was performed on all tissues for main study animals from the reference and high dose groups (Groups 1 and 4). The histopathological evaluation was limited to the tissues identified as potential target organs (adrenal gland, bone marrow, liver, spleen, injection site, inguinal, mesenteric and popliteal lymph nodes, thymus and gut associated lymphoid tissue - GALT) for main study animals from the intermediate dose groups (Groups 2 and 3) as well as in recovery animals. Additional details along with deviations from these procedures may be found in the main study report.

3.1. Computerized Systems

Critical computerized systems used in this study phase are listed in Text Table 2.

Text Table 2
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	8	Terminal body weight, Organ weight data, gross pathology and histopathology.
Nevis	2	Statistical analyses of numerical terminal data.

4. RESULTS AND DISCUSSIONS

4.1. Mortality

There were no unscheduled deaths during the course of this study.

4.2. Gross Pathology

4.2.1. Terminal Euthanasia Animals (Day 30)

(Table 1 and Appendix 4)

mRNA-1706-related gross pathology findings were observed in lymph nodes (iliac, inguinal, popliteal) and at the injection site and their incidences are summarized in Text Table 3.

Text Table 3
Summary of Gross Pathology Findings – Scheduled Euthanasia (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**100**	**0**	**10**	**50**	**100**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injections (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Abnormal consistency; firm	0	8	9	9	0	4	9	9
Swelling	0	1	3	2	0	5	6	7
Material accumulation; clot	0	0	2	0	0	0	0	0

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	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**100**	**0**	**10**	**50**	**100**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Lymph node[a] (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Enlargement	0	0	0	4	0	1	3	4
Lymph node, inguinal (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Enlargement	0	0	1	0	0	0	0	1
Lymph node, popliteal (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Enlargement	1	3	0	1	0	3	0	0

[a] Iliac left as documented in individual animals.

Macroscopic findings attributed to the administration of mRNA-1706 at the injection site were characterized by firmness, swelling and occasionally by the presence of a clot in the thigh muscle used for the injection. These macroscopic findings were observed in males and females at all dose levels with no clear dose relationship and correlated histologically with inflammation and/or hemorrhage.

In addition, enlargement of the draining lymph nodes (inguinal, popliteal and iliac) was observed in males and females at all dose levels with no evidence of dose relationship and correlated histologically with mixed cell infiltration.

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 reference and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

4.2.2. Recovery Euthanasia Animals (Day 43)

(Table 1 and Appendix 4)

mRNA-1706-related gross findings noted at the terminal euthanasia in the injection site and draining lymph nodes were not observed at the end of the recovery period (Day 43). 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 reference and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

4.3. Organ Weights

4.3.1. Terminal Euthanasia Animals (Day 30)

(Table 2, Table 3, Table 4, Appendix 1, Appendix 2 and Appendix 3)

mRNA-1706-related organ weight changes were observed in the adrenal glands and are summarized in Text Table 4.

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Text Table 4
Summary of Organ Weight Data – Scheduled Euthanasia (Day 30)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**10**	**50**	**100**	**10**	**50**	**100**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Gland, adrenal (No. Weighed)[a]	(10)	(10)	(10)	(10)	(10)	(10)
Absolute value	7	2	14	4	**13**	**21**
% of body weight	**15**	5	**27**	6	11	**23**
% of brain weight	7	-2	11	3	13	**24**

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

The group means for absolute and relative (to body and brain) weight of the adrenal were significantly higher in females given mRNA-1706 at 100 µg/dose compared to the concurrent reference. There was also a trend toward higher group means for absolute and relative (to body and brain) weight in males given mRNA-1706 at 100 µg/dose and females at 50 µg/dose but these values were statistically significant only in for absolute (females) or relative to body (males) weights. These increases of adrenal weights correlated histologically with cortical hypertrophy.

No other mRNA-1706-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective references. 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 terminal body weight and unrelated to administration of mRNA-1706.

4.3.2. Recovery Euthanasia Animals (Day 43)

(Table 2, Table 3, Table 4, Appendix 1, Appendix 2 and Appendix 3)

mRNA-1706-related organ weight changes noted in the adrenal glands at the terminal euthanasia were not observed at the end of the recovery period (Day 43). There were isolated organ weight values that were statistically different from their respective references. 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 terminal body weight and unrelated to administration of mRNA-1706.

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4.4. Histopathology

4.4.1. Terminal Euthanasia Animals (Day 30)

(Table 5 and Appendix 4)

mRNA-1706-related microscopic findings were observed at the injection site, in the draining lymph nodes (inguinal, popliteal, iliac), bone marrow, adrenal glands, liver, mesenteric lymph node, thymus and spleen and their incidence and severity are summarized in Text Table 5.

Text Table 5
Summary of Microscopic Findings – Scheduled Euthanasia (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**100**	**0**	**10**	**50**	**100**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Bone Marrow (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Increased cellularity; myeloid	(0)[a]	(5)	(6)	(7)	(0)	(3)	(5)	(8)
Minimal	0	5	6	7	0	3	5	8
Gland, Adrenal (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Hypertrophy; cortical	(0)	(0)	(5)	(10)	(0)	(0)	(4)	(9)
Minimal	0	0	5	10	0	0	4	9
Liver (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Hypertrophy; Kupffer cell	(0)	(2)	(1)	(2)	(0)	(2)	(2)	(5)
Minimal	0	2	1	2	0	2	2	4
Mild	0	0	0	0	0	0	0	1
Degeneration/necrosis; centrilobular	(0)	(1)	(0)	(0)	(0)	(0)	(1)	(3)
Minimal	0	1	0	0	0	0	1	2
Mild	0	0	0	0	0	0	0	1
Lymph node; inguinal (No. Examined)	(10)	(9)	(8)	(10)	(10)	(10)	(10)	(10)
Infiltration, mixed cell	(0)	(0)	(1)	(1)	(0)	(0)	(1)	(5)
Minimal	0	0	1	1	0	0	1	4
Mild	0	0	0	0	0	0	0	1
Lymph node; popliteal (No. Examined)	(10)	(9)	(9)	(10)	(10)	(10)	(10)	(10)
Infiltration, mixed cell	(0)	(0)	(1)	(3)	(0)	(3)	(5)	(5)
Minimal	0	0	1	2	0	3	5	4
Mild	0	0	0	1	0	0	0	1
Lymph node[b] (No. Examined)	(0)	(0)	(0)	(4)	(0)	(1)	(3)	(4)
Infiltration, mixed cell	-	-	-	(4)	-	(1)	(3)	(4)
Minimal	-	-	-	1	-	1	1	0
Mild	-	-	-	2	-	0	2	3
Moderate	-	-	-	1	-	0	0	1
Lymph node; mesenteric (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Decreased cellularity; lymphoid, paracortex	(0)	(3)	(4)	(4)	(0)	(2)	(4)	(8)
Minimal	0	3	4	4	0	2	4	8

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	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**100**	**0**	**10**	**50**	**100**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injection (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Inflammation	(0)	(10)	(10)	(9)	(2)	(10)	(10)	(10)
Minimal	0	0	0	0	2	1	0	0
Mild	0	5	1	2	0	3	1	0
Moderate	0	5	6	4	0	6	3	2
Marked	0	0	3	3	0	0	6	8
Hemorrhage	(1)	(1)	(5)	(3)	(0)	(1)	(0)	(0)
Minimal	1	1	0	3	0	1	0	0
Mild	0	0	3	0	0	0	0	0
Moderate	0	0	2	0	0	0	0	0
Spleen (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Decreased cellularity; lymphoid, periarteriolar lymphoid sheath	(0)	(9)	(8)	(10)	(0)	(7)	(8)	(10)
Minimal	0	7	4	8	0	6	5	5
Mild	0	2	4	2	0	1	3	5
Single cell necrosis; lymphoid	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(6)
Minimal	0	0	0	1	0	0	0	6
Thymus (No. Examined)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Single cell necrosis; lymphoid	(0)	(0)	(3)	(3)	(0)	(0)	(0)	(8)
Minimal	0	0	3	3	0	0	0	6
Mild	0	0	0	0	0	0	0	2
Decreased cellularity; lymphoid	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Minimal	0	0	0	1	0	0	0	0

[a] Numbers in parentheses represent the number of animals with the finding.
[b] Iliac lymph node, examined only if gross abnormality observed.

At the injection site, the microscopic findings attributed to the administration of mRNA-1706 were minimal to marked inflammation and minimal to moderate hemorrhage. The inflammation was observed in males and females at all dose levels with no dose relationship between 50 µg/dose and 100 µg/dose but with lower severity of the findings at 10 µg/dose. It was characterized locally by extensive infiltration of mixed inflammatory cells, mainly granulocytes, with associated edema and fibrin exudates and correlated macroscopically with firmness of the thigh (abnormal consistency; firm). It was accompanied by mild to moderate hemorrhage (correlating macroscopically with material accumulation; clot) in some males at 50 µg/dose. This inflammatory process was not otherwise associated with degeneration of the muscle. Similar incidence and severity of minimal degeneration/necrosis of myofiber was observed in reference and mRNA-1706-dosed animals and was considered related to the experimental procedures (intramuscular injection).

In the inguinal, popliteal and iliac lymph nodes (considered as draining injection site), there was minimal to mild mixed cell infiltration in males and/or females administered mRNA-1706 at all dose levels. The inflammatory infiltrate was composed of clusters of degenerated granulocytes in the lymph node sinuses or in the adjacent adipose/connective tissue.

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A dose related minimal increase of myeloid cellularity was observed in the bone marrow of males and females at all dose levels.

In the adrenal glands, a dose related minimal cortical hypertrophy was present in males and females administered mRNA-1706 at ≥ 50 µg/dose and correlated with the increased adrenal weights.

In the liver, a low incidence of minimal to mild hypertrophy of the Kupffer cell was observed in males and females at all dose levels with no clear dose relationship. The hypertrophied Kupffer cells sometimes contained finely granular brownish pigment. In one male at 10 µg/dose, one female at 50 µg/dose and three females at 100 µg/dose, there was minimal to mild degeneration in the centrilobular region characterized by presence of mixed inflammatory cell in the sinusoid with single cell necrosis or degeneration of hepatocytes.

Microscopic findings similar in nature were observed in the spleen and mesenteric lymph nodes at all dose levels as well as in thymus at ≥ 50 µg/dose. They consisted of minimal to mild decreased lymphoid cellularity and/or single cell necrosis of lymphocyte. The decreased lymphoid cellularity was present in the periarteriolar sheath of the spleen, in the cortex of the thymus and in the paracortex of the mesenteric lymph node. In these areas, the lymphoid cells were less densely populated with prominent dendric cells. Single cell lymphoid necrosis was observed in the depleted region in these organs, mainly at 100 µg/dose.

After evaluation of all dose group animals, the GALT was no longer considered as a target organ.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in reference and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

4.4.2. Recovery Euthanasia Animals (Day 43)

(Table 5 and Appendix 4)

Microscopic findings noted in the adrenal glands, bone marrow, lymph nodes (mesenteric, popliteal, inguinal), thymus, spleen and liver at the terminal euthanasia were not observed at the end of the recovery period (Day 43) and therefore, considered completely recovered.

At the injection site, the inflammation and hemorrhage present at the end of dosing were no longer observed but minimal mononuclear cell infiltration was noted in males and females at 100 µg/dose as well as in one control female. This microscopic finding was interpreted to result from the healing process from previous inflammation at the injection site. The incidence and severity are summarized in Text Table 6.

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Text Table 6
Summary of Microscopic Findings – Scheduled Euthanasia (Day 43)

	Males		females	
Group	**1**	**4**	**1**	**4**
Dose (µg/dose)	**0**	**100**	**0**	**100**
No. Animals Examined	**5**	**5**	**5**	**5**
Site, injections (No. Examined)	(5)	(5)	(5)	(5)
Infiltration; mononuclear cell	(0)[a]	(5)	(1)	(2)
Minimal	0	5	1	2

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

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in reference and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

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5. CONCLUSIONS

The intramuscular injection of mRNA-1706 to rats for 1 month (3 doses) at all dose levels resulted in inflammation and hemorrhage at the injection site (correlating with abnormal consistency; firm and material accumulation; clot, respectively) with mixed cell infiltration in the draining lymph nodes (inguinal, popliteal and iliac, correlating with enlargement), increased myeloid cellularity in the bone marrow, decreased lymphoid cellularity in the periarteriolar sheath of the spleen and paracortex of the mesenteric lymph node and Kupffer cell hypertrophy in the liver (with occasional centrilobular degeneration). At ≥ 50 μg/dose, additional microscopic findings attributed to the administration of mRNA-1706 were cortical hypertrophy in the adrenal glands (correlating with higher adrenal weights) and single cell necrosis in the thymus. Microscopic changes observed only at 100 μg/dose, were single cell necrosis of lymphocyte in the spleen and decreased lymphoid cellularity in the thymus.

All macroscopic and microscopic findings as well as difference in organ weights were completely recovered at the end of the 2-week recovery period except at the injection site where mononuclear cell infiltration was observed and considered as the healing process from previous inflammation.

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6. REPORT APPROVAL

(b) (6) _____Date: 31-oct-2017

Appendix 17

Table 1
Incidence of Necropsy Findings by Organ/Group/Sex

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Incidence of Necropsy Findings by Organ/Group/Sex Explanation Page

Abbreviation	Description
GALT	Gut Associated Lymphoid Tissue

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BODY CAVITY, NASAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE MARROW								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE, FEMUR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE, STERNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BRAIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
CERVIX								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
EPIDIDYMIS								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	9	10	.	.	.	.
Small	0	0	1	0	.	.	.	.
ESOPHAGUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
EYE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GALT								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, ADRENAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	9	10	10	9	10	9
Small	0	0	1	0	0	0	0	0
Focus; dark	0	0	0	0	0	1	0	1
Focus; pale	0	0	1	0	0	0	0	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	10	10	10	10	10	10
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
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	10	10	10	10	10	10	10
HEART								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

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Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
KIDNEY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
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	9	10	10	10	10	10	10	10
Parasite	1	0	0	0	0	0	0	0
LARYNX								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LIVER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	7	9	7	8	7	5	7	6
Focus; pale	3	1	3	2	3	5	3	4
Small	0	0	0	0	0	1	0	0
LUNG								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	6	6	8	10	10	9
Focus; dark	0	1	4	4	1	0	0	1
Focus; pale	0	0	0	0	1	0	0	0
LYMPH NODE								
Submitted	0	0	0	4	0	1	3	4
Enlargement	.	.	.	4	.	1	3	4
LYMPH NODE, INGUINAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	9	10	10	10	9	9
Enlargement	0	0	1	0	0	0	0	1
Focus; dark	0	0	0	0	0	0	1	0

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	10	9	10	10	10	10
Focus; dark	0	0	0	1	0	0	0	0
Enlargement	0	1	0	0	0	0	0	0
LYMPH NODE, MESENTERIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LYMPH NODE, POPLITEAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	7	9	9	10	7	10	10
Focus; dark	0	0	1	0	0	0	0	0
Enlargement	1	3	0	1	0	3	0	0
MUSCLE, SKELETAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
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	.	.	.	.	9	9	9	9
Cyst; pale	.	.	.	.	1	1	1	1
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	9	2	1	1	10	3	1	1
Abnormal consistency; firm	0	8	9	9	0	4	9	9
Swelling	0	1	3	2	0	5	6	7

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SITE, INJECTION (Continued...)								
Material accumulation; clot	0	0	2	0	0	0	0	0
Focus; dark	1	2	0	2	0	0	0	0
SKIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	8	9	10	10	10
Scab; dark	0	0	0	2	1	0	0	0
SMALL INTESTINE, DUODENUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, ILEUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, JEJUNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
Diverticulum	0	0	0	0	0	0	0	0
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	10	8	9	10	9	10	10
Focus; dark	0	0	1	1	0	0	0	0
Focus; depressed	0	0	1	0	0	0	0	0

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
STOMACH (Continued...)								
Nodule	0	0	0	0	0	1	0	0
TESTIS								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	9	10	.	.	.	.
Abnormal consistency; soft	0	0	1	0	.	.	.	.
Small	0	0	1	0	.	.	.	.
Focus; pale	0	0	1	0	.	.	.	.
THYMUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	7	7	8	8	8	9	8	8
Focus; dark	3	3	2	2	2	1	2	2
Small	0	0	0	1	0	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	.	.	.	.	9	10	10	9
Small	.	.	.	.	1	0	0	0
Thin	.	.	.	.	1	0	0	0
Nodule	.	.	.	.	0	0	0	1
VAGINA								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	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	.	.
Small	0	0	.	.
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 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, ADRENAL				
Submitted	5	5	5	5
No Visible Lesions	4	4	5	5
Small	0	0	0	0
Focus; dark	0	0	0	0
Focus; pale	1	1	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	5
HEART				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
KIDNEY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
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
Parasite	0	0	0	0
LARYNX				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LIVER				
Submitted	5	5	5	5
No Visible Lesions	4	4	5	5
Focus; pale	1	1	0	0
Small	0	0	0	0
LUNG				
Submitted	5	5	5	5
No Visible Lesions	4	3	5	5
Focus; dark	1	2	0	0
Focus; pale	0	0	0	0
LYMPH NODE				
Submitted	2	0	0	0
Enlargement	2	.	.	.
LYMPH NODE, INGUINAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Enlargement	0	0	0	0
Focus; dark	0	0	0	0

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, MANDIBULAR				
Submitted	5	5	5	5
No Visible Lesions	5	4	4	3
Focus; dark	0	1	1	2
Enlargement	0	0	1	1
LYMPH NODE, MESENTERIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LYMPH NODE, POPLITEAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	4
Focus; dark	0	0	0	0
Enlargement	0	0	0	1
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
Cyst; pale	.	.	0	0
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
Abnormal consistency; firm	0	0	0	0
Swelling	0	0	0	0

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
SITE, INJECTION (Continued...)				
Material accumulation; clot	0	0	0	0
Focus; dark	0	0	0	0
SKIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Scab; dark	0	0	0	0
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	4	5	5
Diverticulum	0	1	0	0
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	5	5	5	5
STOMACH				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Focus; dark	0	0	0	0
Focus; depressed	0	0	0	0

