charles river

FINAL REPORT

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 Doses) Intramuscular Injection Toxicity 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: 5002045

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

QA INSPECTION DATES

		Dates Findings Submitted to:	
Date(s) of Audit	Phase(s) Audited	Study Director	Study Director Management
04-Oct-2016 - 05-Oct-2016	Final Study Plan	05-Oct-2016	05-Oct-2016
18-Oct-2016	Study Plan Amendment 1	19-Oct-2016	19-Oct-2016
20-Oct-2016	Addition of Study Plan to Provantis	20-Oct-2016	20-Oct-2016
21-Oct-2016	Dose Preparation	21-Oct-2016	21-Oct-2016
16-Nov-2016	Study Plan Amendment 2	16-Nov-2016	16-Nov-2016
18-Nov-2016	Necropsy	18-Nov-2016	18-Nov-2016
21-Nov-2016	Coagulation Analysis	21-Nov-2016	21-Nov-2016
08-Dec-2016	Sample Transfer	08-Dec-2016	08-Dec-2016
13-Dec-2016	Study Plan Amendment 3	13-Dec-2016	13-Dec-2016
16-Jan-2017 - 18-Jan-2017	Data Review - Animal Care	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Shipping/Receiving	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Veterinary Services	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Clinical Pathology	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Formulations	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Technical Operations	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Report Preparation	19-Jan-2017	19-Jan-2017
18-Jan-2017	Draft Phase Report - Ophthalmology	19-Jan-2017	19-Jan-2017
18-Jan-2017	Draft Report - Materials and Methods	20-Jan-2017	20-Jan-2017
25-Jan-2017	Study Plan Amendment 4	25-Jan-2017	25-Jan-2017
27-Jan-2017 - 30-Jan-2017	Data Review - Analytical Chemistry	31-Jan-2017	31-Jan-2017
27-Jan-2017 - 30-Jan-2017	Draft Phase Report - Dose Formulation Analysis	31-Jan-2017	31-Jan-2017
14-Feb-2017	Data Review - Bioanalysis & Immunology	15-Feb-2017	15-Feb-2017
14-Feb-2017	Draft Phase Report - Immunology	15-Feb-2017	15-Feb-2017
15-Feb-2017 - 16-Feb-2017	Data Review - Shipping/Receiving	17-Feb-2017	17-Feb-2017
15-Feb-2017 - 16-Feb-2017	Data Review - Histology	17-Feb-2017	17-Feb-2017
15-Feb-2017 - 16-Feb-2017	Data Review - Necropsy	17-Feb-2017	17-Feb-2017
15-Feb-2017 - 16-Feb-2017	Report Preparation	17-Feb-2017	17-Feb-2017
16-Feb-2017	Study Plan Amendment 5	16-Feb-2017	16-Feb-2017
22-Feb-2017 - 23-Feb-2017	Draft Report - Results	23-Feb-2017	23-Feb-2017
12-May-2017	Study Plan Amendment 6	15-May-2017	15-May-2017

QUALITY ASSURANCE STATEMENT - Study Number: 5002045

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
24-May-2017	Report Preparation	25-May-2017	25-May-2017
24-May-2017	Final Report	25-May-2017	25-May-2017
02-Jun-2017	Revised Draft Phase Report - Immunology	02-Jun-2017	02-Jun-2017
05-Jun-2017	Final Phase Report - Dose Formulation Analysis	05-Jun-2017	05-Jun-2017
24-Oct-2017	Final Report	25-Oct-2017	25-Oct-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 Quality Assurance Statements for the work conducted at the Test Sites were reviewed and are included in the appropriate section of this report.

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

(b) (6)

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01Nov2017

Date

COMPLIANCE STATEMENT

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

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

Exceptions from the above regulations are listed below:

- Characterization of the Test Item was performed by the Sponsor 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 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: 01 Nov 2017

(b) (6)

1. RESPONSIBLE PERSONNEL

1.1. Test Facility

Study Director (b) (6)

Test Facility Management (b) (6)

1.2. Individual Scientists (IS) at Test Facility

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

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

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

Immunology
(Cytokine Analysis)
(b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke, QC, Canada

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

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

1.4. PIs at Sponsor-designated Test Site

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

2. SUMMARY

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 study design was as follows:

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level[a,b] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[b] (mg/mL)	Number of Animal			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1706	10 / 13	200	0.05 / 0.07	10	10	-	-
3	mRNA-1706	50 / 65	200	0.25 / 0.33	10	10	-	-
4	mRNA-1706	100 / 129	200	0.5 / 0.65	10	10	5	5

- = Not applicable

[a] The End-of-use bulk Test Item purity analysis indicated RNA degradation while the concentration and particle size analysis were within specification. Study animals showed a significant average antibody response against the ZIKV lysate and increased average antibody titers following the final dose indicating that the potential decrease in purity did not affect activity. As the original doses were not adjusted for purity of the drug product, but based on total mRNA concentration, the nominal dose levels were maintained in the report, tables and appendices.

[b] Values based on Summary of Analysis (SoA) issued on 11 Oct 2016 / Values based on SoA issued on 03 May 2017 (Refer to memorandum in Appendix 2).

The following parameters and end points were evaluated in this study: mortality, clinical signs, local irritation, body weights, food consumption, ophthalmology, clinical pathology parameters (hematology, coagulation, and clinical chemistry), cytokines, anti-therapeutic antibody (ATA), gross necropsy findings, organ weights, and histopathologic examination.

All animals given mRNA-1706 showed detectable antibody responses against ZIKV lysate at the end of the dosing period, and higher antibody titers following the two-week recovery period.

There were no mortalities during the course of the study.

There were no mRNA-1706 related changes in ophthalmology and organ weights.

Edema and, less frequent, erythema, were noted at the injection site following the first dose for males and females given ≥ 13 µg/dose. The incidence and severity of the findings were dose-dependent with increased incidence and severity noted at higher doses of mRNA-1706. Injection site observations consisted of slight to moderate edema with occasional severe edema noted at the highest dose tested and slight to mild erythema. The apex of severity was generally 24 hours post dose and was decreased 72 hours post dose. Between Days 2 and 4 only, the severity of the edema in females given 129 µg/dose was increased and correlated with warmness of the skin observed clinically. Increased severity reaction was noted following the third (last) dose in both genders. Minimal decreases in body weight gain and food consumption were observed during dosing weeks for males and females given 129 µg/dose. During the off-dose

weeks and recovery period, higher body weight gains were noted for both sexes while food consumption returned to control values.

Macroscopic and microscopic changes correlative with the injection site reaction were noted, such as swelling, abnormal firm consistency, lymph nodes enlargement, minimal to moderate inflammation at the injection site and minimal to mild mixed cells infiltration in and around the popliteal and inguinal lymph nodes. Clinical pathology changes suggestive of inflammation were observed in all males and females treated with mRNA-1706 and include: minimal to moderate increases in neutrophil, eosinophil (males and females ≥ 13 µg/dose) and large unstained cell counts with concomitant increases in white blood cells (males ≥ 13 µg/dose), minimal decreases in lymphocyte counts (females ≥ 13 µg/dose), minimal decreases in reticulocyte counts (males ≥ 13 µg/dose) and/or platelet counts (males 129 µg/dose, females ≥ 65 µg/dose), mild increases in fibrinogen and/or minimal increases in globulin with concomitant decreases in A/G ratio (males ≥ 13 µg/dose). Increases in IP-10, MCP-1, MIP-1α (female only) and/or TNF-α (male only) were noted at ≥ 129 µg/dose. The highest cytokine levels were generally reached on Day 29 and correlated with the severity of edema/erythema noted at the injection site. At the end of the recovery period, all mRNA-1706-related changes return to control values or were partially (lymph nodes enlargement without microscopic correlates) or fully recovered.

In the spleen, minimal to mild depletion of lymphocytes in the periarteriolar sheath was present in a dose-related trend for both male and female rats given ≥ 13 µg/dose. These changes were fully resolved at the end of the recovery period.

In the liver of males given ≥ 13 µg/dose, the incidence of minimal hepatocytic vacuolation showed a dose-related trend. No macroscopic changes correlated with this finding and changes were fully recovered at the end of the recovery period.

In conclusion, administration of mRNA-1706 by intramuscular injection for 1 month (3 doses) was clinically well tolerated in rats up to 129 µg/dose. A positive antibody response against ZIKV was determined at the end of the dosing period which persisted, as determined by a higher antibody titers noted following a two-week recovery period. At ≥ 13 µg/dose, dose-dependent changes in clinical signs, clinical pathology parameters and cytokines levels were consistent with an inflammatory response at the injection site. Dose-dependent target organ effects were limited to the injection site, tissues surrounding lymph nodes regional to the injection site, spleen, and liver of animals given mRNA-1706. At the end of the recovery period, all changes were partially or 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 was based on:

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

The Study Director signed the study plan on 04 Oct 2016, and dosing of males was initiated on 20 Oct 2016 for males and on 21 Oct 2016 for females. The in-life phase of the study was completed on 19 Nov 2016 (Main Study animals) and 02 Dec 2016 (Recovery animals). The experimental start date was 05 Oct 2016, the experimental completion date was on 09 Mar 2017. The study plan, study plan amendments, and deviations are presented in Appendix 1.

4. MATERIALS AND METHODS

4.1. Test and Reference Items

4.1.1. Test Item

Identification:		mRNA-1706
	Batch (Lot) No.:	MTDP16064
	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.
	Concentration:	1.7 / 2.2* mg/mL
	Physical Description:	White to off-white lipid nanoparticle dispersion
	Storage Conditions:	Kept in a refrigerator set to maintain 4°C
	Supplier:	Moderna Therapeutics, Inc.

* Concentration based on SoA released on 11 Oct 2016 / Concentration based on SoA released on 03 May 2017 (refer to memorandum in Appendix 2)

4.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS), pH 7.2
Batch (Lot) Nos.:	1809319, 1759866 and 1740269
Expiration Dates:	Jul 2018 (Lot No. 1809319), Feb 2018 (Lot No. 1759866) and Nov 2017 (Lot No. 1740269).
Physical Description:	Clear liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C
Supplier:	Gibco

4.3. Test Item Characterization

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

4.4. Analysis of Test Item

A sample (2 vials) of the Test Item was taken at the completion of the dosing period. Analysis of the 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 were performed by IEX- HPLC, Differential Light Scattering (DLS) and capillary electrophoresis (CE) using validated analytical procedures.

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

4.5. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 vial or 1 mL) 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 were discarded prior to report finalization.

4.7. Dose Formulation and Analysis

4.7.1. Preparation of Reference Item

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

The Reference Item, Phosphate Buffered Saline, 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 stored in a refrigerator set to maintain 4°C until use. They were removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

Details of the preparation and dispensing of the Reference Item were retained in the study records.

4.7.2. Preparation of Test Item

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

Test Item 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 stored in a refrigerator set to maintain 4°C. The dose formulations were allowed to warm to room temperature for at least 30 minutes prior to dosing.

Any residual volumes of formulated Test Item were stored in a refrigerator set at 4°C and were shipped to the Sponsor on ice packs for analysis. Residual volumes of formulated Test Item were analyzed for mRNA/lipid identity confirmation. Results were provided to the Test Facility and were not reported.

Details of the preparation and dispensing of the Test Item were retained in the study records.

4.7.3. Sample Collection and Analysis

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

Text Table 2
Dose Formulation Sample Collection Schedule

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

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

Samples to be analyzed were transferred on the date prepared or within 3 days of preparation to the Analytical Chemistry Department of the Test Facility for analysis.

4.7.3.1. Analytical Method

Analyses described below were performed by IEX-HPLC using a validated analytical procedure (CR MTL Study No. 1801737).

4.7.3.2. Concentration Analysis

Duplicate set of samples collected on Days 1 and 29 (0.5 mL each, collected from the middle stratum, except on Day 1 where samples were collected from the top, middle and bottom strata) were transferred (on ice pack) to the analytical laboratory for analysis. Triplicate set of samples

(duplicate for Group 1) were retained at the Test Facility as backup samples. Concentration results were considered acceptable when the mean sample concentration results were within or equal to ± 15% of the theoretical concentration. Each individual sample concentration result was considered acceptable if it was within or equal to ± 20%. After acceptance of the analytical results, backup samples were discarded.

4.7.3.3. Homogeneity Analysis

On Day 1, duplicate sets of samples (0.5 mL each, collected from the top, middle and bottom strata for Groups 2 to 4 and from the middle stratum for Group 1) were transferred (on ice pack) to the analytical laboratory for analysis; similarly, triplicate sets of samples (duplicate for Group 1) were retained at the Test Facility as backup samples. Homogeneity results were considered acceptable if the relative standard deviation of the mean values at each sampling stratum was ≤ 5%. After acceptance of the analytical results, backup samples were discarded.

4.7.3.4. Stability Analysis

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

4.8. Test System

4.8.1. Receipt

On October 5, 2016, one hundred and twenty (60 males and 60 females) Crl:CD(SD) Sprague-Dawley rats were received from Charles River Canada, Inc., St. Constant, QC, Canada. At dosing onset, the animals were approximately 8 weeks old and the males weighed between 240 and 298 grams and the females, between 200 and 246 grams.

4.8.2. Justification for Test System and Number of Animals

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

The total number of animals used in this study was considered to be the minimum required to properly characterize the effects of the Test Item. This study was designed such that it did 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

At study assignment, each animal was identified using a subcutaneously implanted electronic identification chip. Animals were also identified using a non-toxic pen, as needed.

4.8.4. Environmental Acclimation

A minimum acclimation period of at least 15 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 in poor health, at extremes of body weight range or with ophthalmic findings were not assigned to groups.

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

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

4.8.6. Husbandry

4.8.6.1. Housing

Animals were group-housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions were maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The 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 numbers, 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 maintained. A 12-hour light/12-hour dark cycle was maintained, except when interrupted for designated procedures.

4.8.6.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 (14% protein) was provided ad libitum throughout the study, except during designated procedures. Wet pellets were provided as judged necessary.

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

It was considered that there were no known contaminants in the feed that would have interfered with the objectives of the study.

4.8.6.4. Water

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

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

It was considered that there were no known contaminants in the water that could have interfered with the outcome of the study.

4.8.6.5. Animal Enrichment

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

4.8.6.6. Veterinary Care

Veterinary care was available throughout the course of the study, and animals were examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations 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)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	Animals Nos.			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	1001-1003, 1104, 1005-1010	1501-1510	1011-1015	1511-1515
2	mRNA-1706	10 / 13	200	0.05 / 0.07	2001-2010	2501-2510	-	-
3	mRNA-1706	50 / 65	200	0.25 / 0.33	3001-3010	3501-3510	-	-
4	mRNA-1706	100 / 129	200	0.5 / 0.65	4001-4004, 4105, 4006-4010	4501-4510	4011-4015	4511-4515

- = Not applicable
[a] Values based on SoA issued on 11 Oct 2016 / Values based on SoA issued on 03 May 2017 (refer to memorandum in Appendix 2).

On Day -1, Animal No. 4005 was euthanized following complications from a skin lesion on the right hind limb, resulting from an accidental cut during shaving. This animal was replaced with a spare animal to become Animal No. 4105. On Day 1, prior to dosing initiation, due to compromising clinical signs (inguinal skin lesion), Animal No. 1004 was replaced with a spare animal to become Animal No. 1104. The final allocation of animals is listed under Text Table 3.

4.9.1. Administration of Test Materials

The Test and Reference Items were administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site was alternated on each dosing occasion. 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 was shaved if required to improve visualization of the injection sites. The injection site was documented in the raw data for each dose administered.

A low incidence of dosing reflux was observed for individual animals, mainly following Days 1 and 29 dosing. As reflux occurred only once per affected animal, was scattered in all dosing groups, including controls, it was considered to have no impact on overall exposure and on the study outcome.

4.9.2. Justification of Route and Dose Levels

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

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

4.10. In-life Procedures, Observations, and Measurements

The in-life procedures, observations, and measurements listed below were performed for Main and Recovery study animals.

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 (for exceptions, refer to Appendix 1). 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 their cage, and a detailed clinical observation was performed weekly, beginning Week -1.

4.10.3. Local Irritation Assessment

On days of dosing and at least 24 and 72 hours postdose (end of each group), all animals had the dose injection site examined for signs of erythema/edema (for exceptions, refer to Appendix 1). Examinations were also performed weekly when there was no dosing and during the recovery period. On Day 29, no assessment was performed on Main Study animals at 72 hours postdose as these animals were sent to necropsy on Day 30.