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
STOMACH (Continued...)				
Nodule	0	0	0	0
TESTIS				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
Abnormal consistency; soft	0	0	.	.
Small	0	0	.	.
Focus; pale	0	0	.	.
THYMUS				
Submitted	5	5	5	5
No Visible Lesions	5	4	5	5
Focus; dark	0	1	0	0
Small	0	0	0	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
Small	.	.	0	0
Thin	.	.	0	0
Nodule	.	.	0	0
VAGINA				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5

Appendix 17
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002231

Key Page

Measurement/Statistics

Measurement	Descriptive	Comparative	Arithmetic/Adjusted	Transformation
Pathology Observation	Count Positives			

Group Information

Short Name	Long Name	Report Headings		
1	1	0	ug/dose	Group 1
2	2	10	ug/dose	Group 2
3	3	50	ug/dose	Group 3
4	4	100	ug/dose	Group 4

Removal Reason Grouping

Grouping Name	Abbreviation	Removal Reasons
TERMINAL EUTHANASIA	TERM	TERMINAL EUTHANASIA
RECOVERY EUTHANASIA	REC	RECOVERY EUTHANASIA

Appendix 17

Table 2
Summary of Absolute Organ Weights

Appendix 17
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	Mean	491.4	2.0736	1.2109	0.05326	0.01312	1.3265	0.01713
	SD	47.7	0.0785	0.2152	0.00738	0.00234	0.1441	0.00240
	N	10	10	10	10	10	10	10
2M	Mean	458.7	2.0821	1.2105	0.05718	0.01271	1.4378	0.01887
	SD	30.0	0.0950	0.0928	0.00606	0.00080	0.1726	0.00317
	N	10	10	10	10	10	10	10
	%Diff G1	-6.7	0.4099	-0.0330	7.36012	-3.12500	8.3905	10.15762
3M	Mean	475.0	2.1591	1.2560	0.05439	0.01264	1.3068	0.01763
	SD	45.4	0.0994	0.1098	0.00868	0.00140	0.2048	0.00377
	N	10	10	10	10	10	10	10
	%Diff G1	-3.3	4.1233	3.7245	2.12167	-3.65854	-1.4851	2.91886
4M	Mean	439.5a	2.1200	1.2519	0.06066	0.01321	1.4341	0.01673
	SD	31.9	0.0727	0.0979	0.00903	0.00135	0.1877	0.00304
	N	10	10	10	10	10	10	10
	%Diff G1	-10.6	2.2377	3.3859	13.89410	0.68598	8.1116	-2.33508

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

Appendix 17
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	Mean	1.4402	2.7328	13.7275	1.5047	--	0.8297	3.7646
	SD	0.1794	0.3476	1.5591	0.1145	--	0.1232	0.5553
	N	10	10	10	10	--	10	10
2M	Mean	1.4539	2.6600	13.0092	1.5581	--	0.9606	3.7974
	SD	0.1394	0.2373	1.4634	0.0780	--	0.1269	0.3380
	N	10	10	10	10	--	10	10
	%Diff G1	0.9513	-2.6639	-5.2326	3.5489	--	15.7768	0.8713
3M	Mean	1.5500	2.7080	14.0866	1.5697	--	1.0289b	3.8536
	SD	0.2232	0.1974	1.6814	0.1127	--	0.1407	0.3626
	N	10	10	10	10	--	10	10
	%Diff G1	7.6239	-0.9075	2.6159	4.3198	--	24.0087	2.3641
4M	Mean	1.4535	2.6565	12.2712	1.5094	--	0.8787	3.8422
	SD	0.2653	0.3672	1.2527	0.1515	--	0.0982	0.3934
	N	10	10	10	10	--	10	10
	%Diff G1	0.9235	-2.7920	-10.6086	0.3124	--	5.9057	2.0613

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

Appendix 17
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		THYMUS g	UTERUS g
1M	Mean	0.2673	--
	SD	0.0970	--
	N	10	--
2M	Mean	0.2431	--
	SD	0.0703	--
	N	10	--
	%Diff G1	-9.0535	--
3M	Mean	0.2722	--
	SD	0.0978	--
	N	10	--
	%Diff G1	1.8331	--
4M	Mean	0.2371	--
	SD	0.0619	--
	N	10	--
	%Diff G1	-11.2982	--

Appendix 17
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1F	Mean	259.3	1.9336	--	0.05920	0.01688	--	0.01419
	SD	18.5	0.0442	--	0.00896	0.00203	--	0.00142
	N	10	10	--	10	10	--	10
2F	Mean	252.9	1.9376	--	0.06138	0.01558	--	0.01454
	SD	8.6	0.0750	--	0.00560	0.00221	--	0.00171
	N	10	10	--	10	10	--	10
	%Diff G1	-2.5	0.2069	--	3.68243	-7.70142	--	2.46653
3F	Mean	265.2	1.9385	--	0.06715a	0.01785	--	0.01457
	SD	18.6	0.0618	--	0.00590	0.00260	--	0.00245
	N	10	10	--	10	10	--	10
	%Diff G1	2.3	0.2534	--	13.42905	5.74645	--	2.67794
4F	Mean	254.2	1.8883	--	0.07139b	0.01566	--	0.01416
	SD	20.9	0.0434	--	0.00757	0.00173	--	0.00185
	N	10	10	--	10	10	--	10
	%Diff G1	-2.0	-2.3428	--	20.59122	-7.22749	--	-0.21142

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

Appendix 17
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	Mean	1.0401	1.6275	7.0897	1.2012	0.0899	0.5497	--
	SD	0.1701	0.1570	0.6179	0.1071	0.0176	0.0583	--
	N	10	10	10	10	10	10	--
2F	Mean	0.9946	1.6804	7.3599	1.2257	0.0973	0.5836	--
	SD	0.1099	0.1677	1.0341	0.0739	0.0180	0.0498	--
	N	10	10	10	10	10	10	--
	%Diff G1	-4.3746	3.2504	3.8112	2.0396	8.2314	6.1670	--
3F	Mean	1.0667	1.7765	7.6202	1.1857	0.1028	0.6075	--
	SD	0.1583	0.2267	0.5629	0.0880	0.0116	0.0743	--
	N	10	10	10	10	10	10	--
	%Diff G1	2.5574	9.1551	7.4827	-1.2904	14.3493	10.5148	--
4F	Mean	0.9776	1.7024	7.4969	1.1561	0.1125	0.5743	--
	SD	0.1047	0.1635	0.7841	0.0774	0.0447	0.1123	--
	N	10	10	10	10	10	10	--
	%Diff G1	-6.0090	4.6022	5.7435	-3.7546	25.1390	4.4752	--

Appendix 17
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		THYMUS g	UTERUS g
1F	Mean	0.2510	0.9152
	SD	0.0697	0.3692
	N	10	10
2F	Mean	0.2581	0.7748
	SD	0.0520	0.3808
	N	10	10
	%Diff G1	2.8287	-15.3409
3F	Mean	0.2711	0.7617
	SD	0.0914	0.2584
	N	10	10
	%Diff G1	8.0080	-16.7723
4F	Mean	0.2496	0.6704
	SD	0.0593	0.2113
	N	10	10
	%Diff G1	-0.5578	-26.7483

Appendix 17
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	Mean	512.0	2.1418	1.3226	0.04946	0.01370	1.3720	0.02158
	SD	20.2	0.1105	0.0474	0.00452	0.00243	0.2190	0.00284
	N	5	5	5	5	5	5	5
4M	Mean	468.0b	2.0950	1.2668	0.04684	0.01156	1.3662	0.02260
	SD	18.3	0.0569	0.0603	0.00805	0.00070	0.1631	0.00354
	N	5	5	5	5	5	5	5
	%Diff G1	-8.6	-2.1851	-4.2190	-5.29721	-15.62044	-0.4227	4.72660

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

Appendix 17
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	Mean	1.7490	2.8698	13.9466	1.5176	--	0.8474	4.1992
	SD	0.1266	0.0898	0.8894	0.1157	--	0.1199	0.2197
	N	5	5	5	5	--	5	5
4M	Mean	1.5348a	2.6668a	11.7828b	1.4518	--	0.8236	3.8232a
	SD	0.0785	0.1470	0.7729	0.0530	--	0.1085	0.1825
	N	5	5	5	5	--	5	5
	%Diff G1	-12.2470	-7.0737	-15.5149	-4.3358	--	-2.8086	-8.9541

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

Appendix 17
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		THYMUS g	UTERUS g
1M	Mean	0.2382	--
	SD	0.0382	--
	N	5	--
4M	Mean	0.1906	--
	SD	0.0330	--
	N	5	--
	%Diff G1	-19.9832	--

Appendix 17
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1F	Mean	271.4	1.9434	--	0.05658	0.01798	--	0.01370
	SD	10.9	0.0718	--	0.00598	0.00208	--	0.00318
	N	5	5	--	5	5	--	5
4F	Mean	273.8	2.0070	--	0.05772	0.01768	--	0.01520
	SD	13.4	0.0446	--	0.00768	0.00172	--	0.00286
	N	5	5	--	5	5	--	5
	%Diff G1	0.9	3.2726	--	2.01485	-1.66852	--	10.94891

Appendix 17
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	Mean	1.0848	1.6760	7.2790	1.1130	0.0842	0.5798	--
	SD	0.0291	0.1741	0.5813	0.0698	0.0043	0.1191	--
	N	5	5	5	5	5	5	--
4F	Mean	1.1094	1.7822	7.5814	1.2138a	0.0950a	0.5128	--
	SD	0.0596	0.1911	0.9571	0.0531	0.0078	0.0383	--
	N	5	5	5	5	5	5	--
	%Diff G1	2.2677	6.3365	4.1544	9.0566	12.8266	-11.5557	--

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

Appendix 17
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		THYMUS g	UTERUS g
1F	Mean	0.2374	0.8178
	SD	0.0414	0.2059
	N	5	5
4F	Mean	0.2726	0.6894
	SD	0.0639	0.2806
	N	5	5
	%Diff G1	14.8273	-15.7007

Appendix 17

Table 3
Summary of Organ Weights Relative to Body Weight

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.42481	0.24563	0.01084	0.00266	0.27110	0.00351	0.29279
	SD	0.03499	0.03494	0.00111	0.00030	0.02823	0.00055	0.01700
	N	10	10	10	10	10	10	10
2M	Mean	0.45518	0.26434	0.01245a	0.00278	0.31445	0.00413	0.31674
	SD	0.02912	0.01993	0.00089	0.00018	0.03987	0.00076	0.01859
	N	10	10	10	10	10	10	10
	%Diff G1	7.15037	7.61843	14.92329	4.42778	15.98729	17.79652	8.18087
3M	Mean	0.45699	0.26563	0.01143	0.00268	0.27947	0.00372	0.32751
	SD	0.03329	0.02623	0.00133	0.00034	0.06404	0.00076	0.04843
	N	10	10	10	10	10	10	10
	%Diff G1	7.57613	8.14227	5.49612	0.61852	3.08429	6.09431	11.85899
4M	Mean	0.48465b	0.28547b	0.01381c	0.00300a	0.32640a	0.00380	0.32993
	SD	0.03883	0.02258	0.00192	0.00019	0.03436	0.00061	0.04785
	N	10	10	10	10	10	10	10
	%Diff G1	14.08756	16.21896	27.40931	12.98105	20.39666	8.41849	12.68369

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

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.55481	2.81566	0.30708	--	0.16834	0.76489	0.05383
	SD	0.02582	0.43527	0.01572	--	0.01241	0.08362	0.01526
	N	10	10	10	--	10	10	10
2M	Mean	0.57948	2.83556	0.34028b	--	0.20926c	0.82816	0.05267
	SD	0.02666	0.24470	0.01642	--	0.02055	0.05370	0.01336
	N	10	10	10	--	10	10	10
	%Diff G1	4.44647	0.70661	10.81008	--	24.30764	8.27118	-2.15692
3M	Mean	0.57190	2.96483	0.33209a	--	0.21695c	0.81643	0.05743
	SD	0.03488	0.18586	0.02936	--	0.02500	0.09414	0.02074
	N	10	10	10	--	10	10	10
	%Diff G1	3.08003	5.29768	8.14297	--	28.87812	6.73733	6.69392
4M	Mean	0.60293a	2.79408	0.34328b	--	0.20029b	0.87540a	0.05374
	SD	0.05157	0.24238	0.01989	--	0.02107	0.08114	0.01243
	N	10	10	10	--	10	10	10
	%Diff G1	8.67198	-0.76644	11.78542	--	18.97875	14.44761	-0.16979

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

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		UTERUS %
1M	Mean	--
	SD	--
	N	--
2M	Mean	--
	SD	--
	N	--
	%Diff G1	--
3M	Mean	--
	SD	--
	N	--
	%Diff G1	--
4M	Mean	--
	SD	--
	N	--
	%Diff G1	--

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	Mean	0.74893	--	0.02291	0.00653	--	0.00548	0.40291
	SD	0.05300	--	0.00377	0.00080	--	0.00046	0.07700
	N	10	--	10	10	--	10	10
2F	Mean	0.76652	--	0.02427	0.00617	--	0.00575	0.39272
	SD	0.02895	--	0.00210	0.00092	--	0.00070	0.03466
	N	10	--	10	10	--	10	10
	%Diff G1	2.34855	--	5.95840	-5.51804	--	5.04055	-2.52890
3F	Mean	0.73477	--	0.02540	0.00676	--	0.00551	0.40259
	SD	0.06406	--	0.00246	0.00106	--	0.00092	0.05281
	N	10	--	10	10	--	10	10
	%Diff G1	-1.89009	--	10.85072	3.57903	--	0.53846	-0.07862
4F	Mean	0.74738	--	0.02826b	0.00617	--	0.00560	0.38491
	SD	0.06495	--	0.00376	0.00062	--	0.00080	0.03045
	N	10	--	10	10	--	10	10
	%Diff G1	-0.20721	--	23.37383	-5.43300	--	2.16440	-4.46535

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

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	Mean	0.62709	2.73762	0.46428	0.03461	0.21212	--	0.09654
	SD	0.03065	0.19762	0.04113	0.00593	0.01900	--	0.02459
	N	10	10	10	10	10	--	10
2F	Mean	0.66351	2.90231	0.48462	0.03840	0.23054	--	0.10171
	SD	0.05021	0.31918	0.02371	0.00628	0.01444	--	0.01803
	N	10	10	10	10	10	--	10
	%Diff G1	5.80822	6.01579	4.38063	10.94338	8.68551	--	5.35625
3F	Mean	0.67101	2.88043	0.44741	0.03876	0.22876	--	0.10180
	SD	0.07838	0.22432	0.02106	0.00335	0.01964	--	0.03158
	N	10	10	10	10	10	--	10
	%Diff G1	7.00416	5.21635	-3.63436	11.97828	7.84678	--	5.44458
4F	Mean	0.67167	2.94922	0.45616	0.04447	0.22456	--	0.09756
	SD	0.06084	0.19973	0.02951	0.01834	0.03096	--	0.01764
	N	10	10	10	10	10	--	10
	%Diff G1	7.10921	7.72933	-1.75078	28.48124	5.86406	--	1.05052

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		UTERUS %
1F	Mean	0.35057
	SD	0.13403
	N	10
2F	Mean	0.30779
	SD	0.15590
	N	10
	%Diff G1	-12.20325
3F	Mean	0.28676
	SD	0.09489
	N	10
	%Diff G1	-18.20021
4F	Mean	0.26306
	SD	0.07812
	N	10
	%Diff G1	-24.96086

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.41914	0.25875	0.00966	0.00267	0.26717	0.00423	0.34126
	SD	0.03285	0.01588	0.00084	0.00038	0.03485	0.00064	0.01178
	N	5	5	5	5	5	5	5
4M	Mean	0.44845	0.27073	0.01003	0.00248	0.29289	0.00483	0.32873
	SD	0.02678	0.00940	0.00185	0.00023	0.04299	0.00077	0.02704
	N	5	5	5	5	5	5	5
	%Diff G1	6.99297	4.62838	3.80875	-7.13523	9.62621	14.29093	-3.67133

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.56072	2.72772	0.29644	--	0.16592	0.82192	0.04659
	SD	0.01064	0.20860	0.01960	--	0.02535	0.06548	0.00764
	N	5	5	5	--	5	5	5
4M	Mean	0.57058	2.51699	0.31077	--	0.17649	0.81678	0.04067
	SD	0.03845	0.11694	0.02045	--	0.02690	0.01517	0.00667
	N	5	5	5	--	5	5	5
	%Diff G1	1.75742	-7.72545	4.83502	--	6.36839	-0.62517	-12.70073

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		UTERUS %
1M	Mean	--
	SD	--
	N	--
4M	Mean	--
	SD	--
	N	--
	%Diff G1	--

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	Mean	0.71639	--	0.02082	0.00665	--	0.00502	0.40028
	SD	0.02205	--	0.00159	0.00098	--	0.00098	0.02103
	N	5	--	5	5	--	5	5
4F	Mean	0.73426	--	0.02104	0.00648	--	0.00560	0.40556
	SD	0.03554	--	0.00207	0.00085	--	0.00134	0.02145
	N	5	--	5	5	--	5	5
	%Diff G1	2.49447	--	1.07119	-2.59630	--	11.40185	1.31762

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	Mean	0.61639	2.68590	0.41038	0.03107	0.21307	--	0.08720
	SD	0.04104	0.24659	0.02657	0.00213	0.03863	--	0.01273
	N	5	5	5	5	5	--	5
4F	Mean	0.65004	2.76315	0.44385	0.03469a	0.18714	--	0.09886
	SD	0.04968	0.24804	0.02210	0.00224	0.00672	--	0.01842
	N	5	5	5	5	5	--	5
	%Diff G1	5.45969	2.87593	8.15449	11.66056	-12.17210	--	13.37038

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

Appendix 17
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		UTERUS %
1F	Mean	0.29997
	SD	0.06697
	N	5
4F	Mean	0.25326
	SD	0.10576
	N	5
	%Diff G1	-15.57027