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

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

4.10.4. Body Weights

Animals were weighed individually weekly. A fasted weight was recorded on the day of necropsy (for exceptions, refer to Appendix 1).

4.10.5. Food Consumption

Food consumption was quantitatively measured weekly starting on Day -7 and continuing weekly throughout the dosing and recovery periods (refer to Appendix 1 for one exception).

4.10.6. Ophthalmic Examinations

All animals had funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations, once prior to dosing initiation and on Day 28 for males and Day 27 for females. The mydriatic used was Atropine 0.126%.

4.11. Laboratory Evaluations

4.11.1. Clinical Pathology

4.11.1.1. Sample Collection

Blood was collected at termination, 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

X = Sample collected
[a] Samples were only collected from Main Study Animals on Day 30.

4.11.1.2. Hematology

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

Text Table 5
Hematology Parameters

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

A blood smear was prepared from each hematology sample. Blood smears were labeled, stained, and stored.

4.11.1.3. Coagulation

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

Text Table 6
Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

4.11.1.4. Clinical Chemistry

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

Text Table 7
Clinical Chemistry Parameters

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

4.11.2. Cytokine Analysis

Blood was collected from a jugular vein from all Recovery animals as specified in Text Table 8. After collection, blood samples for serum collection were transferred at ambient room

temperature and blood samples for plasma collection were transferred on wet ice to the appropriate laboratory for processing.

Text Table 8
Sample Collection Schedule and Information

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

X = Sample collected; N/A = not applicable

Samples were analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 was conducted using a multiplex Luminex method. An ELISA method was used for the analysis of IFN-α. 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.

Note that the IFN-α results were considered invalid since samples were analyzed with an ELISA kit which detects anti-IFN-α antibodies instead of the cytokine IFN-α. As the wrong assay reagents were used and as there is no remaining samples to repeat the analysis; results were maintained in the raw data but were not reported (Refer to Appendix 1).

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

4.11.3. Anti-therapeutic Antibody (ATA) Sample Collection, Processing and Analysis

Before the initiation of dosing and at study termination (i.e. Day 30 for Main Study animals and Day 43 for Recovery animals), a target volume of 0.5 mL of blood was collected in serum separator tubes by jugular venipuncture and via abdominal aorta, while under isoflurane anesthesia (terminal).

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; for exceptions, refer to Appendix 1). 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, and were analyzed for rat anti-ZIKA antibodies using a qualified ELISA method.

Any residual/retained samples were discarded before the issuance of the Final.

4.12. Terminal Procedures

Terminal procedures are summarized in Text Table 9.

Text Table 9
Terminal Procedures

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

X = Procedure conducted; - = Not applicable.
[a] See Section 4.12.5 for listing of tissues.
[b] Animals euthanized before the initiation of dosing.

4.12.1. Unscheduled Deaths

Before the initiation of dosing, one male was euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia and was subjected to complete necropsy examination and limited tissue retention (standard diagnostic tissue list).

4.12.2. Scheduled Euthanasia

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

4.12.3. Necropsy

Main Study and Recovery animals had 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. 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

Injection Site	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[c]
Cervix	Lymph node, Popliteal[c]
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[d]	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.
[C] Lymph node draining the administration site used on Day 29 (unilateral examination).
[d] Gross lesions were collected and examined only on animals presenting gross abnormalities.

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 (refer to Appendix 1 for exceptions).

4.12.7. Histopathology

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

Target tissues identified by the pathologist (i.e. site, injection; lymph node, inguinal; lymph node, popliteal; liver; spleen) were evaluated and reported.

4.12.8. Peer Review

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

The peer review statement is included in Appendix 18.

4.12.9. Bone Marrow Smear Analysis

Two bone marrow smears were prepared from each euthanized animal, air dried and stained with Wright's Giemsa stain.

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

Text Table 12
Statistical Matrix

	Statistical Method
Variables for Inferential Analysis	**Parametric/Non-parametric**
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokine Analysis	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons were made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

6.1. Parametric/Non-parametric

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

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

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 (using SAS)	Nevis 2 (SAS 9.2)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 5.4 (M5) 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
BioPlex Manager	4.1	Biomarker data collection
Softmax Pro GxP	5.0.1	IFN-α data collection
Watson LIMS	7.2.0.02	Biomarker data analysis

8. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, documentation, study plan, study plan amendments, samples, specimens, and final reports from this study will be transferred to CR MTL archive by no later than the date of final report issue. One year after issue of the audited draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

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

All records, retained samples and specimens, and reports generated from phases or segments performed by Test Facility-designated subcontractors were returned to the Test Facility for archiving. Archival location and duration are detailed in the applicable PI report(s).

All records, retained samples and specimens, and reports generated from phases or segments performed by Sponsor-designated subcontractors were maintained at Integrated BioTherapeutics, Inc. Rockville, MD, USA for archiving. The materials will be retained for at least three years.

9. RESULTS

9.1. Dose Formulation Analyses

(Appendix 3)

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

9.2. End of Use Bulk Test Item Analysis

(Appendix 3 and Appendix 15)

Concentration and particle size results obtained were consistent with the Certificate of Analysis.

The End of Use bulk Test Item analysis demonstrated a purity of (b) (4), which is lower than the original purity results of (b) (4), provided by the Sponsor per the Certificate of Analysis.

Although the purity analysis indicated RNA degradation, the concentration and particle size were within specification. Study animals showed a significant average antibody response against the ZIKV lysate and increased average antibody titers following the final dose indicating that the potential decrease in purity did not affect activity. As the original doses were not adjusted for purity of the drug product, but based on total mRNA concentration, the nominal dose levels were maintained in the report, tables and appendices.

9.3. Mortality

(Appendix 4)

There were no mortalities during the course of the study.

9.4. Clinical Observations

(Table 1 and Appendix 5)

mRNA-1706-related clinical signs were limited to warm to the touch noted on Day 2, for females given 129 µg/dose.

9.5. Local Irritation Assessment

(Appendix 6)

Edema and, less frequent, erythema, were noted at the injection site following the first dose for males and females given ≥ 13 µg/dose. The incidence and severity of the findings were dose-dependent with increased incidence and severity noted at higher doses of mRNA-1706. Injection site observations consisted of slight to moderate edema with occasional severe edema noted at the highest dose tested and slight to mild erythema. The apex of severity was generally 24 hours post dose and was decreased 72 hours post dose. Between Days 2 and 4 only, the severity of the edema in females given 129 µg/dose was increased and correlated with warmness of the skin observed clinically. Increased severity reaction was noted following the third (last) dose in both genders.

9.6. Body Weights and Body Weight Gains

(Figure 1, Figure 2, Table 2, Table 3, Appendix 7, and Appendix 8)

During the weeks of dosing, males and females given 129 µg/dose tend to gain less weight (0.68X and 0.64X controls, respectively) while the body weight gain was higher during the off-dose weeks (1.1X and 1.3X controls, respectively) and Week 2 of the recovery period (1.4X and 3.9X controls, respectively).

9.7. Food Consumption

(Table 4 and Appendix 9)

Slight decreases in food consumption were noted for males and females given 129 µg/dose during dosing weeks and return close to control values during the off-dose weeks and the recovery period.

9.8. 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 expected in this population of animals.

9.9. Hematology

(Table 5 and Appendix 10)

mRNA-1706-related hematology changes were noted for males and females at ≥ 13 µg/dose. Decreases in reticulocyte (RETIC) and/or platelet (PLT) counts, increases in neutrophil (NEUT), eosinophil (EOS) and/or large unstained cell (LUC) counts (with concomitant increases in white blood cell (WBC) counts) and decreases in lymphocyte counts (LYM). These changes are illustrated in Text Table 14.