Appendix 17

Table 4
Summary of Organ Weights Relative to Brain Weight

Appendix 17
Table 4
Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	58.43048	2.56877	0.63189	63.92957	0.82923	69.38507	131.59128
	SD	10.36592	0.34790	0.10306	5.86889	0.13491	7.53941	14.18264
	N	10	10	10	10	10	10	10
2M	Mean	58.12737	2.74579	0.61060	68.98409	0.90849	69.86994	127.80296
	SD	3.39342	0.25553	0.02978	6.96295	0.15958	6.32831	10.40891
	N	10	10	10	10	10	10	10
	%Diff G1	-0.51875	6.89127	-3.36891	7.90640	9.55758	0.69881	-2.87886
3M	Mean	58.26681	2.51460	0.58614	60.75515	0.81593	71.61402	125.55304
	SD	5.58534	0.34411	0.06707	10.68102	0.16516	8.01674	9.49676
	N	10	10	10	10	10	10	10
	%Diff G1	-0.28011	-2.10848	-7.23873	-4.96550	-1.60451	3.21244	-4.58863
4M	Mean	59.10565	2.86010	0.62366	67.67879	0.79061	68.73378	125.43249
	SD	5.00105	0.40486	0.06534	8.92549	0.15087	13.61941	17.86434
	N	10	10	10	10	10	10	10
	%Diff G1	1.15551	11.34143	-1.30192	5.86462	-4.65790	-0.93867	-4.68024

Appendix 17
Table 4
Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	Mean	663.64960	72.51618	--	39.98047	181.62591	12.91193	--
	SD	87.90588	3.86731	--	5.46215	26.57291	4.71564	--
	N	10	10	--	10	10	10	--
2M	Mean	624.92811	74.95226	--	46.14616a	182.29351	11.68310	--
	SD	64.22077	4.64480	--	5.67522	12.50725	3.37021	--
	N	10	10	--	10	10	10	--
	%Diff G1	-5.83463	3.35937	--	15.42173	0.36757	-9.51699	--
3M	Mean	651.11198	72.69083	--	47.56096b	179.09881	12.58932	--
	SD	53.51486	3.68229	--	5.29009	21.30347	4.50173	--
	N	10	10	--	10	10	10	--
	%Diff G1	-1.88919	0.24085	--	18.96048	-1.39138	-2.49855	--
4M	Mean	579.68093a	71.33055	--	41.51064	181.43401	11.23056	--
	SD	64.86924	8.25916	--	5.13657	20.18247	3.12951	--
	N	10	10	--	10	10	10	--
	%Diff G1	-12.65256	-1.63499	--	3.82729	-0.10565	-13.02184	--

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

Appendix 17
Table 4
Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	Mean	--	3.06210	0.87327	--	0.73451	53.82632	84.17150
	SD	--	0.46578	0.10678	--	0.07886	9.05117	7.93479
	N	--	10	10	--	10	10	10
2F	Mean	--	3.16804	0.80482	--	0.75174	51.26894	86.60258
	SD	--	0.26463	0.11645	--	0.09640	4.58318	6.42504
	N	--	10	10	--	10	10	10
	%Diff G1	--	3.46000	-7.83820	--	2.34588	-4.75117	2.88825
3F	Mean	--	3.46723	0.92280	--	0.75205	55.26490	91.96422
	SD	--	0.32103	0.14976	--	0.12632	10.08733	14.45629
	N	--	10	10	--	10	10	10
	%Diff G1	--	13.23075	5.67205	--	2.38781	2.67263	9.25814
4F	Mean	--	3.78202c	0.82879	--	0.74926	51.75366	90.18250
	SD	--	0.40240	0.08429	--	0.09085	5.20025	8.68955
	N	--	10	10	--	10	10	10
	%Diff G1	--	23.51089	-5.09355	--	2.00724	-3.85066	7.14138

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

Appendix 17
Table 4
Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	Mean	366.88310	62.13918	4.64262	28.45229	--	13.00238	47.48035
	SD	33.29984	5.56008	0.86461	3.18335	--	3.68440	19.25288
	N	10	10	10	10	--	10	10
2F	Mean	379.18006	63.30948	5.01541	30.13125	--	13.30272	40.19658
	SD	44.74597	3.97354	0.84172	2.52160	--	2.56651	20.18249
	N	10	10	10	10	--	10	10
	%Diff G1	3.35174	1.88336	8.02956	5.90098	--	2.30990	-15.34060
3F	Mean	394.14917	61.32794	5.30740	31.44465	--	14.08900	39.34541
	SD	40.84579	6.34253	0.61004	4.63118	--	5.21191	13.43736
	N	10	10	10	10	--	10	10
	%Diff G1	7.43181	-1.30553	14.31898	10.51712	--	8.35709	-17.13329
4F	Mean	397.50848	61.23541	5.95925	30.45904	--	13.22056	35.47005
	SD	45.11941	4.00075	2.35097	6.13871	--	3.08817	10.98634
	N	10	10	10	10	--	10	10
	%Diff G1	8.34745	-1.45443	28.35948	7.05304	--	1.67799	-25.29532

Appendix 17
Table 4
Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	61.92680	2.31760	0.64166	64.45198	1.00633	81.92986	134.31782
	SD	4.73867	0.29128	0.12076	12.71134	0.10840	8.47394	8.74578
	N	5	5	5	5	5	5	5
4M	Mean	60.53180	2.24096	0.55152	65.19673	1.08078	73.24936	127.25629
	SD	3.94948	0.41136	0.02381	7.34191	0.18280	2.89577	4.93849
	N	5	5	5	5	5	5	5
	%Diff G1	-2.25265	-3.30723	-14.04782	1.15550	7.39775	-10.59504	-5.25733

Appendix 17
Table 4
Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	Mean	653.39562	71.10021	--	39.74637	196.44984	11.12392	--
	SD	66.29999	7.74978	--	6.73602	13.89181	1.68857	--
	N	5	5	--	5	5	5	--
4M	Mean	562.87479a	69.34746	--	39.34462	182.70536	9.11053	--
	SD	41.70097	3.32974	--	5.29581	12.32564	1.63516	--
	N	5	5	--	5	5	5	--
	%Diff G1	-13.85391	-2.46518	--	-1.01077	-6.99644	-18.09967	--

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

Appendix 17
Table 4
Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	Mean	--	2.90724	0.92889	--	0.70129	55.86351	86.18401
	SD	--	0.22860	0.13713	--	0.13802	2.01377	7.42311
	N	--	5	5	--	5	5	5
4F	Mean	--	2.87606	0.88073	--	0.75751	55.32276	88.78559
	SD	--	0.37586	0.08109	--	0.14286	3.75225	9.06251
	N	--	5	5	--	5	5	5
	%Diff G1	--	-1.07228	-5.18440	--	8.01740	-0.96798	3.01864

Appendix 17
Table 4
Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	Mean	375.28401	57.32449	4.33564	29.81401	--	12.18894	41.93994
	SD	37.44868	4.11251	0.23571	5.86362	--	1.85772	9.73526
	N	5	5	5	5	--	5	5
4F	Mean	377.55031	60.52735	4.73884	25.54137	--	13.56777	34.58361
	SD	44.58343	3.59670	0.45705	1.65109	--	3.08509	15.04117
	N	5	5	5	5	--	5	5
	%Diff G1	0.60389	5.58723	9.29980	-14.33097	--	11.31214	-17.54014

Appendix 17

Table 5
Summary of Microscopic Gradings by Organ/Group/Sex

Appendix 17

Summary of Microscopic Gradings by Organ/Group/Sex Explanation Page

Abbreviation	Description
GALT	Gut Associated Lymphoid Tissue

Appendix 17
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE MARROW								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	5	4	3	10	7	5	2
Increased cellularity; myeloid	0	5	6	7	0	3	5	8
.... minimal	0	5	6	7	0	3	5	8
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

Appendix 17
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
EPIDIDYMIS								
Examined	10	0	1	10	.	.	.	.
No Visible Lesions	9	.	0	10	.	.	.	.
Cellular debris	1	.	0	0	.	.	.	.
.... minimal	1	.	0	0	.	.	.	.
Decreased cellularity; lumen	1	.	1	0	.	.	.	.
.... moderate	1	.	0	0	.	.	.	.
.... marked	0	.	1	0	.	.	.	.
ESOPHAGUS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
EYE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Atrophy; retina	1	.	.	0	0	.	.	0
.... mild	1	.	.	0	0	.	.	0
GALT								
Examined	10	10	9	10	10	10	10	10
No Visible Lesions	10	10	9	10	10	10	10	10
Not Examined: Not Present In Section.	0	0	1	0	0	0	0	0

Appendix 17
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, ADRENAL								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	6	8	4	0	10	10	6	1
Hypertrophy; cortical	0	0	5	10	0	0	4	9
.... minimal	0	0	5	10	0	0	4	9
Vacuolation; cortical	4	2	1	2	0	0	0	0
.... minimal	4	2	1	2	0	0	0	0
GLAND, HARDERIAN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, MAMMARY								
Examined	7	0	0	7	10	0	0	10
No Visible Lesions	7	.	.	7	10	.	.	10
Not Examined: Not Present In Section.	3	0	0	3	0	0	0	0
GLAND, PARATHYROID								
Examined	10	0	0	9	10	0	0	6
No Visible Lesions	10	.	.	9	10	.	.	6
Not Examined: Not Present In Section.	0	0	0	1	0	0	0	4
GLAND, PITUITARY								
Examined	10	0	0	10	10	0	0	10

Appendix 17
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, PITUITARY (Continued...)								
No Visible Lesions	10	.	.	10	10	.	.	10
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	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
HEART								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	8	10	.	.	10
Infiltration, mixed cell; epicardial	0	.	.	1	0	.	.	0
.... minimal	0	.	.	1	0	.	.	0
Infiltration, mixed cell	1	.	.	1	0	.	.	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
HEART (Continued...)								
.... minimal	1	.	.	1	0	.	.	0
KIDNEY								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	4	.	.	8	9	.	.	10
Cast; hyaline	1	.	.	2	0	.	.	0
.... minimal	1	.	.	2	0	.	.	0
Infiltration, mixed cell; interstitial	1	.	.	1	0	.	.	0
.... minimal	1	.	.	1	0	.	.	0
Basophilia; tubular	3	.	.	2	0	.	.	0
.... minimal	3	.	.	2	0	.	.	0
Dilatation; pelvis	2	.	.	0	0	.	.	0
.... mild	2	.	.	0	0	.	.	0
Cyst	0	.	.	0	1	.	.	0
.... minimal	0	.	.	0	1	.	.	0
LARGE INTESTINE, CECUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
LARGE INTESTINE, COLON								
Examined	10	0	0	10	10	0	0	10

Appendix 17
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LARGE INTESTINE, COLON (Continued...)								
No Visible Lesions	10	.	.	10	10	.	.	10
LARGE INTESTINE, RECTUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	8	.	.	9	10	.	.	10
Parasitism; lumen	2	.	.	1	0	.	.	0
LIVER								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	9	7	9	6	9	5	7	5
Necrosis	1	0	0	2	0	0	0	0
.... mild	1	0	0	0	0	0	0	0
.... minimal	0	0	0	2	0	0	0	0
Hypertrophy; kupffer cell	0	2	1	2	0	2	2	5
.... minimal	0	2	1	2	0	2	2	4
.... mild	0	0	0	0	0	0	0	1
Tension lipidosis	0	0	1	1	1	3	2	1
.... minimal	0	0	1	1	1	3	2	1
Degeneration/necrosis; centrilobular	0	1	0	0	0	0	1	3
.... minimal	0	1	0	0	0	0	1	2
.... mild	0	0	0	0	0	0	0	1

Appendix 17
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LIVER (Continued...)								
Atrophy	0	0	0	0	0	1	0	0
.... mild	0	0	0	0	0	1	0	0
LUNG								
Examined	10	1	4	10	10	0	0	10
No Visible Lesions	7	1	1	5	7	.	.	10
Hemorrhage	3	0	2	3	0	.	.	0
.... minimal	3	0	2	2	0	.	.	0
.... mild	0	0	0	1	0	.	.	0
Macrophage aggregation	1	0	1	1	3	.	.	0
.... minimal	1	0	1	1	3	.	.	0
Inflammation, vascular	0	0	0	1	0	.	.	0
.... minimal	0	0	0	1	0	.	.	0
LYMPH NODE								
Examined	0	0	0	4	0	1	3	4
No Visible Lesions	.	.	.	0	.	0	0	0
Infiltration, mixed cell	.	.	.	4	.	1	3	4
.... minimal	.	.	.	1	.	1	1	0
.... mild	.	.	.	2	.	0	2	3
.... moderate	.	.	.	1	.	0	0	1

Appendix 17
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, INGUINAL								
Examined	10	9	8	10	10	10	10	10
No Visible Lesions	9	9	6	9	10	10	7	5
Not Examined: Not Present In Wet Tissues.	0	1	2	0	0	0	0	0
Erythrocytosis; sinus	1	0	1	0	0	0	2	1
.... minimal	1	0	1	0	0	0	2	1
Infiltration, mixed cell	0	0	1	1	0	0	1	5
.... minimal	0	0	1	1	0	0	1	4
.... mild	0	0	0	0	0	0	0	1
LYMPH NODE, MANDIBULAR								
Examined	10	1	0	10	10	0	0	10
No Visible Lesions	10	0	.	10	10	.	.	9
Plasmacytosis	0	1	.	0	0	.	.	1
.... minimal	0	1	.	0	0	.	.	1
Erythrocytosis; sinus	0	0	.	0	0	.	.	0
.... minimal	0	0	.	0	0	.	.	0
LYMPH NODE, MESENTERIC								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	7	6	6	10	8	6	2
Decreased cellularity; lymphoid, paracortex	0	3	4	4	0	2	4	8

Appendix 17
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, MESENTERIC (Continued...)								
.... minimal	0	3	4	4	0	2	4	8
LYMPH NODE, POPLITEAL								
Examined	10	9	9	10	10	10	10	10
No Visible Lesions	10	9	8	7	10	7	5	5
Not Examined: Not Present In Wet Tissues.	0	1	1	0	0	0	0	0
Infiltration, mixed cell	0	0	1	3	0	3	5	5
.... minimal	0	0	1	2	0	3	5	4
.... mild	0	0	0	1	0	0	0	1
Erythrocytosis; sinus	0	0	0	0	0	0	0	0
.... minimal	0	0	0	0	0	0	0	0
MUSCLE, SKELETAL								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	9	.	.	10
Degeneration; myofiber	1	.	.	0	1	.	.	0
.... minimal	1	.	.	0	1	.	.	0
NERVE, OPTIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
NERVE, SCIATIC								

Appendix 17
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
NERVE, SCIATIC (Continued...)								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
OVARY								
Examined	.	.	.	.	10	1	1	10
No Visible Lesions	.	.	.	.	9	1	0	9
Cyst	.	.	.	.	1	0	1	0
.... minimal	.	.	.	.	1	0	1	0
Dilatation; bursal	.	.	.	.	0	0	0	1
.... minimal	.	.	.	.	0	0	0	1
PANCREAS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SITE, INJECTION								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	6	0	0	1	5	0	0	0
Hemorrhage	1	1	5	3	0	1	0	0
.... minimal	1	1	0	3	0	1	0	0
.... moderate	0	0	2	0	0	0	0	0
.... mild	0	0	3	0	0	0	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SITE, INJECTION (Continued...)								
Degeneration/necrosis; myofiber	4	5	3	5	5	3	2	5
.... minimal	4	5	3	5	5	3	2	5
Inflammation	0	10	10	9	2	10	10	10
.... minimal	0	0	0	0	2	1	0	0
.... mild	0	5	1	2	0	3	1	0
.... moderate	0	5	6	4	0	6	3	2
.... marked	0	0	3	3	0	0	6	8
Degeneration/regeneration; myofiber	0	0	0	0	0	0	0	0
.... minimal	0	0	0	0	0	0	0	0
Infiltration, mononuclear cell	0	0	0	0	0	0	0	0
.... minimal	0	0	0	0	0	0	0	0
SKIN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	8	9	.	.	10
Hyperkeratosis	0	.	.	1	0	.	.	0
.... minimal	0	.	.	1	0	.	.	0
Inflammation	0	.	.	1	1	.	.	0
.... mild	0	.	.	0	1	.	.	0
.... moderate	0	.	.	1	0	.	.	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
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
Diverticulum	0	.	.	0	0	.	.	0
.... mild	0	.	.	0	0	.	.	0
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	10	.	.	10	10	.	.	10
SPINAL CORD, THORACIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SPLEEN								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	1	2	0	10	3	2	0
Decreased cellularity; lymphoid, periarteriolar lymphoid sheath	0	9	8	10	0	7	8	10
.... minimal	0	7	4	8	0	6	5	5
.... mild	0	2	4	2	0	1	3	5
Single cell necrosis; lymphoid	0	0	0	1	0	0	0	6
.... minimal	0	0	0	1	0	0	0	6
STOMACH								
Examined	10	0	2	10	10	1	0	10
No Visible Lesions	10	.	1	9	10	0	.	10
Hemorrhage	0	.	1	1	0	0	.	0
.... minimal	0	.	1	1	0	0	.	0
Diverticulum	0	.	0	0	0	1	.	0
.... mild	0	.	0	0	0	1	.	0
TESTIS								
Examined	10	0	1	10	.	.	.	.
No Visible Lesions	9	.	0	10	.	.	.	.
Degeneration/atrophy; seminiferous tubule	1	.	1	0	.	.	.	.

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
TESTIS (Continued...)								
.... marked	1	.	1	0	.	.	.	.
THYMUS								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	5	3	5	3	5	8	7	2
Hemorrhage	5	7	5	7	5	2	3	4
.... minimal	5	7	5	7	5	2	3	4
Decreased cellularity; lymphoid	0	0	0	1	0	0	0	0
.... minimal	0	0	0	1	0	0	0	0
Single cell necrosis; lymphoid	0	0	3	3	0	0	0	8
.... minimal	0	0	3	3	0	0	0	6
.... mild	0	0	0	0	0	0	0	2
TONGUE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
TRACHEA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
URINARY BLADDER								
Examined	10	0	0	10	10	0	0	10

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	100 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
URINARY BLADDER (Continued...)								
No Visible Lesions	10	.	.	10	10	.	.	10
UTERUS								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	9
Metaplasia, squamous	.	.	.	.	0	.	.	1
.... minimal	.	.	.	.	0	.	.	1
VAGINA								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
ARTERY, AORTA				
Examined	0	0	0	0
BONE MARROW				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Increased cellularity; myeloid	0	0	0	0
.... minimal	0	0	0	0
BONE, FEMUR				
Examined	0	0	0	0
BONE, STERNUM				
Examined	0	0	0	0
BRAIN				
Examined	0	0	0	0
CERVIX				
Examined	.	.	0	0
EPIDIDYMIS				
Examined	0	0	.	.
ESOPHAGUS				
Examined	0	0	0	0
EYE				
Examined	0	0	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
GALT				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Not Examined: Not Present In Section.	0	0	0	0
GLAND, ADRENAL				
Examined	5	5	5	5
No Visible Lesions	3	2	5	5
Hypertrophy; cortical	0	0	0	0
.... minimal	0	0	0	0
Vacuolation; cortical	2	3	0	0
.... minimal	2	3	0	0
GLAND, HARDERIAN				
Examined	0	0	0	0
GLAND, MAMMARY				
Examined	0	0	0	0
Not Examined: Not Present In Section.	0	0	0	0
GLAND, PARATHYROID				
Examined	0	0	0	0
Not Examined: Not Present In Section.	0	0	0	0
GLAND, PITUITARY				

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, PITUITARY (Continued...)				
Examined	0	0	0	0
GLAND, PROSTATE				
Examined	0	0	.	.
GLAND, SALIVARY, MANDIBULAR				
Examined	0	0	0	0
GLAND, SEMINAL VESICLE				
Examined	0	0	.	.
GLAND, THYROID				
Examined	0	0	0	0
HEART				
Examined	0	0	0	0
KIDNEY				
Examined	0	0	0	0
LARGE INTESTINE, CECUM				
Examined	0	0	0	0
LARGE INTESTINE, COLON				
Examined	0	0	0	0
LARGE INTESTINE, RECTUM				
Examined	0	0	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
LIVER				
Examined	5	5	5	5
No Visible Lesions	5	4	5	5
Necrosis	0	0	0	0
.... mild	0	0	0	0
.... minimal	0	0	0	0
Hypertrophy; kupffer cell	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Tension lipidosis	0	1	0	0
.... minimal	0	1	0	0
Degeneration/necrosis; centrilobular	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Atrophy	0	0	0	0
.... mild	0	0	0	0
LUNG				
Examined	1	2	0	0
No Visible Lesions	1	2	.	.
Hemorrhage	0	0	.	.

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
LUNG (Continued...)				
.... minimal	0	0	.	.
.... mild	0	0	.	.
Macrophage aggregation	0	0	.	.
.... minimal	0	0	.	.
Inflammation, vascular	0	0	.	.
.... minimal	0	0	.	.
LYMPH NODE				
Examined	2	0	0	0
No Visible Lesions	2	.	.	.
Infiltration, mixed cell	0	.	.	.
.... minimal	0	.	.	.
.... mild	0	.	.	.
.... moderate	0	.	.	.
LYMPH NODE, INGUINAL				
Examined	4	5	5	5
No Visible Lesions	4	5	5	5
Not Examined: Not Present In Wet Tissues.	1	0	0	0
Erythrocytosis; sinus	0	0	0	0
.... minimal	0	0	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, INGUINAL (Continued...)				
Infiltration, mixed cell	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
LYMPH NODE, MANDIBULAR				
Examined	0	1	1	2
No Visible Lesions	.	1	0	1
Plasmacytosis	.	0	0	1
.... minimal	.	0	0	1
Erythrocytosis; sinus	.	0	1	1
.... minimal	.	0	1	1
LYMPH NODE, MESENTERIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Decreased cellularity; lymphoid, paracortex	0	0	0	0
.... minimal	0	0	0	0
LYMPH NODE, POPLITEAL				
Examined	5	5	5	5
No Visible Lesions	5	5	5	4
Not Examined: Not Present In Wet Tissues.	0	0	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, POPLITEAL (Continued...)				
Infiltration, mixed cell	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Erythrocytosis; sinus	0	0	0	1
.... minimal	0	0	0	1
MUSCLE, SKELETAL				
Examined	0	0	0	0
NERVE, OPTIC				
Examined	0	0	0	0
NERVE, SCIATIC				
Examined	0	0	0	0
OVARY				
Examined	.	.	0	0
PANCREAS				
Examined	0	0	0	0
SITE, INJECTION				
Examined	5	5	5	5
No Visible Lesions	4	0	4	3
Hemorrhage	0	0	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
SITE, INJECTION (Continued...)				
.... minimal	0	0	0	0
.... moderate	0	0	0	0
.... mild	0	0	0	0
Degeneration/necrosis; myofiber	0	0	0	0
.... minimal	0	0	0	0
Inflammation	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
.... moderate	0	0	0	0
.... marked	0	0	0	0
Degeneration/regeneration; myofiber	1	1	0	0
.... minimal	1	1	0	0
Infiltration, mononuclear cell	0	5	1	2
.... minimal	0	5	1	2
SKIN				
Examined	0	0	0	0
SMALL INTESTINE, DUODENUM				
Examined	0	0	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
SMALL INTESTINE, ILEUM				
Examined	0	0	0	0
SMALL INTESTINE, JEJUNUM				
Examined	0	1	0	0
No Visible Lesions	.	0	.	.
Diverticulum	.	1	.	.
.... mild	.	1	.	.
SPINAL CORD, CERVICAL				
Examined	0	0	0	0
SPINAL CORD, LUMBAR				
Examined	0	0	0	0
SPINAL CORD, THORACIC				
Examined	0	0	0	0
SPLEEN				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Decreased cellularity; lymphoid, periarteriolar lymphoid sheath	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
SPLEEN (Continued...)				
Single cell necrosis; lymphoid	0	0	0	0
.... minimal	0	0	0	0
STOMACH				
Examined	0	0	0	0
TESTIS				
Examined	0	0	.	.
THYMUS				
Examined	5	5	5	5
No Visible Lesions	3	4	4	3
Hemorrhage	2	1	1	2
.... minimal	2	1	1	2
Decreased cellularity; lymphoid	0	0	0	0
.... minimal	0	0	0	0
Single cell necrosis; lymphoid	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
TONGUE				
Examined	0	0	0	0
TRACHEA				

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
TRACHEA (Continued...)				
Examined	0	0	0	0
URINARY BLADDER				
Examined	0	0	0	0
UTERUS				
Examined	.	.	0	0
VAGINA				
Examined	.	.	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002231

Key Page

Measurement/Statistics

Measurement	Descriptive	Comparative	Arithmetic/Adjusted	Transformation
Pathology Observation	Count Positives			

Group Information

Short Name	Long Name	Report Headings		
1	1	0	ug/dose	Group 1
2	2	10	ug/dose	Group 2
3	3	50	ug/dose	Group 3
4	4	100	ug/dose	Group 4

Removal Reason Grouping

Grouping Name	Abbreviation	Removal Reasons
TERMINAL EUTHANASIA	TERM	TERMINAL EUTHANASIA
RECOVERY EUTHANASIA	REC	RECOVERY EUTHANASIA

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Appendix 1
Individual Absolute Organ Weights

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Individual Absolute Organ Weights Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed	OPMP	Only one of the paired organs present – Macroscopic pathology
AVS	Suspected aberrant value	OPOP	Only one of the paired organs present
COME	See Comment Value Excluded	OUM	Organ unidentifiable macroscopically
COMI	See Comment Value Included	MPE	Macroscopic pathology – Excluded from mean
LIBW	Lung infused before weighing	MPI	Macroscopic pathology – Included in mean
NC	Not calculable	TERR	Technical error
OA	Omitted activity	UPTD	Unable to perform due to technical difficulty
ONP	Organ not present	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)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	1001	452	1.966	1.258	0.0463	0.0127	1.279	0.0195
	1002	424	2.070	0.677	0.0401	0.0102	1.225	0.0126
	1003	429	1.989	1.075	0.0508	0.0103	1.235	0.0190
	1004	523	2.119	1.328	0.0568	0.0142	1.101	0.0156
	1005	496	2.014	1.296	0.0652	0.0134	1.234	0.0177
	1006	533	2.210	1.393	0.0601	0.0171	1.584	0.0157
	1007	499	2.159	1.103	0.0552	0.0133	1.361	0.0148
	1008	500	2.121	1.267	0.0477	0.0105	1.503	0.0183
	1009	480	2.019	1.345	0.0522	0.0135	1.327	0.0178
	1010	578	2.069	1.367	0.0582	0.0160	1.416	0.0203
2M	2001	493	2.090	1.183	0.0593	0.0125	1.687	0.0188
	2002	424	2.005	1.096	0.0531	0.0124	1.269	0.0171
	2003	470	2.218	1.317	0.0643	0.0132	1.574	0.0168
	2004	439	1.879	1.064	0.0509	0.0119	1.184	0.0208
	2005	440	2.123	1.139	0.0557	0.0123	1.555	0.0267
	2006	443	2.110	1.276	0.0471	0.0136	1.429	0.0163
	2007	453	2.162	1.170	0.0600	0.0136	1.553	0.0176
	2008	478	2.020	1.247	0.0635	0.0121	1.450	0.0167
	2009	517	2.135	1.312	0.0645	0.0139	1.184	0.0205
	2010	430	2.079	1.301	0.0534	0.0116	1.493	0.0174

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	1001	1.431	2.440	15.296	1.372	--	0.710	3.678
	1002	1.218	2.226	11.003	1.353	--	0.666	2.415
	1003	1.262	2.221	16.353	1.375	--	0.734	3.337
	1004	1.503	2.894	13.655	1.497	--	0.883	4.205
	1005	1.346	2.786	12.671	1.544	--	0.827	4.130
	1006	1.703	3.107	13.065	1.702	--	1.002	4.134
	1007	1.442	2.834	14.099	1.565	--	0.763	3.600
	1008	1.455	3.018	13.536	1.595	--	0.788	3.916
	1009	1.283	2.613	12.503	1.460	--	0.883	4.156
	1010	1.759	3.189	15.094	1.584	--	1.041	4.075
2M	2001	1.607	2.786	12.315	1.644	--	0.873	3.689
	2002	1.261	2.366	11.370	1.554	--	0.909	3.502
	2003	1.393	2.756	13.988	1.595	--	0.872	3.983
	2004	1.360	2.413	12.420	1.478	--	0.852	3.291
	2005	1.285	2.352	12.919	1.427	--	0.918	3.739
	2006	1.417	2.653	14.452	1.565	--	0.938	3.651
	2007	1.583	2.642	11.509	1.469	--	1.048	3.799
	2008	1.500	2.873	12.845	1.635	--	1.005	3.801
	2009	1.684	3.100	16.123	1.650	--	1.278	4.565
	2010	1.449	2.659	12.151	1.564	--	0.913	3.954

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Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1M	1001	0.275	--
	1002	0.221	--
	1003	0.200	--
	1004	0.188	--
	1005	0.323	--
	1006	0.305	--
	1007	0.181	--
	1008	0.264	--
	1009	0.211	--
	1010	0.505	--
2M	2001	0.206	--
	2002	0.156	--
	2003	0.252	--
	2004	0.289	--
	2005	0.291	--
	2006	0.185	--
	2007	0.265	--
	2008	0.248	--
	2009	0.383	--
	2010	0.156	--

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Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
3M	3001	576	2.403	1.330	0.0678	0.0131	1.212	0.0207
	3002	466	2.106	1.321	0.0604	0.0143	1.459	0.0184
	3003	510	2.128	1.302	0.0588	0.0142	1.145	0.0143
	3004	432	2.100	1.354	0.0469	0.0108	1.427	0.0176
	3005	503	2.156	1.347	0.0518	0.0125	1.077	0.0169
	3006	466	2.019	1.228	0.0486	0.0118	1.445	0.0187
	3007	464	2.148	1.276	0.0549	0.0118	1.107	0.0157
	3008	419	2.155	1.191	0.0478	0.0120	1.731	0.0143
	3009	472	2.207	1.224	0.0657	0.0111	1.202	0.0262
	3010	442	2.169	0.987MPI	0.0412MPI	0.0148	1.263	0.0135
4M	4001	453	2.072	1.259	0.0642	0.0129	1.207	0.0224
	4002	487	2.226	1.288	0.0711	0.0152	1.645	0.0168
	4003	418	2.200	1.203	0.0534	0.0114	1.331	0.0188
	4004	428	2.224	1.267	0.0693	0.0144	1.361	0.0144
	4005	414	2.114	1.092	0.0532	0.0125	1.423	0.0178
	4006	398	2.132	1.346	0.0667	0.0113	1.452	0.0123
	4007	465	2.044	1.334	0.0605	0.0143	1.336	0.0182
	4008	489	2.073	1.388	0.0664	0.0143	1.852	0.0185
	4009	423	2.037	1.102	0.0601	0.0136	1.292	0.0147
	4010	420	2.078	1.240	0.0417	0.0122	1.442	0.0134

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Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
3M	3001	1.979	2.912	17.920	1.817	--	1.210	3.557
	3002	1.448	2.475	12.475	1.465	--	0.979	4.110
	3003	1.540	2.885	14.505	1.576	--	0.899	3.963
	3004	1.361	2.553	12.758	1.477	--	0.838	3.957
	3005	1.534	2.806	14.636	1.548	--	1.180	4.427
	3006	1.331	2.848	13.512	1.550	--	0.891	4.077
	3007	1.435	2.805	13.011	1.528	--	1.166	3.972
	3008	1.920	2.327	13.056	1.714	--	0.930	3.621
	3009	1.542	2.819	15.726	1.551	--	1.167	3.738
	3010	1.410	2.650	13.267	1.471	--	1.029	3.114MPI
4M	4001	1.547	2.366	11.237	1.425	--	0.898	3.889
	4002	1.614	3.136	13.542	1.539	--	0.905	3.905
	4003	1.281	2.316	11.540	1.420	--	0.858	3.701
	4004	1.351	2.583	11.950	1.523	--	0.824	3.806
	4005	1.351	2.550	12.324	1.396	--	0.964	3.512
	4006	1.208	2.337	9.748	1.332	--	0.795	4.005
	4007	2.121	2.842	13.241	1.755	--	1.087	4.436
	4008	1.392	3.371	13.191	1.792	--	0.860	4.272
	4009	1.262	2.322	12.056	1.461	--	0.723	3.011
	4010	1.408	2.742	13.883	1.451	--	0.873	3.885

Appendix 17
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
3M	3001	0.299	--
	3002	0.443	--
	3003	0.290	--
	3004	0.307	--
	3005	0.219	--
	3006	0.156	--
	3007	0.189	--
	3008	0.190	--
	3009	0.417	--
	3010	0.212	--
4M	4001	0.378	--
	4002	0.230	--
	4003	0.220	--
	4004	0.185MPI	--
	4005	0.227	--
	4006	0.169	--
	4007	0.302	--
	4008	0.245	--
	4009	0.188	--
	4010	0.227	--

Appendix 17
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1F	1501	252	2.037	--	0.0601	0.0172	--	0.0130
	1502	272	1.911	--	0.0525	0.0136	--	0.0164
	1503	234	1.915	--	0.0666	0.0161	--	0.0119
	1504	246	1.898	--	0.0728	0.0158	--	0.0133
	1505	266	1.934	--	0.0511	0.0182	--	0.0140
	1506	283	1.954	--	0.0597	0.0158	--	0.0140
	1507	233	1.897	--	0.0460	0.0174	--	0.0134
	1508	274	1.891	--	0.0624	0.0205	--	0.0154
	1509	252	1.931	--	0.0508	0.0151	--	0.0161
	1510	281	1.968	--	0.0700	0.0191	--	0.0144
2F	2501	251	1.883	--	0.0594	0.0193	--	0.0163
	2502	242	1.860	--	0.0559	0.0144	--	0.0123
	2503	246	1.822	--	0.0555	0.0133	--	0.0164
	2504	256	1.976	--	0.0725	0.0164	--	0.0162
	2505	255	1.937	--	0.0543	0.0121	--	0.0144
	2506	264	1.890	--	0.0665	0.0158	--	0.0130
	2507	270	2.051	--	0.0598	0.0145	--	0.0149
	2508	249	2.040	--	0.0629	0.0151	--	0.0125
	2509	248	1.972	--	0.0639	0.0185	--	0.0163
	2510	248	1.945	--	0.0631	0.0164	--	0.0131

Appendix 17
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	1501	0.993	1.580	6.304	1.121	0.092	0.480	--
	1502	1.036	1.626	7.037	1.202	0.092	0.580	--
	1503	1.436	1.434	6.359	1.026	0.075	0.491	--
	1504	0.888	1.661	6.857	1.171	0.072	0.443	--
	1505	0.993	1.765	8.442	1.391	0.094MPI	0.622	--
	1506	1.066	1.882	7.537	1.272	0.087	0.582	--
	1507	0.833	1.366	6.844	1.195	0.072	0.572	--
	1508	1.183	1.700	7.063	1.089	0.077	0.599	--
	1509	0.930	1.522	7.003	1.299	0.115	0.550	--
	1510	1.043	1.739	7.451	1.246	0.123	0.578	--
2F	2501	0.902	1.564	7.195	1.313	0.104	0.585	--
	2502	0.882	1.469	5.858	1.233	0.099	0.567	--
	2503	0.892	1.397	6.499MPI	1.132	0.086	0.490	--
	2504	1.155	1.860	7.537	1.257	0.110	0.594	--
	2505	0.914	1.755	8.409	1.264	0.104	0.602	--
	2506	1.096	1.762	7.587	1.251	0.077	0.682	--
	2507	1.143	1.940	9.548	1.322	0.138MPI	0.625	--
	2508	1.055	1.703	7.366	1.222	0.083	0.576	--
	2509	1.005	1.644	6.764	1.167	0.088	0.556	--
	2510	0.902	1.710	6.836	1.096	0.084	0.559	--

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1F	1501	0.196	0.349
	1502	0.242	1.123
	1503	0.201	0.709MPI
	1504	0.177	0.973
	1505	0.406	1.528
	1506	0.247	0.591
	1507	0.252	0.480
	1508	0.336	1.077
	1509	0.218	1.150
	1510	0.235	1.172
2F	2501	0.231	0.911
	2502	0.248	0.479
	2503	0.172	1.169
	2504	0.313	0.508
	2505	0.223	0.509
	2506	0.341	0.653
	2507	0.317	0.652
	2508	0.220	0.715
	2509	0.254	0.490
	2510	0.262	1.662