Text Table 14
Hematology Changes in Rats Administered mRNA-1706

Dose (µg/dose)	13		65		129	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
WBC						
Day 30	**1.6**	–	**2.3**	–	**1.8**	–
Day 43					–	–
NEUT						
Day 30	8.2	**5.5**	**14.1**	**7.2**	**11.7**	**7.0**
Day 43					–	–
LYM						
Day 30	–	0.82	–	**0.47**	–	**0.39**
Day 43					–	–
EOS						
Day 30	2.1	**4.0**	**2.7**	**3.1**	2.1	**3.6**
Day 43					–	–
LUC						
Day 30	**6.0**	–	**4.1**	–	2.4	–
Day 43					–	–
RETIC						
Day 30	**0.77**	–	**0.68**	–	**0.69**	–
Day 43					–	–
PLT						
Day 30	0.92	0.97	0.92	**0.87**	0.85	**0.76**
Day 43					–	–

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

Mild increases in WBC counts (up to 2.3X controls) were noted in males given ≥ 13 µg/dose, mainly due to minimal to moderate increases in NEUT, EOS and LUC (up to 14.1X, 2.7X and 6.0X controls, respectively). Minimal to mild increases in NEUT and EOS (up to 7.2X and 4.0X controls, respectively) with minimal decreases in LYM (down to 0.39X compared to control) were noted for females at ≥ 13 µg/dose.

Minimal decreases in RETIC was noted for males at ≥ 13 µg/dose (down to 0.68X controls).

Minimal decreases in PLT were noted in males given 129 µg/dose (down to 0.85X controls) and females given ≥ 65 µg/dose (down to 0.76X controls).

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.

9.10. Coagulation

(Table 6 and Appendix 11)

mRNA-1706-related increases in fibrinogen (FIB) were noted at ≥ 13 µg/dose. The changes are illustrated in Text Table 15.

Text Table 15
Coagulation Changes in Rats Administered mRNA-1706

Dose (µg/dose)	13		65		129	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
FIB						
Day 30	**2.2**	**2.0**	**2.5**	**2.2**	**2.4**	**1.9**
Day 43					–	–

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

Mild increases in FIB were noted for males and females given ≥ 13 µg/dose (up to 2.5X and 2.2X controls, respectively).

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.

9.11. Clinical Chemistry

(Table 7 and Appendix 12)

mRNA-1706-related clinical chemistry changes in globulin (GLOB) and A/G ratio were noted for males given ≥ 13 µg/dose. These changes are illustrated in Text Table 16.

Text Table 16
Clinical Chemistry Changes in Rats Administered mRNA-1706

Dose (µg/dose)	13		65		129	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
GLOB						
Day 30	**1.3**	–	**1.3**	–	**1.3**	–
Day 43					–	–
A/G						
Day 30	**0.70**	–	**0.71**	–	**0.71**	–
Day 43					–	–

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

Minimal increases in GLOB were noted for males at ≥ 13 µg/dose (up to 1.3X controls) and affected the A/G ratio in that gender (down to 0.70Xto controls).

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.

9.12. Cytokines

(Appendix 14)

Increases in IP-10 and MCP-1 concentrations were observed in males and females. Higher IP-10 concentrations were observed on Day 29, 6 hours post-dose in males and on Day 1, 6 hours post-dose in females while higher MCP-1 concentrations were observed on Day 29, 6 hours post-dose for both genders. These changes were statistically significant when compared to controls. At the end of the recovery period, IP-10 and MCP-1 levels were back to the control range.

No changes in MIP-1α were noted in males. In females, increases in MIP-1α concentrations were observed on Day 15 and Day 29, 6 hours post-dose. Peak concentrations were generally reached on Day 29, 6 hours post-dose. The changes observed were statistically significant. MIP-1α concentrations were back to the control range at the end of the recovery period.

No changes in TNF-α were noted in females given mRNA-1706. Statistically significant increases were however observed in treated males on Day 15, 6 hours post-dose.

No mRNA-1706-related changes were observed in IL-1β and IL-6.

Note that the IFN-α results are considered invalid since samples were analyzed with a rat interferon alpha antibody ELISA kit which detect anti-IFN-α antibodies instead of the cytokine IFN-α.

9.13. Anti-therapeutic Antibody (ATA) Analysis

(Appendix 16)

On Day 30, sera from animals given mRNA-1706 at 13 µg/dose, 65 µg/dose, 129 µg/dose on Days 1, 15, and 29 intramuscularly showed detectable antibody responses against the ZIKV lysate. On Day 43, the antibody titers were higher than those on Day 30.

9.14. Gross Pathology

(Appendix 17)

9.14.1. Terminal Euthanasia(Day 30)

mRNA-1706-related gross pathology findings were limited to the injection site (firm consistency, swelling) and to the inguinal, popliteal, and iliac lymph nodes (enlargement), and are summarized in Text Table 17.

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

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**13**	**65**	**129**	**0**	**13**	**65**	**129**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, injection (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency, firm	0	10	10	10	0	10	10	10
Swelling	0	4	7	7	0	6	8	9
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	2	5	6	0	1	1	4
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	8	7	0	4	5	4
Lymph node[a,b] (No. Examined)	0	1	7	4	0	2	4	6
Enlargement	0	1	7	4	0	2	4	6

[a] The tissue, Lymph node, included iliac and mediastinal lymph nodes at collection. Here, only iliac lymph nodes are presented.
[b] Tissues presented are considered as gross lesions.

Other gross findings observed were considered incidental, of the nature commonly observed in this strain and age of Sprague-Dawley rats, and/or were of similar incidence in control and Test Item-treated animals and, therefore, were considered not mRNA-1706-related.

9.14.2. Recovery Euthanasia(Day 43)

(Appendix 17)

mRNA-1706-related enlargement of the lymph nodes noted at the terminal euthanasia was still observed, but at a lower incidence, in males at the end of the recovery period (Day 43) and is summarized in Text Table 18, however no microscopic correlate was noted at this time point. Injection sites were grossly unremarkable at the end of the recovery period.

Text Table 18
Summary of Gross Pathology Findings – Recovery Euthanasia (Day 43)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**13**	**65**	**129**	**0**	**13**	**65**	**129**
No. Animals Examined	**5**	**-**	**-**	**5**	**5**	**-**	**-**	**5**
Lymph node, inguinal (No. Examined)	5	-	-	5	5	-	-	5
Enlargement	0	-	-	2	0	-	-	0
Lymph node, popliteal (No. Examined)	5	-	-	5	5	-	-	5
Enlargement	0	-	-	2	0	-	-	0

Other gross findings observed were considered incidental, of the nature commonly observed in this strain and age of Sprague-Dawley rats, and/or were of similar incidence in control and treated animals and, therefore, were considered not mRNA-1706-related.

9.15. Organ Weights

(Appendix 17)

There were no mRNA-1706-related organ weight changes noted at the terminal and recovery necropsies.

There were isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, the organ weight differences observed were considered incidental and/or related to difference of sexual maturity and not mRNA-1706-related.

9.16. Histopathology

(Appendix 17)

9.16.1. Terminal Euthanasia (Day 30)

mRNA-1706-related microscopic findings were noted in the liver of males, and in both genders in the spleen, the injection site, and in tissues surrounding lymph nodes regional to the injection site, and are summarized in Text Table 19.

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

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**13**	**65**	**129**	**0**	**13**	**65**	**129**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Liver (No. Examined)	10	10	10	10	10	10	10	10
Vacuolation	(1)	(3)	(4)	(5)	(7)	(8)	(8)	(5)
Minimal	1	3	4	5	7	8	8	5
Spleen (No. Examined)	10	10	10	10	10	10	10	10
Decreased cellularity; lymphoid, periarteriolar lymphoid sheath	(0)	(4)	(7)	(10)	(0)	(5)	(9)	(10)
Minimal	0	4	7	7	0	5	9	5
Mild	0	0	0	3	0	0	0	5
Site, injection (No. Examined)	10	10	10	10	10	10	10	10
Inflammation	(0)[a]	(10)	(10)	(10)	(0)	(10)	(10)	(10)
Minimal	0	0	0	0	0	1	0	0
Mild	0	0	0	0	0	6	2	4
Moderate	0	10	10	10	0	3	8	6
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Infiltration, mixed cell	(0)	(0)	(0)	(2)	(0)	(0)	(1)	(3)
Minimal	0	0	0	1	0	0	0	0
Mild	0	0	0	1	0	0	1	3
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Infiltration, mixed cell	(0)	(6)	(7)	(8)	(0)	(9)	(10)	(9)
Minimal	0	0	2	6	0	7	4	2
Mild	0	6	5	2	0	2	6	7

[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 Sprague-Dawley rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered not mRNA-1706-related.

9.16.2. Recovery Euthanasia (Day 43)

Findings noted at the terminal euthanasia were not observed at the end of the recovery period (Day 43). Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of Sprague-Dawley rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered not mRNA-1706-related.

10. CONCLUSION

In conclusion, administration of mRNA-1706 by intramuscular injection for 1 month (3 doses) was clinically well tolerated in rats up to 129 µg/dose. A positive antibody response against ZIKV was determined at the end of the dosing period which persisted, as determined by a higher antibody titers noted following a two-week recovery period. At ≥ 13 µg/dose, dose-dependent changes in clinical signs, clinical pathology parameters and cytokines levels were consistent with an inflammatory response at the injection site. Dose-dependent target organ effects were limited to the injection site, tissues surrounding lymph nodes regional to the injection site, spleen, and liver of animals given mRNA-1706. At the end of the recovery period, all changes were partially or fully recovered.

Figure 1

Summary of Body Weights - Males

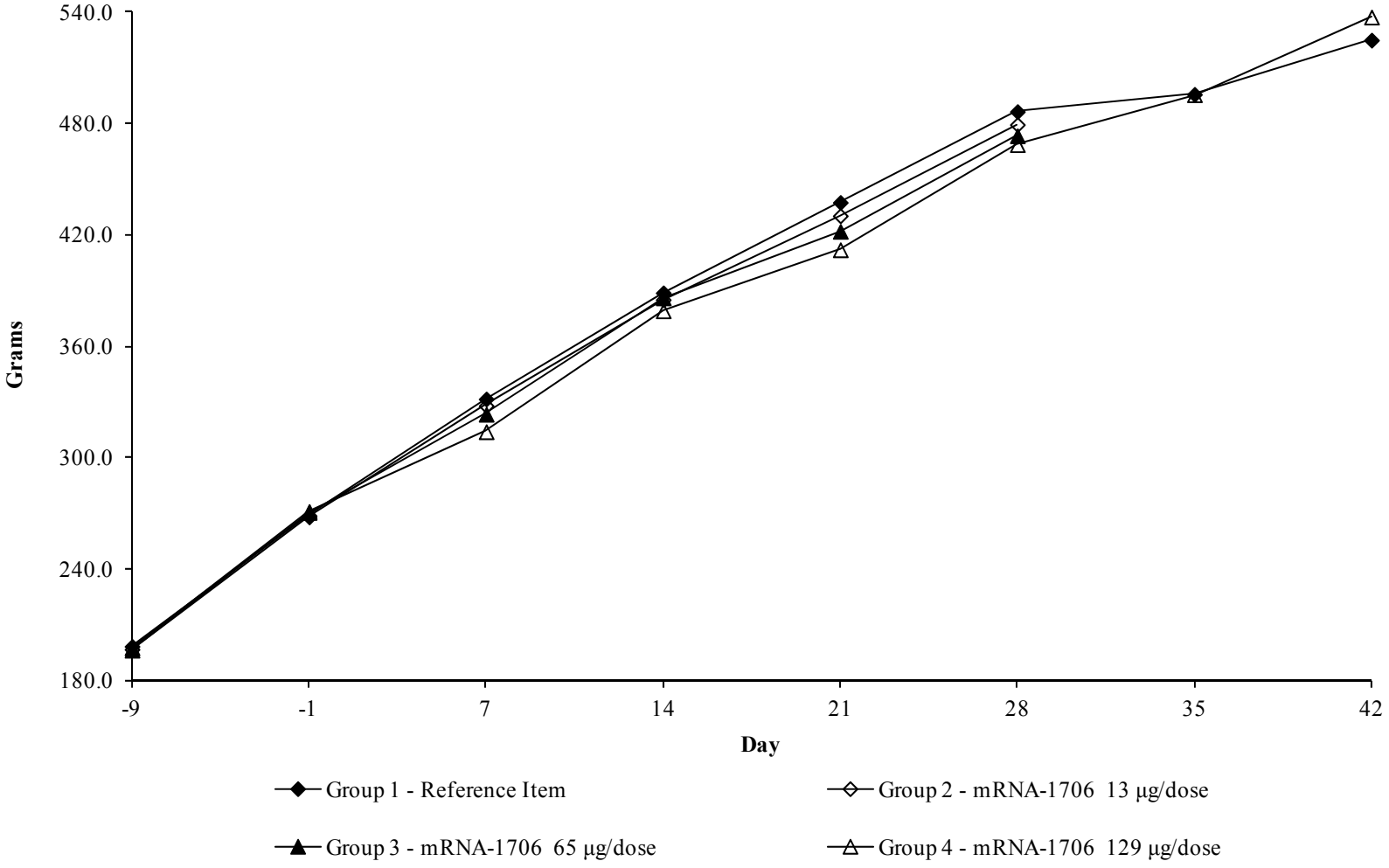

Figure 2

Summary of Body Weights - Females

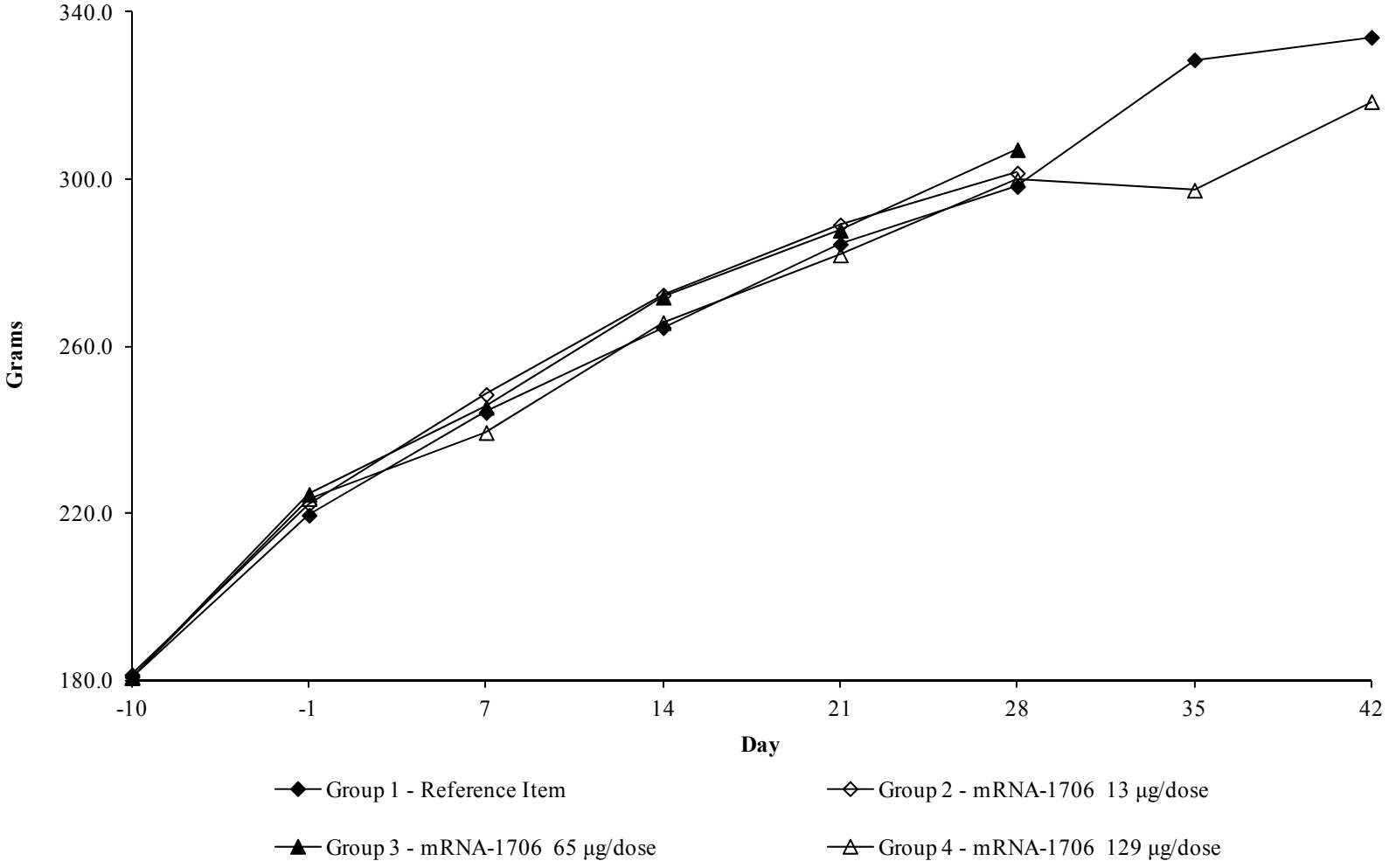

Table 1

Summary of Clinical Observations

5002045

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	13 ug/dose	65 ug/dose	129 ug/dose
Skin, Red				
Number of Observations	.	1	.	.
Number of Animals	.	1	.	.
Days from - to	.	21 21	.	.
Skin, Scab				
Number of Observations	14	3	2	14
Number of Animals	6	3	1	6
Days from - to	14 43	-1 30	-1 7	-1 43
Fur, Erected				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	-14 -14	.
Fur, Staining, Brown				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	43 43
Fur, Staining, Red				
Number of Observations	1	.	.	2
Number of Animals	1	.	.	1
Days from - to	28 28	.	.	21 28
Fur, Thin Cover				
Number of Observations	.	1	2	11
Number of Animals	.	1	2	6
Days from - to	.	28 28	-1 -1	-1 30
Nictitating MembraneProtruding				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	-14 -14