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
3F	3501	257	1.994	--	0.0688	0.0204	--	0.0121
	3502	260	1.951	--	0.0687	0.0152	--	0.0147
	3503	242	2.032	--	0.0586	0.0180	--	0.0171
	3504	260	1.968	--	0.0720	0.0203	--	0.0140
	3505	255	1.905	--	0.0605	0.0160	--	0.0157
	3506	271	1.939	--	0.0735	0.0179	--	0.0105
	3507	254	1.901	--	0.0610	0.0176	--	0.0150
	3508	286	1.804	--	0.0686	0.0226	--	0.0135
	3509	307	1.926	--	0.0639	0.0143	--	0.0192
	3510	260	1.965	--	0.0759	0.0162	--	0.0139
4F	4501	219	1.940	--	0.0700	0.0141	--	0.0149
	4502	234	1.886	--	0.0805	0.0144	--	0.0144
	4503	247	1.901	--	0.0630	0.0174	--	0.0164
	4504	283	1.924	--	0.0832	0.0148	--	0.0173
	4505	247	1.835	--	0.0714	0.0145	--	0.0108
	4506	249	1.792	--	0.0707	0.0130	--	0.0139
	4507	266	1.904	--	0.0741	0.0176	--	0.0134
	4508	274	1.904	--	0.0731	0.0181	--	0.0132
	4509	280	1.901	--	0.0569	0.0164	--	0.0146
	4510	243	1.896	--	0.0710	0.0163	--	0.0127

Appendix 17
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
3F	3501	0.888	1.665	7.603	1.183	0.109MPI	0.548	--
	3502	1.031	1.582	7.123	1.099	0.102	0.681	--
	3503	1.085	1.621	6.974	1.090	0.087	0.507	--
	3504	1.014	2.007	7.572	1.155	0.117	0.584	--
	3505	1.074	1.683	7.699	1.196	0.097	0.646	--
	3506	1.007	1.735	6.976	1.204	0.096	0.615	--
	3507	1.008	1.730	8.395	1.197	0.094	0.534	--
	3508	1.491	2.327	8.652	1.350	0.098	0.716	--
	3509	1.040	1.637	7.825	1.302	0.126	0.696	--
	3510	1.029	1.778	7.383	1.081	0.102	0.548	--
4F	4501	0.906	1.660	5.991	1.060	0.076	0.419	--
	4502	0.990	1.509	6.628	1.150	0.088	0.491	--
	4503	0.920	1.671	7.443	1.141	0.236MPI	0.463	--
	4504	1.177	1.718	7.668	1.229	0.092	0.698	--
	4505	0.812	1.596	7.981	1.068	0.099	0.534	--
	4506	0.963	1.742	7.824	1.129	0.103	0.687	--
	4507	1.068	1.748	7.295	1.091	0.110	0.610	--
	4508	1.065	2.120	8.814	1.175	0.106	0.731	--
	4509	0.980	1.617	8.054	1.308	0.103	0.638	--
	4510	0.895	1.643	7.271	1.210	0.112	0.472	--

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
3F	3501	0.171	0.493
	3502	0.246	1.000
	3503	0.247	0.980
	3504	0.223	0.559
	3505	0.338	0.550
	3506	0.317	0.457
	3507	0.146	0.538
	3508	0.467	0.953
	3509	0.257	1.033
	3510	0.299	1.054
4F	4501	0.180	0.488
	4502	0.261	0.475
	4503	0.206	0.603
	4504	0.375	0.680
	4505	0.229	0.519
	4506	0.253	0.569
	4507	0.236	1.128
	4508	0.320	0.637
	4509	0.245	0.649
	4510	0.191	0.956MPI

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Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	1011	522	1.994	1.378	0.0562	0.0136	1.648	0.0189
	1012	488	2.295	1.324	0.0496	0.0119	1.157	0.0235
	1013	494	2.093	1.335	0.0441	0.0123	1.139	0.0216
	1014	520	2.173	1.329	0.0505	0.0128	1.472	0.0252
	1015	536	2.154	1.247	0.0469	0.0179	1.444	0.0187
4M	4011	461	2.096	1.241	0.0455	0.0123	1.187	0.0177
	4012	476	2.144	1.309	0.0347	0.0117	1.292	0.0203
	4013	496	1.998	1.331	0.0517	0.0104	1.291	0.0255
	4014	450	2.123	1.275	0.0561	0.0118	1.598	0.0260
	4015	457	2.114	1.178	0.0462	0.0116	1.463	0.0235

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Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	1011	1.835	2.851	15.033	1.633	--	0.924	4.118
	1012	1.624	2.747	14.118	1.438	--	0.795	4.194
	1013	1.611	2.838	14.019	1.416	--	0.914	4.378
	1014	1.781	2.937	12.552	1.654	--	0.944	4.427
	1015	1.894	2.976	14.011	1.447	--	0.660	3.879
4M	4011	1.625	2.606	11.773	1.447	--	0.777	3.788
	4012	1.522	2.910	12.780	1.375	--	0.691	3.965
	4013	1.417	2.522	12.141	1.452	--	0.815	4.031
	4014	1.526	2.617	10.685	1.524	--	0.848	3.568
	4015	1.584	2.679	11.535	1.461	--	0.987	3.764

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Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1M	1011	0.221	--
	1012	0.261	--
	1013	0.239	--
	1014	0.185	--
	1015	0.285	--
4M	4011	0.178	--
	4012	0.204	--
	4013	0.205	--
	4014	0.140	--
	4015	0.226	--

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Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1F	1511	261	1.963	--	0.0546	0.0191	--	0.0137
	1512	265	1.841	--	0.0492	0.0201	--	0.0103
	1513	268	1.910	--	0.0587	0.0192	--	0.0124
	1514	274	1.971	--	0.0550	0.0159	--	0.0132
	1515	289	2.032	--	0.0654	0.0156	--	0.0189
4F	4511	271	1.933	--	0.0555	0.0159	--	0.0134
	4512	279	2.042	--	0.0516	0.0187	--	0.0132
	4513	291	2.019	--	0.0701	0.0176	--	0.0140
	4514	274	2.040	--	0.0597	0.0162	--	0.0153
	4515	254	2.001	--	0.0517	0.0200	--	0.0201

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Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	1511	1.120	1.464	6.766	1.117	0.087	0.547	--
	1512	1.048	1.566	7.200	1.174	0.083	0.644	--
	1513	1.106	1.711	8.277	1.001	0.079	0.434	--
	1514	1.066	1.715	7.120	1.104	0.090	0.528	--
	1515	1.084	1.924	7.032	1.169	0.082	0.746	--
4F	4511	1.182	1.752	7.058	1.280	0.103	0.491	--
	4512	1.085	2.040	8.599	1.176	0.089	0.546	--
	4513	1.115	1.900	8.644	1.226	0.103	0.545	--
	4514	1.141	1.660	6.887	1.241	0.094	0.525	--
	4515	1.024	1.559	6.719	1.146	0.086	0.457	--

Appendix 17
Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1F	1511	0.197	0.688
	1512	0.203	0.600
	1513	0.226	0.986
	1514	0.290	0.733
	1515	0.271	1.082
4F	4511	0.244	1.174
	4512	0.288	0.616
	4513	0.370	0.443
	4514	0.264	0.622
	4515	0.197	0.592

Appendix 17

Appendix 2
Individual Organ Weights Relative to Body Weight

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Individual Organ Weights Relative to Body Weight Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed	OPMP	Only one of the paired organs present – Macroscopic pathology
AVS	Suspected aberrant value	OPOP	Only one of the paired organs present
COME	See Comment Value Excluded	OUM	Organ unidentifiable macroscopically
COMI	See Comment Value Included	MPE	Macroscopic pathology – Excluded from mean
LIBW	Lung infused before weighing	MPI	Macroscopic pathology – Included in mean
NC	Not calculable	TERR	Technical error
OA	Omitted activity	UPTD	Unable to perform due to technical difficulty
ONP	Organ not present	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)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

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Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1001	0.4350	0.2783	0.01024	0.00281	0.2830	0.00431	0.3166
	1002	0.4882	0.1597	0.00946	0.00241	0.2889	0.00297	0.2873
	1003	0.4636	0.2506	0.01184	0.00240	0.2879	0.00443	0.2942
	1004	0.4052	0.2539	0.01086	0.00272	0.2105	0.00298	0.2874
	1005	0.4060	0.2613	0.01315	0.00270	0.2488	0.00357	0.2714
	1006	0.4146	0.2614	0.01128	0.00321	0.2972	0.00295	0.3195
	1007	0.4327	0.2210	0.01106	0.00267	0.2727	0.00297	0.2890
	1008	0.4242	0.2534	0.00954	0.00210	0.3006	0.00366	0.2910
	1009	0.4206	0.2802	0.01088	0.00281	0.2765	0.00371	0.2673
	1010	0.3580	0.2365	0.01007	0.00277	0.2450	0.00351	0.3043
2M	2001	0.4239	0.2400	0.01203	0.00254	0.3422	0.00381	0.3260
	2002	0.4729	0.2585	0.01252	0.00292	0.2993	0.00403	0.2974
	2003	0.4719	0.2802	0.01368	0.00281	0.3349	0.00357	0.2964
	2004	0.4280	0.2424	0.01159	0.00271	0.2697	0.00474	0.3098
	2005	0.4825	0.2589	0.01266	0.00280	0.3534	0.00607	0.2920
	2006	0.4763	0.2880	0.01063	0.00307	0.3226	0.00368	0.3199
	2007	0.4773	0.2583	0.01325	0.00300	0.3428	0.00389	0.3494
	2008	0.4226	0.2609	0.01328	0.00253	0.3033	0.00349	0.3138
	2009	0.4130	0.2538	0.01248	0.00269	0.2290	0.00397	0.3257
	2010	0.4835	0.3026	0.01242	0.00270	0.3472	0.00405	0.3370

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Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	1001	0.5398	3.3841	0.3035	--	0.1571	0.8137	0.0608
	1002	0.5250	2.5950	0.3191	--	0.1571	0.5696	0.0521
	1003	0.5177	3.8119	0.3205	--	0.1711	0.7779	0.0466
	1004	0.5533	2.6109	0.2862	--	0.1688	0.8040	0.0359
	1005	0.5617	2.5546	0.3113	--	0.1667	0.8327	0.0651
	1006	0.5829	2.4512	0.3193	--	0.1880	0.7756	0.0572
	1007	0.5679	2.8255	0.3136	--	0.1529	0.7214	0.0363
	1008	0.6036	2.7072	0.3190	--	0.1576	0.7832	0.0528
	1009	0.5444	2.6048	0.3042	--	0.1840	0.8658	0.0440
	1010	0.5517	2.6114	0.2740	--	0.1801	0.7050	0.0874
2M	2001	0.5651	2.4980	0.3335	--	0.1771	0.7483	0.0418
	2002	0.5580	2.6816	0.3665	--	0.2144	0.8259	0.0368
	2003	0.5864	2.9762	0.3394	--	0.1855	0.8474	0.0536
	2004	0.5497	2.8292	0.3367	--	0.1941	0.7497	0.0658
	2005	0.5345	2.9361	0.3243	--	0.2086	0.8498	0.0661
	2006	0.5989	3.2623	0.3533	--	0.2117	0.8242	0.0418
	2007	0.5832	2.5406	0.3243	--	0.2313	0.8386	0.0585
	2008	0.6010	2.6872	0.3421	--	0.2103	0.7952	0.0519
	2009	0.5996	3.1186	0.3191	--	0.2472	0.8830	0.0741
	2010	0.6184	2.8258	0.3637	--	0.2123	0.9195	0.0363

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Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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 17
Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
3M	3001	0.4172	0.2309	0.01177	0.00227	0.2104	0.00359	0.3436
	3002	0.4519	0.2835	0.01296	0.00307	0.3131	0.00395	0.3107
	3003	0.4173	0.2553	0.01153	0.00278	0.2245	0.00280	0.3020
	3004	0.4861	0.3134	0.01086	0.00250	0.3303	0.00407	0.3150
	3005	0.4286	0.2678	0.01030	0.00249	0.2141	0.00336	0.3050
	3006	0.4333	0.2635	0.01043	0.00253	0.3101	0.00401	0.2856
	3007	0.4629	0.2750	0.01183	0.00254	0.2386	0.00338	0.3093
	3008	0.5143	0.2842	0.01141	0.00286	0.4131	0.00341	0.4582
	3009	0.4676	0.2593	0.01392	0.00235	0.2547	0.00555	0.3267
	3010	0.4907	0.2233MPI	0.00932MPI	0.00335	0.2857	0.00305	0.3190
4M	4001	0.4574	0.2779	0.01417	0.00285	0.2664	0.00494	0.3415
	4002	0.4571	0.2645	0.01460	0.00312	0.3378	0.00345	0.3314
	4003	0.5263	0.2878	0.01278	0.00273	0.3184	0.00450	0.3065
	4004	0.5196	0.2960	0.01619	0.00336	0.3180	0.00336	0.3157
	4005	0.5106	0.2638	0.01285	0.00302	0.3437	0.00430	0.3263
	4006	0.5357	0.3382	0.01676	0.00284	0.3648	0.00309	0.3035
	4007	0.4396	0.2869	0.01301	0.00308	0.2873	0.00391	0.4561
	4008	0.4239	0.2838	0.01358	0.00292	0.3787	0.00378	0.2847
	4009	0.4816	0.2605	0.01421	0.00322	0.3054	0.00348	0.2983
	4010	0.4948	0.2952	0.00993	0.00290	0.3433	0.00319	0.3352

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Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
3M	3001	0.5056	3.1111	0.3155	--	0.2101	0.6175	0.0519
	3002	0.5311	2.6770	0.3144	--	0.2101	0.8820	0.0951
	3003	0.5657	2.8441	0.3090	--	0.1763	0.7771	0.0569
	3004	0.5910	2.9532	0.3419	--	0.1940	0.9160	0.0711
	3005	0.5579	2.9097	0.3078	--	0.2346	0.8801	0.0435
	3006	0.6112	2.8996	0.3326	--	0.1912	0.8749	0.0335
	3007	0.6045	2.8041	0.3293	--	0.2513	0.8560	0.0407
	3008	0.5554	3.1160	0.4091	--	0.2220	0.8642	0.0453
	3009	0.5972	3.3318	0.3286	--	0.2472	0.7919	0.0883
	3010	0.5995	3.0016	0.3328	--	0.2328	0.7045MPI	0.0480
4M	4001	0.5223	2.4806	0.3146	--	0.1982	0.8585	0.0834
	4002	0.6439	2.7807	0.3160	--	0.1858	0.8018	0.0472
	4003	0.5541	2.7608	0.3397	--	0.2053	0.8854	0.0526
	4004	0.6035	2.7921	0.3558	--	0.1925	0.8893	0.0432MPI
	4005	0.6159	2.9768	0.3372	--	0.2329	0.8483	0.0548
	4006	0.5872	2.4492	0.3347	--	0.1997	1.0063	0.0425
	4007	0.6112	2.8475	0.3774	--	0.2338	0.9540	0.0649
	4008	0.6894	2.6975	0.3665	--	0.1759	0.8736	0.0501
	4009	0.5489	2.8501	0.3454	--	0.1709	0.7118	0.0444
	4010	0.6529	3.3055	0.3455	--	0.2079	0.9250	0.0540

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 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	--

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	1501	0.8083	--	0.02385	0.00683	--	0.00516	0.3940
	1502	0.7026	--	0.01930	0.00500	--	0.00603	0.3809
	1503	0.8184	--	0.02846	0.00688	--	0.00509	0.6137
	1504	0.7715	--	0.02959	0.00642	--	0.00541	0.3610
	1505	0.7271	--	0.01921	0.00684	--	0.00526	0.3733
	1506	0.6905	--	0.02110	0.00558	--	0.00495	0.3767
	1507	0.8142	--	0.01974	0.00747	--	0.00575	0.3575
	1508	0.6901	--	0.02277	0.00748	--	0.00562	0.4318
	1509	0.7663	--	0.02016	0.00599	--	0.00639	0.3690
	1510	0.7004	--	0.02491	0.00680	--	0.00512	0.3712
2F	2501	0.7502	--	0.02367	0.00769	--	0.00649	0.3594
	2502	0.7686	--	0.02310	0.00595	--	0.00508	0.3645
	2503	0.7407	--	0.02256	0.00541	--	0.00667	0.3626
	2504	0.7719	--	0.02832	0.00641	--	0.00633	0.4512
	2505	0.7596	--	0.02129	0.00475	--	0.00565	0.3584
	2506	0.7159	--	0.02519	0.00598	--	0.00492	0.4152
	2507	0.7596	--	0.02215	0.00537	--	0.00552	0.4233
	2508	0.8193	--	0.02526	0.00606	--	0.00502	0.4237
	2509	0.7952	--	0.02577	0.00746	--	0.00657	0.4052
	2510	0.7843	--	0.02544	0.00661	--	0.00528	0.3637

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	1501	0.6270	2.5016	0.4448	0.0365	0.1905	--	0.0778
	1502	0.5978	2.5871	0.4419	0.0338	0.2132	--	0.0890
	1503	0.6128	2.7175	0.4385	0.0321	0.2098	--	0.0859
	1504	0.6752	2.7874	0.4760	0.0293	0.1801	--	0.0720
	1505	0.6635	3.1737	0.5229	0.0353MPI	0.2338	--	0.1526
	1506	0.6650	2.6633	0.4495	0.0307	0.2057	--	0.0873
	1507	0.5863	2.9373	0.5129	0.0309	0.2455	--	0.1082
	1508	0.6204	2.5777	0.3974	0.0281	0.2186	--	0.1226
	1509	0.6040	2.7790	0.5155	0.0456	0.2183	--	0.0865
	1510	0.6189	2.6516	0.4434	0.0438	0.2057	--	0.0836
2F	2501	0.6231	2.8665	0.5231	0.0414	0.2331	--	0.0920
	2502	0.6070	2.4207	0.5095	0.0409	0.2343	--	0.1025
	2503	0.5679	2.6419MPI	0.4602	0.0350	0.1992	--	0.0699
	2504	0.7266	2.9441	0.4910	0.0430	0.2320	--	0.1223
	2505	0.6882	3.2976	0.4957	0.0408	0.2361	--	0.0875
	2506	0.6674	2.8739	0.4739	0.0292	0.2583	--	0.1292
	2507	0.7185	3.5363	0.4896	0.0511MPI	0.2315	--	0.1174
	2508	0.6839	2.9582	0.4908	0.0333	0.2313	--	0.0884
	2509	0.6629	2.7274	0.4706	0.0355	0.2242	--	0.1024
	2510	0.6895	2.7565	0.4419	0.0339	0.2254	--	0.1056