Table 1

Summary of Clinical Observations

5002045

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	13 ug/dose	65 ug/dose	129 ug/dose
Vocalization Increased				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	-1 -1
Caught in Cage				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	7 7	.	.	.
Dehydrated Suspected				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	2 2
Warm to Touch				
Number of Observations	.	.	.	15
Number of Animals	.	.	.	15
Days from - to	.	.	.	2 2
Skin, Red				
Number of Observations	2	.	.	1
Number of Animals	1	.	.	1
Days from - to	42 43	.	.	30 30
Skin, Dry				
Number of Observations	2	.	.	.
Number of Animals	1	.	.	.
Days from - to	42 43	.	.	.
Skin, Lesion				
Number of Observations	2	.	1	.
Number of Animals	2	.	1	.
Days from - to	3 7	.	-1 -1	.

Table 1

Summary of Clinical Observations

5002045

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	13 ug/dose	65 ug/dose	129 ug/dose
Skin, Scab				
Number of Observations	15	3	4	9
Number of Animals	8	1	3	5
Days from - to	-1 30	-1 14	7 30	7 43
Fur, Staining, Red				
Number of Observations	1	.	.	7
Number of Animals	1	.	.	4
Days from - to	43 43	.	.	28 43
Fur, Thin Cover				
Number of Observations	5	3	.	1
Number of Animals	1	1	.	1
Days from - to	-1 30	-1 14	.	21 21
Tail, Sloughing				
Number of Observations	2	.	.	.
Number of Animals	1	.	.	.
Days from - to	28 30	.	.	.
Pinna Partly Missing				
Number of Observations	7	.	4	5
Number of Animals	1	.	1	1
Days from - to	7 43	.	14 30	7 30
Nail Missing				
Number of Observations	3	.	.	.
Number of Animals	1	.	.	.
Days from - to	14 28	.	.	.

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day -9	-1	7	14	21	28	35	42
1M	Mean	198.5	268.9	331.7	388.9	437.6	486.5	495.8	525.0
	SD	10.4	17.6	24.2	30.0	34.5	38.0	36.0	33.6
	N	15	15	15	15	15	15	5	5
2M	Mean	196.9	268.2	328.1	385.2	430.4	479.5	--	--
	SD	5.7	10.2	13.2	14.1	18.8	22.1	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	-0.8	-0.2	-1.1	-1.0	-1.6	-1.4	--	--
3M	Mean	196.4	270.6	323.5	386.2	422.0	473.5	--	--
	SD	5.8	7.9	9.5	12.9	16.3	19.8	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	-1.1	0.6	-2.5	-0.7	-3.6	-2.7	--	--
4M	Mean	197.7	271.1	314.1	379.2	412.1	468.7	495.6	537.4
	SD	9.1	14.2	18.9	24.4	30.4	37.2	58.3	57.2
	N	15	15	15	15	15	15	5	5
	%Diff G1	-0.4	0.8	-5.3	-2.5	-5.8	-3.6	0.0	2.4

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day -10	-1	7	14	21	28	35	42
1F	Mean	180.9	219.6	244.2	264.5	284.5	298.3	328.6	334.0
	SD	7.0	10.2	13.2	16.2	20.6	21.8	30.9	30.6
	N	15	15	15	15	15	15	5	5
2F	Mean	181.4	222.3	248.5	272.3	289.1	301.5	--	--
	SD	4.2	7.9	9.1	14.1	16.5	18.8	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	0.3	1.2	1.8	2.9	1.6	1.1	--	--
3F	Mean	180.9	224.6	245.4	271.8	287.8	307.1	--	--
	SD	4.0	8.6	12.6	20.5	22.7	25.9	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	0.0	2.3	0.5	2.7	1.2	3.0	--	--
4F	Mean	180.7	223.6	239.4	265.7	281.9	299.9	297.4	318.6
	SD	7.0	13.9	16.6	23.5	21.5	22.0	12.6	11.5
	N	15	15	15	15	15	15	5	5
	%Diff G1	-0.1	1.8	-2.0	0.5	-0.9	0.5	-9.5	-4.6

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day Change -9 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change -1 - 28	Change 28 - 35
1M	Mean	70.3	62.9	57.2	48.7	48.9	217.6	20.8
	SD	8.6	10.2	8.4	6.0	6.8	26.2	8.8
	N	15	15	15	15	15	15	5
2M	Mean	71.3	59.9	57.1	45.2	49.1	211.3	--
	SD	7.5	5.8	4.4	7.3	7.0	19.2	--
	N	10	10	10	10	10	10	--
3M	Mean	74.2	52.9a	62.7	35.8f	51.5	202.9	--
	SD	4.3	3.8	6.9	4.6	8.1	16.5	--
	N	10	10	10	10	10	10	--
4M	Mean	73.5	43.0c	65.1e	32.9f	56.7d	197.6	16.2
	SD	7.4	8.1	6.4	9.1	9.4	27.1	7.5
	N	15	15	15	15	15	15	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 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day Change 35 - 42	Change 28 - 42
1M	Mean	29.2	50.0
	SD	5.2	7.0
	N	5	5
2M	Mean	--	--
	SD	--	--
	N	--	--
3M	Mean	--	--
	SD	--	--
	N	--	--
4M	Mean	41.8b	58.0
	SD	4.0	7.1
	N	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 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day Change -10 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change -1 - 28	Change 28 - 35
1F	Mean	38.7	24.6	20.3	19.9	13.8	78.7	26.0
	SD	7.5	6.7	5.0	6.7	5.7	16.0	19.0
	N	15	15	15	15	15	15	5
2F	Mean	40.9	26.2	23.8	16.8	12.4	79.2	--
	SD	6.9	4.1	6.5	4.9	5.8	13.1	--
	N	10	10	10	10	10	10	--
3F	Mean	43.7	20.8	26.4	16.0	19.3a	82.5	--
	SD	6.0	6.1	10.5	8.1	5.1	20.3	--
	N	10	10	10	10	10	10	--
4F	Mean	42.9	15.8b	26.3	16.2	17.9	76.3	9.4
	SD	9.2	9.0	7.9	9.8	4.6	11.8	5.5
	N	15	15	15	15	15	15	5

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 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day Change 35 - 42	Change 28 - 42
1F	Mean	5.4	31.4
	SD	21.7	11.7
	N	5	5
2F	Mean	--	--
	SD	--	--
	N	--	--
3F	Mean	--	--
	SD	--	--
	N	--	--
4F	Mean	21.2	30.6
	SD	1.9	4.4
	N	5	5

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day (From/To)						
		-7/1	1/8	8/15	15/22	22/29	29/36	36/42
1M	Mean	29.27	31.01	32.30	32.97	33.59	31.60	32.86
	SD	2.32	2.37	2.36	2.44	2.24	1.10	1.15
	N	15	15	15	15	15	5	5
2M	Mean	27.90	29.69	32.55	32.17	33.86	--	--
	SD	1.25	0.87	1.14	1.53	1.50	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	-4.67	-4.25	0.77	-2.44	0.79	--	--
3M	Mean	28.19	27.84	32.36	29.21	32.76	--	--
	SD	0.67	0.25	0.97	1.26	1.27	--	--
	N	10	10	7	10	10	--	--
	%Diff G1	-3.68	-10.21	0.18	-11.41	-2.48	--	--
4M	Mean	28.92	27.21	33.90	30.17	35.55	33.48	38.16
	SD	1.85	2.36	2.63	3.08	2.94	4.22	3.78
	N	12	15	15	15	15	5	5
	%Diff G1	-1.20	-12.23	4.95	-8.51	5.81	5.95	16.13

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day (From/To)						
		-7/1	1/8	8/15	15/22	22/29	29/36	36/42
1F	Mean	20.55	21.72	23.35	23.59	24.48	26.84	25.84
	SD	1.16	1.20	1.67	1.38	1.14	0.77	1.04
	N	15	15	15	15	15	5	5
2F	Mean	20.63	21.54	23.15	22.50	23.60	--	--
	SD	0.68	1.02	0.98	1.05	0.92	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	0.41	-0.83	-0.87	-4.61	-3.59	--	--
3F	Mean	21.69	21.64	24.20	23.27	25.85	--	--
	SD	0.65	1.53	2.72	2.45	1.85	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	5.56	-0.37	3.63	-1.34	5.60	--	--
4F	Mean	21.23	20.06	22.85	22.07	24.32	21.58	24.84
	SD	1.23	0.59	1.22	0.96	1.23	0.44	0.05
	N	15	15	15	15	15	5	5
	%Diff G1	3.34	-7.64	-2.17	-6.44	-0.65	-19.60	-3.87

Table 5

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	7.999	0.794	6.906	0.158	0.070	0.014	0.057
	SD	1.232	0.192	1.143	0.034	0.033	0.007	0.013
	N	10	10	10	10	10	10	10
2M	Mean	13.136f	6.501	5.892	0.264b	0.147	0.019	0.341c
	SD	2.148	1.405	1.233	0.128	0.052	0.011	0.113
	N	10	10	10	10	10	10	9
	%Diff G1	64.221	718.766	-14.683	67.089	110.000	35.714	498.441
3M	Mean	18.125f	11.215c	6.231	0.253	0.189b	0.028d	0.234c
	SD	2.435	1.958	1.774	0.148	0.095	0.015	0.079
	N	10	10	10	10	10	10	9
	%Diff G1	126.591	1312.469	-9.774	60.127	170.000	100.000	311.306
4M	Mean	14.212f	9.256c	4.487d	0.211	0.149	0.010	0.137
	SD	3.111	1.479	2.703	0.070	0.124	0.009	0.063
	N	10	10	10	10	10	10	7
	%Diff G1	77.672	1065.743	-35.028	33.544	112.857	-28.571	140.602

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 Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.770	14.41	42.64	54.92	18.55	33.76	12.34
	SD	0.238	0.37	1.15	2.01	0.67	0.44	0.52
	N	10	10	10	10	10	10	10
2M	Mean	7.968	14.67	43.19	54.19	18.41	33.95	12.80
	SD	0.271	0.59	1.60	1.40	0.47	0.28	0.31
	N	10	10	10	10	10	10	10
	%Diff G1	2.548	1.80	1.29	-1.33	-0.75	0.56	3.73
3M	Mean	7.805	14.41	42.63	54.63	18.48	33.82	13.12c
	SD	0.338	0.78	2.21	1.70	0.79	0.65	0.38
	N	10	10	10	10	10	10	10
	%Diff G1	0.450	0.00	-0.02	-0.53	-0.38	0.18	6.32
4M	Mean	7.965	15.00	44.21	55.55	18.83	33.93	13.58c
	SD	0.312	0.53	1.31	1.70	0.73	0.54	0.50
	N	10	10	10	10	10	10	10
	%Diff G1	2.510	4.09	3.68	1.15	1.51	0.50	10.05

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

Table 5

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1117.7	257.59
	SD	172.9	35.75
	N	10	10
2M	Mean	1027.2	198.37c
	SD	255.8	18.00
	N	10	10
	%Diff G1	-8.1	-22.99
3M	Mean	1029.5	174.65c
	SD	158.7	22.90
	N	10	10
	%Diff G1	-7.9	-32.20
4M	Mean	949.6	176.42c
	SD	179.2	35.00
	N	10	10
	%Diff G1	-15.0	-31.51

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

Table 5

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	7.061	0.802	5.959	0.174	0.058	0.010	0.058
	SD	1.321	0.322	1.247	0.066	0.016	0.005	0.038
	N	9	9	9	9	9	9	9
2F	Mean	9.875	4.397a	4.903	0.147	0.232c	0.017	0.177a
	SD	2.542	1.101	1.711	0.064	0.080	0.009	0.125
	N	10	10	10	10	10	10	10
	%Diff G1	39.851	448.102	-17.720	-15.732	301.538	70.000	206.346
3F	Mean	8.931	5.757c	2.813f	0.114	0.178a	0.005	0.070
	SD	2.117	0.917	1.410	0.088	0.111	0.007	0.020
	N	10	10	10	10	10	10	9
	%Diff G1	26.482	617.632	-52.793	-34.650	208.077	-50.000	21.154
4F	Mean	8.316	5.576c	2.308f	0.116	0.206b	0.009	0.112
	SD	2.905	2.377	0.810	0.066	0.085	0.006	0.062
	N	10	10	10	10	10	10	9
	%Diff G1	17.772	595.069	-61.268	-33.503	256.538	-10.000	94.231

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 Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.783	14.24	40.39	51.89	18.31	35.30	10.83
	SD	0.329	0.46	1.27	1.29	0.70	0.52	0.27
	N	9	9	9	9	9	9	9
2F	Mean	7.866	14.49	41.13	52.33	18.43	35.23	11.10
	SD	0.592	0.93	2.90	0.98	0.56	0.55	0.26
	N	10	10	10	10	10	10	10
	%Diff G1	1.062	1.72	1.83	0.85	0.65	-0.20	2.46
3F	Mean	7.975	14.99	42.33	53.12	18.85	35.47	11.91f
	SD	0.392	0.54	1.52	1.73	0.73	0.53	0.36
	N	10	10	10	10	10	10	10
	%Diff G1	2.463	5.23	4.81	2.37	2.94	0.48	9.94
4F	Mean	8.120	15.16a	42.88a	52.84	18.68	35.34	12.22f
	SD	0.435	0.67	2.08	1.17	0.51	0.37	0.41
	N	10	10	10	10	10	10	10
	%Diff G1	4.325	6.43	6.17	1.83	2.01	0.11	12.80

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 Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1145.8	194.90
	SD	85.3	35.25
	N	9	9
2F	Mean	1115.8	150.91b
	SD	127.5	17.17
	N	10	10
	%Diff G1	-2.6	-22.57
3F	Mean	995.0a	176.97
	SD	109.0	33.10
	N	10	10
	%Diff G1	-13.2	-9.20
4F	Mean	866.2c	192.20
	SD	140.9	34.21
	N	10	10
	%Diff G1	-24.4	-1.39

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

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1M	Mean	9.914	1.204	8.326	0.212	0.100	0.016	0.050
	SD	2.212	0.350	2.049	0.073	0.043	0.009	0.025
	N	5	5	5	5	5	5	5
4M	Mean	8.226	1.456	6.430	0.238	0.066	0.016	0.024
	SD	1.949	0.531	1.704	0.144	0.032	0.005	0.009
	N	5	5	5	5	5	5	5
	%Diff G1	-17.026	20.930	-22.772	12.264	-34.000	0.000	-52.000

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.580	13.32	40.38	53.28	17.56	32.98	12.56
	SD	0.285	0.37	1.17	2.02	0.59	0.18	0.90
	N	5	5	5	5	5	5	5
4M	Mean	7.416	13.32	40.72	54.94	17.98	32.72	13.66
	SD	0.199	0.29	0.72	1.28	0.46	0.43	0.71
	N	5	5	5	5	5	5	5
	%Diff G1	-2.164	0.00	0.84	3.12	2.39	-0.79	8.76

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1095.0	221.56
	SD	233.2	25.57
	N	5	5
4M	Mean	1114.6	245.88
	SD	155.1	33.19
	N	5	5
	%Diff G1	1.8	10.98