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	UTERUS %
1F	1501	0.1385
	1502	0.4129
	1503	0.3030MPI
	1504	0.3955
	1505	0.5744
	1506	0.2088
	1507	0.2060
	1508	0.3931
	1509	0.4563
	1510	0.4171
2F	2501	0.3629
	2502	0.1979
	2503	0.4752
	2504	0.1984
	2505	0.1996
	2506	0.2473
	2507	0.2415
	2508	0.2871
	2509	0.1976
	2510	0.6702

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
3F	3501	0.7759	--	0.02677	0.00794	--	0.00471	0.3455
	3502	0.7504	--	0.02642	0.00585	--	0.00565	0.3965
	3503	0.8397	--	0.02421	0.00744	--	0.00707	0.4483
	3504	0.7569	--	0.02769	0.00781	--	0.00538	0.3900
	3505	0.7471	--	0.02373	0.00627	--	0.00616	0.4212
	3506	0.7155	--	0.02712	0.00661	--	0.00387	0.3716
	3507	0.7484	--	0.02402	0.00693	--	0.00591	0.3969
	3508	0.6308	--	0.02399	0.00790	--	0.00472	0.5213
	3509	0.6274	--	0.02081	0.00466	--	0.00625	0.3388
	3510	0.7558	--	0.02919	0.00623	--	0.00535	0.3958
4F	4501	0.8858	--	0.03196	0.00644	--	0.00680	0.4137
	4502	0.8060	--	0.03440	0.00615	--	0.00615	0.4231
	4503	0.7696	--	0.02551	0.00704	--	0.00664	0.3725
	4504	0.6799	--	0.02940	0.00523	--	0.00611	0.4159
	4505	0.7429	--	0.02891	0.00587	--	0.00437	0.3287
	4506	0.7197	--	0.02839	0.00522	--	0.00558	0.3867
	4507	0.7158	--	0.02786	0.00662	--	0.00504	0.4015
	4508	0.6949	--	0.02668	0.00661	--	0.00482	0.3887
	4509	0.6789	--	0.02032	0.00586	--	0.00521	0.3500
	4510	0.7802	--	0.02922	0.00671	--	0.00523	0.3683

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
3F	3501	0.6479	2.9584	0.4603	0.0424MPI	0.2132	--	0.0665
	3502	0.6085	2.7396	0.4227	0.0392	0.2619	--	0.0946
	3503	0.6698	2.8818	0.4504	0.0360	0.2095	--	0.1021
	3504	0.7719	2.9123	0.4442	0.0450	0.2246	--	0.0858
	3505	0.6600	3.0192	0.4690	0.0380	0.2533	--	0.1325
	3506	0.6402	2.5742	0.4443	0.0354	0.2269	--	0.1170
	3507	0.6811	3.3051	0.4713	0.0370	0.2102	--	0.0575
	3508	0.8136	3.0252	0.4720	0.0343	0.2503	--	0.1633
	3509	0.5332	2.5489	0.4241	0.0410	0.2267	--	0.0837
	3510	0.6838	2.8396	0.4158	0.0392	0.2108	--	0.1150
4F	4501	0.7580	2.7356	0.4840	0.0347	0.1913	--	0.0822
	4502	0.6449	2.8325	0.4915	0.0376	0.2098	--	0.1115
	4503	0.6765	3.0134	0.4619	0.0955MPI	0.1874	--	0.0834
	4504	0.6071	2.7095	0.4343	0.0325	0.2466	--	0.1325
	4505	0.6462	3.2312	0.4324	0.0401	0.2162	--	0.0927
	4506	0.6996	3.1422	0.4534	0.0414	0.2759	--	0.1016
	4507	0.6571	2.7425	0.4102	0.0414	0.2293	--	0.0887
	4508	0.7737	3.2168	0.4288	0.0387	0.2668	--	0.1168
	4509	0.5775	2.8764	0.4671	0.0368	0.2279	--	0.0875
	4510	0.6761	2.9922	0.4979	0.0461	0.1942	--	0.0786

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	UTERUS %
3F	3501	0.1918
	3502	0.3846
	3503	0.4050
	3504	0.2150
	3505	0.2157
	3506	0.1686
	3507	0.2118
	3508	0.3332
	3509	0.3365
	3510	0.4054
4F	4501	0.2228
	4502	0.2030
	4503	0.2441
	4504	0.2403
	4505	0.2101
	4506	0.2285
	4507	0.4241
	4508	0.2325
	4509	0.2318
	4510	0.3934MPI

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Appendix 2
Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1011	0.3820	0.2640	0.01077	0.00261	0.3157	0.00362	0.3515
	1012	0.4703	0.2713	0.01016	0.00244	0.2371	0.00482	0.3328
	1013	0.4237	0.2702	0.00893	0.00249	0.2306	0.00437	0.3261
	1014	0.4179	0.2556	0.00971	0.00246	0.2831	0.00485	0.3425
	1015	0.4019	0.2326	0.00875	0.00334	0.2694	0.00349	0.3534
4M	4011	0.4547	0.2692	0.00987	0.00267	0.2575	0.00384	0.3525
	4012	0.4504	0.2750	0.00729	0.00246	0.2714	0.00426	0.3197
	4013	0.4028	0.2683	0.01042	0.00210	0.2603	0.00514	0.2857
	4014	0.4718	0.2833	0.01247	0.00262	0.3551	0.00578	0.3391
	4015	0.4626	0.2578	0.01011	0.00254	0.3201	0.00514	0.3466

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Appendix 2
Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	1011	0.5462	2.8799	0.3128	--	0.1770	0.7889	0.0423
	1012	0.5629	2.8930	0.2947	--	0.1629	0.8594	0.0535
	1013	0.5745	2.8379	0.2866	--	0.1850	0.8862	0.0484
	1014	0.5648	2.4138	0.3181	--	0.1815	0.8513	0.0356
	1015	0.5552	2.6140	0.2700	--	0.1231	0.7237	0.0532
4M	4011	0.5653	2.5538	0.3139	--	0.1685	0.8217	0.0386
	4012	0.6113	2.6849	0.2889	--	0.1452	0.8330	0.0429
	4013	0.5085	2.4478	0.2927	--	0.1643	0.8127	0.0413
	4014	0.5816	2.3744	0.3387	--	0.1884	0.7929	0.0311
	4015	0.5862	2.5241	0.3197	--	0.2160	0.8236	0.0495

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Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	UTERUS %
1M	1011	--
	1012	--
	1013	--
	1014	--
	1015	--
4M	4011	--
	4012	--
	4013	--
	4014	--
	4015	--

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Appendix 2
Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	1511	0.7521	--	0.02092	0.00732	--	0.00525	0.4291
	1512	0.6947	--	0.01857	0.00758	--	0.00389	0.3955
	1513	0.7127	--	0.02190	0.00716	--	0.00463	0.4127
	1514	0.7193	--	0.02007	0.00580	--	0.00482	0.3891
	1515	0.7031	--	0.02263	0.00540	--	0.00654	0.3751
4F	4511	0.7133	--	0.02048	0.00587	--	0.00494	0.4362
	4512	0.7319	--	0.01849	0.00670	--	0.00473	0.3889
	4513	0.6938	--	0.02409	0.00605	--	0.00481	0.3832
	4514	0.7445	--	0.02179	0.00591	--	0.00558	0.4164
	4515	0.7878	--	0.02035	0.00787	--	0.00791	0.4031

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Appendix 2
Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	1511	0.5609	2.5923	0.4280	0.0333	0.2096	--	0.0755
	1512	0.5909	2.7170	0.4430	0.0313	0.2430	--	0.0766
	1513	0.6384	3.0884	0.3735	0.0295	0.1619	--	0.0843
	1514	0.6259	2.5985	0.4029	0.0328	0.1927	--	0.1058
	1515	0.6657	2.4332	0.4045	0.0284	0.2581	--	0.0938
4F	4511	0.6465	2.6044	0.4723	0.0380	0.1812	--	0.0900
	4512	0.7312	3.0821	0.4215	0.0319	0.1957	--	0.1032
	4513	0.6529	2.9704	0.4213	0.0354	0.1873	--	0.1271
	4514	0.6058	2.5135	0.4529	0.0343	0.1916	--	0.0964
	4515	0.6138	2.6453	0.4512	0.0339	0.1799	--	0.0776

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Appendix 2
Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	UTERUS %
1F	1511	0.2636
	1512	0.2264
	1513	0.3679
	1514	0.2675
	1515	0.3744
4F	4511	0.4332
	4512	0.2208
	4513	0.1522
	4514	0.2270
	4515	0.2331

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Appendix 3
Individual Organ Weights Relative to Brain Weight

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Individual Organ Weights Relative to Brain Weight Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed	OPMP	Only one of the paired organs present – Macroscopic pathology
AVS	Suspected aberrant value	OPOP	Only one of the paired organs present
COME	See Comment Value Excluded	OUM	Organ unidentifiable macroscopically
COMI	See Comment Value Included	MPE	Macroscopic pathology – Excluded from mean
LIBW	Lung infused before weighing	MPI	Macroscopic pathology – Included in mean
NC	Not calculable	TERR	Technical error
OA	Omitted activity	UPTD	Unable to perform due to technical difficulty
ONP	Organ not present	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)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

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Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1001	63.9878	2.35504	0.64598	65.0560	0.99186	72.7874	124.1099
	1002	32.7053	1.93720	0.49275	59.1787	0.60870	58.8406	107.5362
	1003	54.0473	2.55405	0.51785	62.0915	0.95525	63.4490	111.6642
	1004	62.6711	2.68051	0.67013	51.9585	0.73620	70.9297	136.5739
	1005	64.3496	3.23734	0.66534	61.2711	0.87885	66.8322	138.3317
	1006	63.0317	2.71946	0.77376	71.6742	0.71041	77.0588	140.5882
	1007	51.0885	2.55674	0.61603	63.0384	0.68550	66.7902	131.2645
	1008	59.7360	2.24894	0.49505	70.8628	0.86280	68.5997	142.2914
	1009	66.6171	2.58544	0.66865	65.7256	0.88162	63.5463	129.4205
	1010	66.0706	2.81295	0.77332	68.4389	0.98115	85.0169	154.1324
2M	2001	56.6029	2.83732	0.59809	80.7177	0.89952	76.8900	133.3014
	2002	54.6633	2.64838	0.61845	63.2918	0.85287	62.8928	118.0050
	2003	59.3778	2.89901	0.59513	70.9648	0.75744	62.8043	124.2561
	2004	56.6259	2.70889	0.63332	63.0122	1.10697	72.3789	128.4194
	2005	53.6505	2.62365	0.57937	73.2454	1.25765	60.5276	110.7866
	2006	60.4739	2.23223	0.64455	67.7251	0.77251	67.1564	125.7346
	2007	54.1166	2.77521	0.62905	71.8316	0.81406	73.2192	122.2017
	2008	61.7327	3.14356	0.59901	71.7822	0.82673	74.2574	142.2277
	2009	61.4520	3.02108	0.65105	55.4567	0.96019	78.8759	145.1991
	2010	62.5782	2.56854	0.55796	71.8134	0.83694	69.6970	127.8980

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Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	1001	778.0264	69.7864	--	36.1139	187.0804	13.9878	--
	1002	531.5459	65.3623	--	32.1739	116.6667	10.6763	--
	1003	822.1719	69.1302	--	36.9030	167.7728	10.0553	--
	1004	644.4077	70.6465	--	41.6706	198.4427	8.8721	--
	1005	629.1460	76.6634	--	41.0626	205.0645	16.0377	--
	1006	591.1765	77.0136	--	45.3394	187.0588	13.8009	--
	1007	653.0338	72.4873	--	35.3404	166.7439	8.3835	--
	1008	638.1895	75.2004	--	37.1523	184.6299	12.4470	--
	1009	619.2670	72.3130	--	43.7345	205.8445	10.4507	--
	1010	729.5312	76.5587	--	50.3142	196.9551	24.4079	--
2M	2001	589.2344	78.6603	--	41.7703	176.5072	9.8565	--
	2002	567.0823	77.5062	--	45.3367	174.6633	7.7805	--
	2003	630.6583	71.9116	--	39.3147	179.5762	11.3616	--
	2004	660.9899	78.6589	--	45.3433	175.1464	15.3805	--
	2005	608.5257	67.2162	--	43.2407	176.1187	13.7070	--
	2006	684.9289	74.1706	--	44.4550	173.0332	8.7678	--
	2007	532.3312	67.9463	--	48.4736	175.7169	12.2572	--
	2008	635.8911	80.9406	--	49.7525	188.1683	12.2772	--
	2009	755.1756	77.2834	--	59.8595	213.8173	17.9391	--
	2010	584.4637	75.2285	--	43.9153	190.1876	7.5036	--

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Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
3M	3001	55.3475	2.82147	0.54515	50.4370	0.86142	82.3554	121.1819
	3002	62.7255	2.86800	0.67901	69.2783	0.87369	68.7559	117.5214
	3003	61.1842	2.76316	0.66729	53.8064	0.67199	72.3684	135.5733
	3004	64.4762	2.23333	0.51429	67.9524	0.83810	64.8095	121.5714
	3005	62.4768	2.40260	0.57978	49.9536	0.78386	71.1503	130.1484
	3006	60.8222	2.40713	0.58445	71.5701	0.92620	65.9237	141.0599
	3007	59.4041	2.55587	0.54935	51.5363	0.73091	66.8063	130.5866
	3008	55.2668	2.21810	0.55684	80.3248	0.66357	89.0951	107.9814
	3009	55.4599	2.97689	0.50295	54.4631	1.18713	69.8686	127.7300
	3010	45.5048MPI	1.89949MPI	0.68234	58.2296	0.62241	65.0069	122.1761
4M	4001	60.7625	3.09846	0.62259	58.2529	1.08108	74.6622	114.1892
	4002	57.8616	3.19407	0.68284	73.8994	0.75472	72.5067	140.8805
	4003	54.6818	2.42727	0.51818	60.5000	0.85455	58.2273	105.2727
	4004	56.9694	3.11601	0.64748	61.1960	0.64748	60.7464	116.1421
	4005	51.6556	2.51656	0.59130	67.3132	0.84201	63.9073	120.6244
	4006	63.1332	3.12852	0.53002	68.1051	0.57692	56.6604	109.6154
	4007	65.2642	2.95988	0.69961	65.3620	0.89041	103.7671	139.0411
	4008	66.9561	3.20309	0.68982	89.3391	0.89243	67.1491	162.6146
	4009	54.0992	2.95042	0.66765	63.4266	0.72165	61.9539	113.9912
	4010	59.6728	2.00674	0.58710	69.3936	0.64485	67.7575	131.9538

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Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
3M	3001	745.7345	75.6138	--	50.3537	148.0233	12.4428	--
	3002	592.3552	69.5632	--	46.4862	195.1567	21.0351	--
	3003	681.6259	74.0602	--	42.2462	186.2312	13.6278	--
	3004	607.5238	70.3333	--	39.9048	188.4286	14.6190	--
	3005	678.8497	71.7996	--	54.7310	205.3340	10.1577	--
	3006	669.2422	76.7707	--	44.1308	201.9316	7.7266	--
	3007	605.7263	71.1359	--	54.2831	184.9162	8.7989	--
	3008	605.8469	79.5360	--	43.1555	168.0278	8.8167	--
	3009	712.5510	70.2764	--	52.8772	169.3702	18.8944	--
	3010	611.6644	67.8193	--	47.4412	143.5685MPI	9.7741	--
4M	4001	542.3263	68.7741	--	43.3398	187.6931	18.2432	--
	4002	608.3558	69.1375	--	40.6559	175.4268	10.3324	--
	4003	524.5455	64.5455	--	39.0000	168.2273	10.0000	--
	4004	537.3201	68.4802	--	37.0504	171.1331	8.3183MPI	--
	4005	582.9707	66.0360	--	45.6008	166.1306	10.7379	--
	4006	457.2233	62.4765	--	37.2889	187.8518	7.9268	--
	4007	647.7984	85.8611	--	53.1800	217.0254	14.7750	--
	4008	636.3242	86.4448	--	41.4858	206.0781	11.8186	--
	4009	591.8508	71.7231	--	35.4934	147.8154	9.2293	--
	4010	668.0943	69.8268	--	42.0115	186.9586	10.9240	--

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Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	1501	--	2.95042	0.84438	--	0.63819	48.7482	77.5650
	1502	--	2.74725	0.71167	--	0.85819	54.2125	85.0863
	1503	--	3.47781	0.84073	--	0.62141	74.9869	74.8825
	1504	--	3.83562	0.83246	--	0.70074	46.7861	87.5132
	1505	--	2.64219	0.94105	--	0.72389	51.3444	91.2616
	1506	--	3.05527	0.80860	--	0.71648	54.5548	96.3153
	1507	--	2.42488	0.91724	--	0.70638	43.9114	72.0084
	1508	--	3.29984	1.08408	--	0.81438	62.5595	89.8995
	1509	--	2.63076	0.78198	--	0.83376	48.1616	78.8193
	1510	--	3.55691	0.97053	--	0.73171	52.9980	88.3638
2F	2501	--	3.15454	1.02496	--	0.86564	47.9023	83.0589
	2502	--	3.00538	0.77419	--	0.66129	47.4194	78.9785
	2503	--	3.04610	0.72997	--	0.90011	48.9572	76.6740
	2504	--	3.66903	0.82996	--	0.81984	58.4514	94.1296
	2505	--	2.80330	0.62468	--	0.74342	47.1864	90.6040
	2506	--	3.51852	0.83598	--	0.68783	57.9894	93.2275
	2507	--	2.91565	0.70697	--	0.72647	55.7289	94.5880
	2508	--	3.08333	0.74020	--	0.61275	51.7157	83.4804
	2509	--	3.24037	0.93813	--	0.82657	50.9635	83.3671
	2510	--	3.24422	0.84319	--	0.67352	46.3753	87.9177

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Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	1501	309.4747	55.0319	4.5164	23.5641	--	9.6220	17.1330
	1502	368.2365	62.8990	4.8142	30.3506	--	12.6635	58.7650
	1503	332.0627	53.5770	3.9164	25.6397	--	10.4961	37.0235MPI
	1504	361.2750	61.6965	3.7935	23.3404	--	9.3256	51.2645
	1505	436.5047	71.9235	4.8604MPI	32.1613	--	20.9928	79.0072
	1506	385.7216	65.0972	4.4524	29.7851	--	12.6407	30.2456
	1507	360.7802	62.9942	3.7955	30.1529	--	13.2841	25.3031
	1508	373.5061	57.5886	4.0719	31.6764	--	17.7684	56.9540
	1509	362.6618	67.2708	5.9555	28.4827	--	11.2895	59.5546
	1510	378.6077	63.3130	6.2500	29.3699	--	11.9411	59.5528
2F	2501	382.1030	69.7292	5.5231	31.0674	--	12.2677	48.3802
	2502	314.9462	66.2903	5.3226	30.4839	--	13.3333	25.7527
	2503	356.6959MPI	62.1295	4.7201	26.8935	--	9.4402	64.1603
	2504	381.4271	63.6134	5.5668	30.0607	--	15.8401	25.7085
	2505	434.1249	65.2555	5.3691	31.0790	--	11.5126	26.2777
	2506	401.4286	66.1905	4.0741	36.0847	--	18.0423	34.5503
	2507	465.5290	64.4564	6.7284MPI	30.4729	--	15.4559	31.7894
	2508	361.0784	59.9020	4.0686	28.2353	--	10.7843	35.0490
	2509	343.0020	59.1785	4.4625	28.1947	--	12.8803	24.8479
	2510	351.4653	56.3496	4.3188	28.7404	--	13.4704	85.4499

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Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
3F	3501	--	3.45035	1.02307	--	0.60682	44.5336	83.5005
	3502	--	3.52127	0.77909	--	0.75346	52.8447	81.0866
	3503	--	2.88386	0.88583	--	0.84154	53.3957	79.7736
	3504	--	3.65854	1.03150	--	0.71138	51.5244	101.9817
	3505	--	3.17585	0.83990	--	0.82415	56.3780	88.3465
	3506	--	3.79061	0.92316	--	0.54152	51.9340	89.4791
	3507	--	3.20884	0.92583	--	0.78906	53.0247	91.0047
	3508	--	3.80266	1.25277	--	0.74834	82.6497	128.9911
	3509	--	3.31776	0.74247	--	0.99688	53.9979	84.9948
	3510	--	3.86260	0.82443	--	0.70738	52.3664	90.4835
4F	4501	--	3.60825	0.72680	--	0.76804	46.7010	85.5670
	4502	--	4.26829	0.76352	--	0.76352	52.4920	80.0106
	4503	--	3.31405	0.91531	--	0.86270	48.3956	87.9011
	4504	--	4.32432	0.76923	--	0.89917	61.1746	89.2931
	4505	--	3.89101	0.79019	--	0.58856	44.2507	86.9755
	4506	--	3.94531	0.72545	--	0.77567	53.7388	97.2098
	4507	--	3.89181	0.92437	--	0.70378	56.0924	91.8067
	4508	--	3.83929	0.95063	--	0.69328	55.9349	111.3445
	4509	--	2.99316	0.86270	--	0.76802	51.5518	85.0605
	4510	--	3.74473	0.85970	--	0.66983	47.2046	86.6561

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1706 10 µg/dose
Group 3 - mRNA-1706 50 µg/dose
Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
3F	3501	381.2939	59.3280	5.4664MPI	27.4824	--	8.5757	24.7242
	3502	365.0948	56.3301	5.2281	34.9052	--	12.6089	51.2558
	3503	343.2087	53.6417	4.2815	24.9508	--	12.1555	48.2283
	3504	384.7561	58.6890	5.9451	29.6748	--	11.3313	28.4045
	3505	404.1470	62.7822	5.0919	33.9108	--	17.7428	28.8714
	3506	359.7731	62.0939	4.9510	31.7174	--	16.3486	23.5688
	3507	441.6097	62.9669	4.9448	28.0905	--	7.6802	28.3009
	3508	479.6009	74.8337	5.4324	39.6896	--	25.8869	52.8271
	3509	406.2825	67.6012	6.5421	36.1371	--	13.3437	53.6345
	3510	375.7252	55.0127	5.1908	27.8880	--	15.2163	53.6387
4F	4501	308.8144	54.6392	3.9175	21.5979	--	9.2784	25.1546
	4502	351.4316	60.9756	4.6660	26.0339	--	13.8388	25.1856
	4503	391.5308	60.0210	12.4145MPI	24.3556	--	10.8364	31.7201
	4504	398.5447	63.8773	4.7817	36.2786	--	19.4906	35.3430
	4505	434.9319	58.2016	5.3951	29.1008	--	12.4796	28.2834
	4506	436.6071	63.0022	5.7478	38.3371	--	14.1183	31.7522
	4507	383.1408	57.3004	5.7773	32.0378	--	12.3950	59.2437
	4508	462.9202	61.7122	5.5672	38.3929	--	16.8067	33.4559
	4509	423.6718	68.8059	5.4182	33.5613	--	12.8880	34.1399
	4510	383.4916	63.8186	5.9072	24.8945	--	10.0738	50.4219MPI

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1011	69.1073	2.81846	0.68205	82.6479	0.94784	92.0261	142.9789
	1012	57.6906	2.16122	0.51852	50.4139	1.02397	70.7625	119.6950
	1013	63.7840	2.10702	0.58767	54.4195	1.03201	76.9709	135.5948
	1014	61.1597	2.32398	0.58905	67.7405	1.15969	81.9604	135.1588
	1015	57.8923	2.17734	0.83101	67.0381	0.86815	87.9294	138.1616
4M	4011	59.2080	2.17080	0.58683	56.6317	0.84447	77.5286	124.3321
	4012	61.0541	1.61847	0.54571	60.2612	0.94683	70.9888	135.7276
	4013	66.6166	2.58759	0.52052	64.6146	1.27628	70.9209	126.2262
	4014	60.0565	2.64249	0.55582	75.2708	1.22468	71.8794	123.2690
	4015	55.7237	2.18543	0.54872	69.2053	1.11164	74.9290	126.7266

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	1011	753.9117	81.8957	--	46.3390	206.5196	11.0832	--
	1012	615.1634	62.6580	--	34.6405	182.7451	11.3725	--
	1013	669.8041	67.6541	--	43.6694	209.1734	11.4190	--
	1014	577.6346	76.1160	--	43.4422	203.7276	8.5136	--
	1015	650.4643	67.1773	--	30.6407	180.0836	13.2312	--
4M	4011	561.6889	69.0363	--	37.0706	180.7252	8.4924	--
	4012	596.0821	64.1325	--	32.2295	184.9347	9.5149	--
	4013	607.6577	72.6727	--	40.7908	201.7518	10.2603	--
	4014	503.2972	71.7852	--	39.9435	168.0641	6.5944	--
	4015	545.6481	69.1107	--	46.6887	178.0511	10.6906	--

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	1511	--	2.78146	0.97300	--	0.69791	57.0555	74.5797
	1512	--	2.67246	1.09180	--	0.55948	56.9256	85.0625
	1513	--	3.07330	1.00524	--	0.64921	57.9058	89.5812
	1514	--	2.79046	0.80670	--	0.66971	54.0842	87.0117
	1515	--	3.21850	0.76772	--	0.93012	53.3465	94.6850
4F	4511	--	2.87118	0.82256	--	0.69322	61.1485	90.6363
	4512	--	2.52693	0.91577	--	0.64643	53.1342	99.9021
	4513	--	3.47202	0.87172	--	0.69341	55.2254	94.1060
	4514	--	2.92647	0.79412	--	0.75000	55.9314	81.3725
	4515	--	2.58371	0.99950	--	1.00450	51.1744	77.9110

Appendix 17
Appendix 3
Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1706 100 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	1511	344.6765	56.9027	4.4320	27.8655	--	10.0357	35.0484
	1512	391.0918	63.7697	4.5084	34.9810	--	11.0266	32.5910
	1513	433.3508	52.4084	4.1361	22.7225	--	11.8325	51.6230
	1514	361.2380	56.0122	4.5662	26.7884	--	14.7133	37.1892
	1515	346.0630	57.5295	4.0354	36.7126	--	13.3366	53.2480
4F	4511	365.1319	66.2183	5.3285	25.4009	--	12.6229	60.7346
	4512	421.1068	57.5906	4.3585	26.7385	--	14.1038	30.1665
	4513	428.1327	60.7231	5.1015	26.9936	--	18.3259	21.9416
	4514	337.5980	60.8333	4.6078	25.7353	--	12.9412	30.4902
	4515	335.7821	57.2714	4.2979	22.8386	--	9.8451	29.5852

Appendix 17

Appendix 4
Individual Gross and Microscopic Findings

Appendix 17

Individual Gross and Microscopic Findings Explanation Page

Abbreviation	Description	Abbreviation	Description
AB	Abdominal region	LJ	Lower jaw
AX	Axillary region	LN	Lymph node
BC	Body cavity	LT	Left
BI	Bilateral	LU	Lumbar region
CGEP	Complete gross examination performed	MF	Multifocal
CR	Cranium	MU	Muzzle
DC	Dorsal cervical region	NBF	Neutral buffered formalin
DT	Dorsal thoracic region	Ø	In diameter
F	Focal	PO	Periorbital region
FL	Forelimb	RT	Right
FP	Forepaw	SA	Sacral region
G	Gross Pathology	SC	Scapular region
GALT	Gut associated lymphoid tissue	SI	Small intestine
GL	Gland	SR	Scrotum
HL	Hindlimb	TGL	Trackable Gross Lesion
HP	Hindpaw	UG	Urogenital region
IG	Inguinal region	VC	Ventral cervical region
IS	Interscapular region	VT	Ventral thoracic region
LI	Large Intestine		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study:

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1706	10
3	mRNA-1706	50
4	mRNA-1706	100

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Appendix 4

Individual Gross and Microscopic Findings
5002231

Animal:	1001	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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 : Vacuolation; cortical, bilateral, minimal
KIDNEY : Infiltration, mixed cell; interstitial, unilateral, focal, minimal
LUNG : Hemorrhage; focal, 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; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002231

Animal:	1002	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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)
THYMUS : Focus; dark : 2, right (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EPIDIDYMIS : Cellular debris; bilateral, minimal
EPIDIDYMIS : Decreased cellularity; unilateral, moderate, lumen
GLAND, ADRENAL : Vacuolation; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Basophilia; tubular, unilateral, focal, minimal
LUNG : Hemorrhage; multifocal, minimal
LUNG : Macrophage aggregation; multifocal, minimal
TESTIS : Degeneration/atrophy; bilateral, diffuse, marked, seminiferous tubule
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G) | THYMUS : Focus; dark : 2, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; ESOPHAGUS; EYE; GALT; 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; LIVER; 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; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

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Appendix 4

Individual Gross and Microscopic Findings
5002231

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal:	1003	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EYE : Atrophy; unilateral, focal, mild, retina
GLAND, ADRENAL : Vacuolation; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Basophilia; tubular, bilateral, multifocal, minimal
LYMPH NODE, INGUINAL : Erythrocytosis; minimal, sinus
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; GALT; 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; LIVER; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	1004	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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 : Cast; hyaline, unilateral, multifocal, minimal
KIDNEY : Dilatation; bilateral, mild, pelvis
LARGE INTESTINE, RECTUM : Parasitism; lumen
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
THYMUS : Hemorrhage; multifocal, 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, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002231

Animal:	1005	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LARGE INTESTINE, RECTUM : Parasite : 1
SITE, INJECTION : Focus; dark : 1, left (TGL)
THYMUS : Focus; dark : >10, left lobe (TGL)

Any remaining study plan 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 : Basophilia; tubular, bilateral, multifocal, minimal
LARGE INTESTINE, RECTUM : Parasitism; lumen
SITE, INJECTION : Hemorrhage; focal, minimal : subcutis [SITE, INJECTION : Focus; dark : 1, left (G)]
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, left lobe (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; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002231

Animal:	1006	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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)

Any remaining study plan 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
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002231

Animal:	1007	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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 : Dilatation; bilateral, mild, pelvis
MUSCLE, SKELETAL : Degeneration; focal, minimal, myofiber

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; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002231

Animal:	1008	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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, left lateral, near hilus, right lateral (TGL)

Any remaining study plan 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; focal, mild : with hemorrhage/inflammation [LIVER : Focus; pale : 1, left lateral, near hilus, right lateral (G)]

THYMUS : Hemorrhage; multifocal, 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; 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; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002231

Animal:	1009	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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 : Vacuolation; cortical, bilateral, minimal
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber

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, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; 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:

GLAND, MAMMARY - Not Present In Section.

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Appendix 4

Individual Gross and Microscopic Findings
5002231

Animal:	1010	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : 8, left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

HEART : Infiltration, mixed cell; focal, minimal : with degeneration
LUNG : Hemorrhage; multifocal, minimal
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 8, left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal: 1011	Group: 1		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal 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, right cranial (TGL)

Any remaining study plan 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 : Vacuolation; cortical, bilateral, minimal
THYMUS : Hemorrhage; multifocal, minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1, right cranial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	1012	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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 study plan 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]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, INGUINAL - Not Present In Wet Tissues.

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Individual Gross and Microscopic Findings
5002231

Animal: 1013	Group: 1		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal 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 study plan 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 : Vacuolation; cortical, bilateral, minimal
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 1014	Group: 1		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal 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 : Pancreatic, axillary left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Degeneration/regeneration; focal, minimal, myofiber
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : Pancreatic, axillary left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	1015	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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; pale : >10, bilateral (TGL)
LIVER : Focus; pale : 1, fissure, medial lobe (TGL)
LYMPH NODE : Enlargement : Axillary left (TGL)

Any remaining study plan 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]:

NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, medial lobe (G) | GLAND, ADRENAL : Focus; pale : >10, bilateral (G) | LYMPH NODE : Enlargement : Axillary left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 1501	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal 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)

Any remaining study plan 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; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LUNG : Macrophage aggregation; focal, minimal
SITE, INJECTION : Degeneration/necrosis; multifocal, 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, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; 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

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Individual Gross and Microscopic Findings
5002231

Animal:	1502	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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
THYMUS : Hemorrhage; multifocal, 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; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	1503	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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:

UTERUS : Small : Horn left (TGL)
UTERUS : Thin : Horn left (TGL)

Any remaining study plan 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
LUNG : Macrophage aggregation; focal, minimal
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
NO CORRELATE : No correlating lesion [UTERUS : Small : Horn left (G) | UTERUS : Thin : Horn left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; 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

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Individual Gross and Microscopic Findings
5002231

Animal:	1504	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan 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]:

THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	1505	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LUNG : Focus; dark : 1 to >10 (TGL)
OVARY : Cyst; pale : 1, left (TGL)

Any remaining study plan 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
OVARY : Cyst; unilateral, focal, minimal [OVARY : Cyst; pale : 1, left (G)]
THYMUS : Hemorrhage; focal, minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G) | LUNG : Focus; dark : 1 to >10 (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; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	1506	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 lobe. (TGL)

Any remaining study plan 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
MUSCLE, SKELETAL : Degeneration; focal, minimal, myofiber
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, left lobe. (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; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	1507	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Degeneration/necrosis; focal, minimal, myofiber
SITE, INJECTION : Inflammation; 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; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	1508	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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 : Cyst; unilateral, focal, minimal
NERVE, OPTIC : One Of A Pair Available For Evaluation.
NERVE, OPTIC : Examined
SITE, INJECTION : Degeneration/necrosis; focal, minimal, myofiber
SITE, INJECTION : Inflammation; 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; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 1509	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal 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 : >10, left lobe (TGL)
SKIN : Scab; dark : 5, cranium (TGL)

Any remaining study plan 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
LUNG : Macrophage aggregation; multifocal, minimal [LUNG : Focus; pale : >10, left lobe (G)]
SKIN : Inflammation; regionally extensive, mild : with epidermal hyperplasia, swelling and crust [SKIN : Scab; dark : 5, cranium (G)]
THYMUS : Hemorrhage; multifocal, 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; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	1510	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; 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

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Individual Gross and Microscopic Findings
5002231

Animal: 1511	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal 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 study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Infiltration, mononuclear cell; focal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 1512	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal 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 study plan 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]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 1513	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal 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 study plan 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]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 1514	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal 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 study plan 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]:

THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 1515	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal 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 : 1 to 3, bilateral (TGL)
LYMPH NODE, MANDIBULAR : Enlargement : Left (TGL)

Any remaining study plan 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]:

LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : 1 to 3, bilateral (G)]

NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Enlargement : Left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2001	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Focus; dark : 3, left (TGL)

Any remaining study plan 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 : Degeneration/necrosis; centrilobular, multifocal, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Focus; dark : 3, left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2002	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)

Any remaining study plan 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 : Hypertrophy; minimal, kupffer cell
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2003	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
THYMUS : Focus; dark : 4 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 4 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2004	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Enlargement : bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Vacuolation; cortical, bilateral, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; minimal [LYMPH NODE, MANDIBULAR : Enlargement : bilateral (G)]
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2005	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 4 (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : left (G) | LUNG : Focus; dark : 1 to 4 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2006	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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 cellularity; myeloid, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, INGUINAL - Not Present In Wet Tissues.

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Individual Gross and Microscopic Findings
5002231

Animal: 2007	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
SITE, INJECTION : Focus; dark : 5, left (TGL)
THYMUS : Focus; dark : >10, left lobe (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
SITE, INJECTION : Hemorrhage; multifocal, minimal [SITE, INJECTION : Focus; dark : 5, left (G)]
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : >10, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2008	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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 cellularity; myeloid, minimal
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2009	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2010	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
THYMUS : Focus; dark : 1, left (TGL)

Any remaining study plan 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 : Vacuolation; cortical, bilateral, minimal
LIVER : Hypertrophy; minimal, kupffer cell : with pigment
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 1, left (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, POPLITEAL - Not Present In Wet Tissues.

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Individual Gross and Microscopic Findings
5002231

Animal: 2501	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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, left (TGL)
LYMPH NODE : Enlargement : Iliac left (TGL)

Any remaining study plan 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]:

LYMPH NODE : Infiltration, mixed cell; minimal : with hemorrhage [LYMPH NODE : Enlargement : Iliac left (G)]
SITE, INJECTION : Inflammation; moderate
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Focus; dark : 1, left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2502	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Swelling : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
LIVER : Hypertrophy; minimal, kupffer cell
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Hemorrhage; multifocal, minimal
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Swelling : left (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, medial lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2503	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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, papillary process of caudate. fissure, right medial (TGL)
LIVER : Small : Papillary process of caudate (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan 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; focal, minimal [LIVER : Focus; pale : 1, papillary process of caudate. fissure, right medial (G)]
LIVER : Atrophy; mild : with atrophy [LIVER : Small : Papillary process of caudate (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2504	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Swelling : left (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, medial lobe (G)]
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2505	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]

SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2506	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan 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 : Hypertrophy; minimal, kupffer cell
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2507	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Left (TGL)
OVARY : Cyst; pale : 1, left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
STOMACH : Nodule; [a] : 1, pale, firm, mucosa, glandular (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
STOMACH : Diverticulum; focal, mild [STOMACH : Nodule; [a] : 1, pale, firm, mucosa, glandular (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : Left (G) | OVARY : Cyst; pale : 1, left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; OVARY; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal: 2508	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan 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]:

LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; focal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2509	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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, left medial (TGL)

Any remaining study plan 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; focal, minimal [LIVER : Focus; pale : 1, fissure, left medial (G)]
SITE, INJECTION : Inflammation; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 2510	Group: 2	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Inflammation; minimal
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 3001	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Focus; dark : 3, left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Material accumulation; clot : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Hemorrhage; focal, moderate [SITE, INJECTION : Material accumulation; clot : left (G)]
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Focus; dark : 3, left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 3002	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1 to 3 (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
STOMACH : Focus; depressed : 2, dark, linear, mucosa, glandular (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LUNG : Hemorrhage; multifocal, minimal [LUNG : Focus; dark : 1 to 3 (G)]
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [STOMACH : Focus; depressed : 2, dark, linear, mucosa, glandular (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; STOMACH; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal: 3003	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 >10 (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
THYMUS : Focus; dark : 2, right lobe (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
LIVER : Hypertrophy; minimal, kupffer cell
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LUNG : Macrophage aggregation; multifocal, minimal
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 2, right lobe (G)]
THYMUS : Single cell necrosis; lymphoid, minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 2 to >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal: 3004	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining study plan 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 : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE, INGUINAL : Infiltration, mixed cell; minimal [LYMPH NODE, INGUINAL : Enlargement : left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal
THYMUS : Single cell necrosis; lymphoid, minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; LIVER; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal: 3005	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal: 3006	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Material accumulation; clot : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Hemorrhage; focal, moderate [SITE, INJECTION : Material accumulation; clot : left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 3007	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1 to 3 (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE, INGUINAL : Erythrocytosis; minimal, sinus
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Hemorrhage; multifocal, mild
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1 to 3 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; LIVER; LUNG; LYMPH NODE, MESENTERIC; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal: 3008	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : 2, left lobe (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LUNG : Hemorrhage; focal, minimal [LUNG : Focus; dark : 2, left lobe (G)]
SITE, INJECTION : Hemorrhage; multifocal, mild
SITE, INJECTION : Inflammation; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, MESENTERIC; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

GALT - Not Present In Section.
LYMPH NODE, INGUINAL - Not Present In Wet Tissues.
LYMPH NODE, POPLITEAL - Not Present In Wet Tissues.

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Individual Gross and Microscopic Findings
5002231

Animal: 3009	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
STOMACH : Focus; dark : >10, mucosa, glandular (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G)]
STOMACH : Hemorrhage; multifocal, minimal [STOMACH : Focus; dark : >10, mucosa, glandular (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; LIVER; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, INGUINAL - Not Present In Wet Tissues.

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Individual Gross and Microscopic Findings
5002231

Animal: 3010	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
GLAND, ADRENAL : Small : bilateral (TGL)
GLAND, ADRENAL : Focus; pale : >10, bilateral (TGL)
LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
TESTIS : Abnormal consistency; soft : left (TGL)
TESTIS : Small : left (TGL)
TESTIS : Focus; pale : 2, left (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan 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 : Decreased cellularity; unilateral, marked, lumen [EPIDIDYMIS : Small : left (G)]
GLAND, ADRENAL : Vacuolation; cortical, bilateral, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Hemorrhage; multifocal, mild
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath
TESTIS : Degeneration/atrophy; unilateral, diffuse, marked, seminiferous tubule [TESTIS : Abnormal consistency; soft : left (G) | TESTIS : Small : left (G) | TESTIS : Focus; pale : 2, left (G)]
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10 (G)]
THYMUS : Single cell necrosis; lymphoid, minimal
NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Small : bilateral (G) | GLAND, ADRENAL : Focus; pale : >10, bilateral (G) | LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

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Individual Gross and Microscopic Findings
5002231

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	3501	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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:

OVARY : Cyst; pale : 1, right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)
THYMUS : Focus; dark : 3, left lobe (TGL)

Any remaining study plan 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 : Hypertrophy; minimal, kupffer cell
LIVER : Degeneration/necrosis; centrilobular, multifocal, minimal
OVARY : Cyst; unilateral, focal, minimal [OVARY : Cyst; pale : 1, right (G)]
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : 3, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 3502	Group: 3	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 3503	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 50 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal 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 : Left (TGL)

Any remaining study plan 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]:

LYMPH NODE, INGUINAL : Infiltration, mixed cell; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : Left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, MESENTERIC; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 3504	Group: 3	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	3505	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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, INGUINAL : Focus; dark : 1 to 2, bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE, INGUINAL : Erythrocytosis; minimal, sinus [LYMPH NODE, INGUINAL : Focus; dark : 1 to 2, bilateral (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; LIVER; LYMPH NODE, MESENTERIC; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	3506	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
THYMUS : Focus; dark : >10, left lobe (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal:	3507	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan 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; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE : Infiltration, mixed cell; mild : iliac left [LYMPH NODE : Enlargement : Iliac left (G)]
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 3508	Group: 3	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining study plan 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 : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE : Infiltration, mixed cell; minimal : iliac left [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, INGUINAL : Erythrocytosis; minimal, sinus
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; LIVER; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 3509	Group: 3	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Enlargement : Iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LIVER : Hypertrophy; minimal, kupffer cell
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LYMPH NODE : Infiltration, mixed cell; mild : iliac left [LYMPH NODE : Enlargement : Iliac left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

GALT; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 3510	Group: 3	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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]:

LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Inflammation; moderate
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4001	Group: 4		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 100 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal 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 : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SKIN : Scab; dark : 1, hindlimb right, adjacent to injection site right (TGL)

Any remaining study plan 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 : Hypertrophy; cortical, bilateral, minimal
HEART : Infiltration, mixed cell; focal, minimal
LIVER : Necrosis; multifocal, minimal : subcapsular
LIVER : Hypertrophy; minimal, kupffer cell
LUNG : Inflammation, vascular; multifocal, minimal
LYMPH NODE : Infiltration, mixed cell; mild : iliac left [LYMPH NODE : Enlargement : iliac left (G)]
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SKIN : Inflammation; regionally extensive, moderate : with epidermal hyperplasia/crust [SKIN : Scab; dark : 1, hindlimb right, adjacent to injection site right (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002231

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; GLAND, THYROID; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; 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

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Individual Gross and Microscopic Findings
5002231

Animal: 4002	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
KIDNEY : Cast; hyaline, unilateral, focal, minimal
KIDNEY : Infiltration, mixed cell; interstitial, unilateral, focal, minimal
KIDNEY : Basophilia; tubular, bilateral, multifocal, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
SITE, INJECTION : Hemorrhage; multifocal, minimal
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath : with pigment
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002231

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; 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; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; 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; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal: 4003	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LIVER : Necrosis; multifocal, minimal : subcapsular
LYMPH NODE : Infiltration, mixed cell; mild : iliac left [LYMPH NODE : Enlargement : iliac left (G)]
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10 (G)]
THYMUS : Single cell necrosis; lymphoid, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; 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; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4004	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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, left lobe (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : 1, right (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Focus; dark : 1, left (TGL)
THYMUS : Focus; dark : 4, right (TGL)
THYMUS : Small : right (TGL)

Any remaining study plan 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 : Hypertrophy; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
HEART : Infiltration, mixed cell; epicardial, focal, minimal
LARGE INTESTINE, RECTUM : Parasitism; lumen
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (G)]

LUNG : Hemorrhage; focal, minimal [LUNG : Focus; dark : 1, left lobe (G)]
SITE, INJECTION : Hemorrhage; multifocal, minimal [SITE, INJECTION : Focus; dark : 1, left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 4, right (G)]
THYMUS : Decreased cellularity; lymphoid, minimal [THYMUS : Small : right (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : 1, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002231

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal: 4005	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 3, right middle, left lobe (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
STOMACH : Hemorrhage; multifocal, minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G) | LUNG : Focus; dark : 2 to 3, right middle, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; 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; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

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Individual Gross and Microscopic Findings
5002231

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4006	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LUNG : Hemorrhage; focal, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath
SPLEEN : Single cell necrosis; lymphoid, minimal
THYMUS : Hemorrhage; multifocal, minimal
THYMUS : Single cell necrosis; lymphoid, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; 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; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; 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; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal: 4007	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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, left lobe, right middle, right caudal, right accessory (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
SITE, INJECTION : Focus; dark : 1 (TGL)
STOMACH : Focus; dark : 3, mucosa, glandular (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Cast; hyaline, unilateral, focal, minimal
KIDNEY : Basophilia; tubular, unilateral, focal, minimal
LIVER : Hypertrophy; minimal, kupffer cell
LUNG : Hemorrhage; multifocal, mild [LUNG : Focus; dark : 1 to 2, left lobe, right middle, right caudal, right accessory (G)]
LYMPH NODE : Infiltration, mixed cell; minimal : iliac left [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, INGUINAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Hemorrhage; multifocal, minimal [SITE, INJECTION : Focus; dark : 1 (G)]
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
NO CORRELATE : No correlating lesion [STOMACH : Focus; dark : 3, mucosa, glandular (G)]

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Individual Gross and Microscopic Findings
5002231

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; 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; 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; 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

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Individual Gross and Microscopic Findings
5002231

Animal: 4008	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining study plan 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 : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
THYMUS : Hemorrhage; multifocal, minimal
THYMUS : Single cell necrosis; lymphoid, 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, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; 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; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal: 4009	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1 to 3 (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
GLAND, ADRENAL : Vacuolation; cortical, bilateral, minimal
LUNG : Macrophage aggregation; multifocal, minimal
LYMPH NODE : Infiltration, mixed cell; moderate : iliac left [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1 to 3 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; 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; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

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Individual Gross and Microscopic Findings
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None

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Individual Gross and Microscopic Findings
5002231

Animal: 4010	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SKIN : Scab; dark : 1, tail, tip (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
GLAND, ADRENAL : Vacuolation; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SKIN : Hyperkeratosis; focal, minimal : tail [SKIN : Scab; dark : 1, tail, tip (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; 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; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; 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; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

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Individual Gross and Microscopic Findings
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None

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Individual Gross and Microscopic Findings
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Animal: 4011	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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 study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4012	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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, right middle, right caudal, right accessory (TGL)

Any remaining study plan 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 : Vacuolation; cortical, bilateral, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1, right middle, right caudal, right accessory (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal: 4013	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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 middle, right caudal (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan 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 : Vacuolation; cortical, bilateral, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
SITE, INJECTION : Degeneration/regeneration; multifocal, minimal, myofiber
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal : with fibrosis
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10 (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : >10, right (G) | LUNG : Focus; dark : 1, right middle, right caudal (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4014	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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; pale : >10, bilateral (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal
NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Focus; pale : >10, bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4015	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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:

SMALL INTESTINE, JEJUNUM : Diverticulum : 1, caudal (TGL)

Any remaining study plan 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 : Vacuolation; cortical, bilateral, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal
SMALL INTESTINE, JEJUNUM : Diverticulum; mild [SMALL INTESTINE, JEJUNUM : Diverticulum : 1, caudal (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4501	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Hypertrophy; mild, kupffer cell : with pigment
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Degeneration/necrosis; centrilobular, multifocal, mild
LYMPH NODE : Infiltration, mixed cell; mild : iliac left [LYMPH NODE : Enlargement : Iliac left (G)]
LYMPH NODE, INGUINAL : Infiltration, mixed cell; minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; marked
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath : with pigment
SPLEEN : Single cell necrosis; lymphoid, minimal
THYMUS : Single cell necrosis; lymphoid, mild
UTERUS : Metaplasia, squamous; focal, minimal : endometrial gland

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002231

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, 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; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4502	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Hypertrophy; minimal, kupffer cell : with pigment
LIVER : Degeneration/necrosis; centrilobular, multifocal, minimal
LYMPH NODE, INGUINAL : Infiltration, mixed cell; minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath : with pigment
SPLEEN : Single cell necrosis; lymphoid, minimal
THYMUS : Single cell necrosis; lymphoid, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002231

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; 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; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4503	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Enlargement : Iliac left (TGL)
OVARY : Cyst; pale : 1, left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LIVER : Hypertrophy; minimal, kupffer cell
LYMPH NODE : Infiltration, mixed cell; mild : iliac left [LYMPH NODE : Enlargement : Iliac left (G)]
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
OVARY : Dilatation; bursal, unilateral, minimal [OVARY : Cyst; pale : 1, left (G)]
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

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Individual Gross and Microscopic Findings
5002231

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal: 4504	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : >10 (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining study plan 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 : Hypertrophy; cortical, bilateral, minimal
LIVER : Hypertrophy; minimal, kupffer cell : with pigment
LIVER : Degeneration/necrosis; centrilobular, multifocal, minimal [LIVER : Focus; pale : >10 (G)]
LYMPH NODE, INGUINAL : Infiltration, mixed cell; minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath : with pigment
SPLEEN : Single cell necrosis; lymphoid, minimal
THYMUS : Single cell necrosis; lymphoid, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; 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; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4505	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Enlargement : Iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE : Infiltration, mixed cell; moderate : iliac left [LYMPH NODE : Enlargement : Iliac left (G)]
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
THYMUS : Single cell necrosis; lymphoid, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal: 4506	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LYMPH NODE, INGUINAL : Erythrocytosis; minimal, sinus
LYMPH NODE, INGUINAL : Infiltration, mixed cell; minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
THYMUS : Hemorrhage; multifocal, minimal
THYMUS : Single cell necrosis; lymphoid, minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002231

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR; 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; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4507	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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, left lobe (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath : with pigment
SPLEEN : Single cell necrosis; lymphoid, minimal
THYMUS : Hemorrhage; multifocal, minimal
THYMUS : Single cell necrosis; lymphoid, minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; 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; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

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Individual Gross and Microscopic Findings
5002231

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4508	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
THYMUS : Focus; dark : >10, left lobe (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Hypertrophy; minimal, kupffer cell
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
SPLEEN : Single cell necrosis; lymphoid, minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, left lobe (G)]
THYMUS : Single cell necrosis; lymphoid, mild

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002231

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; 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

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Individual Gross and Microscopic Findings
5002231

Animal: 4509	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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 : Enlargement : Iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan 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 : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE : Infiltration, mixed cell; mild : iliac left [LYMPH NODE : Enlargement : Iliac left (G)]
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation; marked [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath : with pigment

Histo Pathology - The following Tissues were Within Normal Limits:

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; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; 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; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal: 4510	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal 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, left (TGL)
LIVER : Focus; pale : >10 (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
THYMUS : Focus; dark : 6, left (TGL)
UTERUS : Nodule; [a] : 1, pale, firm, wall, horn left (TGL)

Any remaining study plan 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 cellularity; myeloid, minimal
GLAND, ADRENAL : Hypertrophy; cortical, bilateral, minimal
LYMPH NODE, INGUINAL : Infiltration, mixed cell; mild [LYMPH NODE, INGUINAL : Enlargement : left (G)]
LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, minimal, paracortex
SITE, INJECTION : Degeneration/necrosis; multifocal, minimal, myofiber
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath : with pigment
SPLEEN : Single cell necrosis; lymphoid, minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 6, left (G)]
THYMUS : Single cell necrosis; lymphoid, minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : >10 (G) | GLAND, ADRENAL : Focus; dark : 1, left (G) | UTERUS : Nodule; [a] : 1, pale, firm, wall, horn left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002231

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR; 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; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

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Individual Gross and Microscopic Findings
5002231

Animal: 4511	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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 : 1 to 4, bilateral (TGL)

Any remaining study plan 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]:

NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Focus; dark : 1 to 4, bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4512	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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 : Left (TGL)

Any remaining study plan 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]:

LYMPH NODE, POPLITEAL : Erythrocytosis; minimal, sinus
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal
THYMUS : Hemorrhage; multifocal, minimal
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4513	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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 : 1 to 2, bilateral (TGL)
LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (TGL)

Any remaining study plan 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]:

LYMPH NODE, MANDIBULAR : Plasmacytosis; minimal [LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (G)]

LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal, sinus [LYMPH NODE, MANDIBULAR : Focus; dark : 1 to 2, bilateral (G)]

SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4514	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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 study plan 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]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Animal: 4515	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 100 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal 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 study plan 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]:

THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GALT; GLAND, ADRENAL; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002231

Key Page

Codes

(TGL) = Trackable Gross Lesion, (MPF) = Major Pathological Finding, (?) = Questionable, (E) = Excluded,
(C) = Clinical Observation, (M) = Mass, (G) = Gross Pathology, (H) = Histo Pathology

Group Information

Short Name	Long Name
1	1
2	2
3	3
4	4

Appendix 18

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messenger therapeutics

Toxicology/Pathology Department
200 Tech Square • Cambridge, MA 02139
Phone 617-714-6500 • Fax 617-583-1998

PEER-REVIEW STATEMENT

Study Number: 5002231

Study Title: A 1 Month (3 doses) Intramuscular Injection Vaccine Study of mRNA-1706 in Sprague-Dawley Rats With a 2-Week Recovery Period.

EXPERIMENTAL DESIGN:

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1706	10	200	0.05	10	10	-	-
3	mRNA-1706	50	200	0.25	10	10	-	-
4	mRNA-1706	100	200	0.5	10	10	5	5

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: 1002,1005,1008,1013,1503,1507, 4002, 4005, 4008, 4501, 4506, 4509.
3. The following organs from all animals in all Groups (including recovery) were reviewed: Bone Marrow, Injection Site, Adrenal, Thymus, Lymph node mesenteric and Spleen. Sciatic nerve in Groups 1 and 4 male and Liver in Groups 1 and 4 male, Group 4 female and recovery animals from both sexes.
4. 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)

Date : November 07 2017

(b) (6)

Date : 23-NOV-2017