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	Mean	6.810	0.664	5.900	0.120	0.068	0.010	0.042
	SD	1.901	0.288	1.628	0.059	0.022	0.007	0.020
	N	5	5	5	5	5	5	5
4F	Mean	6.462	0.756	5.498	0.112	0.050	0.008	0.038
	SD	2.512	0.329	2.131	0.048	0.012	0.008	0.025
	N	5	5	5	5	5	5	5
	%Diff G1	-5.110	13.855	-6.814	-6.667	-26.471	-20.000	-9.524

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.480	13.30	39.70	53.10	17.78	33.50	11.28
	SD	0.489	0.84	2.06	0.99	0.22	0.57	0.13
	N	5	5	5	5	5	5	5
4F	Mean	7.060	12.82	38.96	55.22a	18.14	32.86	13.16d
	SD	0.227	0.19	0.39	1.52	0.42	0.26	0.46
	N	5	5	5	5	5	5	5
	%Diff G1	-5.615	-3.61	-1.86	3.99	2.02	-1.91	16.67

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

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1100.0	166.46
	SD	58.7	42.62
	N	5	5
4F	Mean	1231.0	225.46a
	SD	135.3	24.89
	N	5	5
	%Diff G1	11.9	35.44

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 Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	15.12	15.57	300.8
	SD	1.40	0.69	28.9
	N	10	10	10
2M	Mean	13.86	18.27f	662.0f
	SD	0.49	0.67	51.0
	N	10	10	10
	%Diff G1	-8.33	17.34	120.1
3M	Mean	12.79b	19.95f	742.3f
	SD	0.51	0.70	55.1
	N	10	10	10
	%Diff G1	-15.41	28.13	146.8
4M	Mean	19.78	12.37f	727.7f
	SD	2.14	0.53	56.5
	N	10	10	10
	%Diff G1	30.82	-20.55	141.9

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 Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	15.04	15.64	236.3
	SD	0.60	0.74	21.2
	N	9	9	9
2F	Mean	15.33	18.76c	478.6c
	SD	0.90	1.14	24.4
	N	10	10	10
	%Diff G1	1.90	19.91	102.5
3F	Mean	15.29	19.17c	510.5c
	SD	0.48	0.93	29.8
	N	10	10	10
	%Diff G1	1.63	22.54	116.0
4F	Mean	16.45b	20.28c	457.5c
	SD	1.07	0.71	34.9
	N	10	10	10
	%Diff G1	9.34	29.63	93.6

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

Table 6

Summary of Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	17.02	15.96	271.2
	SD	0.84	0.66	15.7
	N	5	5	5
4M	Mean	17.43	15.88	254.8
	SD	0.97	0.49	18.1
	N	4	4	4
	%Diff G1	2.38	-0.53	-6.1

Table 6

Summary of Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.14	15.48	226.8
	SD	0.62	0.24	19.9
	N	5	5	5
4F	Mean	17.70	16.00a	206.4
	SD	0.53	0.37	19.7
	N	5	5	5
	%Diff G1	3.27	3.36	-9.0

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 Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	71.9	42.9	161.0	2.0	346.5	0.070	13.8
	SD	17.1	9.6	39.5	0.0	187.2	0.017	2.3
	N	10	10	10	10	10	10	10
2M	Mean	90.8	44.1	161.9	2.0	631.7	0.087	17.5a
	SD	23.4	7.7	30.2	0.0	382.2	0.025	2.8
	N	10	10	10	10	10	10	10
	%Diff G1	26.3	2.8	0.6	0.0	82.3	24.286	26.8
3M	Mean	78.8	38.9	164.7	2.0	410.9	0.097a	17.5a
	SD	15.6	4.8	23.6	0.0	197.7	0.025	2.8
	N	10	10	10	10	10	10	10
	%Diff G1	9.6	-9.3	2.3	0.0	18.6	38.571	26.8
4M	Mean	96.1a	42.5	212.2b	2.0	521.0	0.102a	16.9a
	SD	18.2	10.5	42.0	0.0	285.9	0.029	3.0
	N	10	10	10	10	10	10	10
	%Diff G1	33.7	-0.9	31.8	0.0	50.4	45.714	22.5

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

Table 7

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	0.30	211.0	78.4	83.8	5.63	3.86	1.77
	SD	0.00	48.6	20.1	45.9	0.21	0.11	0.22
	N	10	10	10	10	10	10	10
2M	Mean	0.36	177.6	65.5	55.6	5.78	3.49f	2.29f
	SD	0.05	35.1	11.1	21.0	0.23	0.12	0.15
	N	10	10	10	10	10	10	10
	%Diff G1	20.00	-15.8	-16.5	-33.7	2.66	-9.59	29.38
3M	Mean	0.42c	173.8	73.2	60.8	5.85	3.55f	2.30f
	SD	0.06	20.1	16.6	17.3	0.20	0.13	0.17
	N	10	10	10	10	10	10	10
	%Diff G1	40.00	-17.6	-6.6	-27.4	3.91	-8.03	29.94
4M	Mean	0.40c	163.3	77.3	69.6	5.83	3.55f	2.28f
	SD	0.05	31.9	17.4	27.8	0.26	0.13	0.21
	N	10	10	10	10	10	10	10
	%Diff G1	33.33	-22.6	-1.4	-16.9	3.55	-8.03	28.81

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 Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	2.21	10.49	8.66	140.4	5.04	101.2
	SD	0.30	0.17	0.74	1.6	0.27	1.6
	N	10	10	10	10	10	10
2M	Mean	1.54c	10.87e	8.47	139.4	5.59e	100.0
	SD	0.11	0.26	0.49	1.2	0.41	1.2
	N	10	10	10	10	10	10
	%Diff G1	-30.32	3.62	-2.19	-0.7	10.91	-1.2
3M	Mean	1.56c	10.88e	8.82	139.5	5.65e	100.4
	SD	0.13	0.35	0.70	1.0	0.36	0.7
	N	10	10	10	10	10	10
	%Diff G1	-29.41	3.72	1.85	-0.6	12.10	-0.8
4M	Mean	1.57c	10.66	9.31	140.1	5.78f	100.5
	SD	0.16	0.24	0.67	1.0	0.42	1.2
	N	10	10	10	10	10	10
	%Diff G1	-28.96	1.62	7.51	-0.2	14.68	-0.7

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 Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	97.5	32.9	95.4	2.0	525.5	0.075	15.1
	SD	26.3	6.1	22.0	0.0	274.0	0.022	1.4
	N	10	10	10	10	10	10	10
2F	Mean	104.9	53.9a	86.9	2.0	457.0	0.092	16.8
	SD	36.6	25.0	19.9	0.0	328.0	0.023	2.8
	N	10	10	10	10	10	10	10
	%Diff G1	7.6	63.8	-8.9	0.0	-13.0	22.667	11.3
3F	Mean	112.1	51.3	109.5	2.0	459.7	0.098	17.3
	SD	27.6	29.5	16.3	0.0	400.6	0.020	2.7
	N	10	10	10	10	10	10	10
	%Diff G1	15.0	55.9	14.8	0.0	-12.5	30.667	14.6
4F	Mean	132.6	41.7	126.4e	2.0	446.2	0.115e	14.8
	SD	63.4	14.3	20.4	0.0	384.2	0.025	2.3
	N	10	10	10	10	10	10	10
	%Diff G1	36.0	26.7	32.5	0.0	-15.1	53.333	-2.0

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 Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	Mean	0.42	129.2	76.5	50.1	6.31	4.54	1.77
	SD	0.06	16.5	12.0	22.0	0.36	0.30	0.22
	N	10	10	10	10	10	10	10
2F	Mean	0.39	149.8	85.6	49.4	6.33	4.36	1.97
	SD	0.03	39.8	15.0	15.1	0.26	0.16	0.16
	N	10	10	10	10	10	10	10
	%Diff G1	-7.14	15.9	11.9	-1.4	0.32	-3.96	11.30
3F	Mean	0.44	144.9	92.3	61.1	6.22	4.26a	1.96
	SD	0.07	20.3	26.8	25.8	0.31	0.23	0.12
	N	10	10	10	10	10	10	10
	%Diff G1	4.76	12.2	20.7	22.0	-1.43	-6.17	10.73
4F	Mean	0.43	143.2	69.3	50.4	5.87b	4.16b	1.71
	SD	0.05	14.3	16.5	11.5	0.30	0.21	0.24
	N	10	10	10	10	10	10	10
	%Diff G1	2.38	10.8	-9.4	0.6	-6.97	-8.37	-3.39

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

Table 7

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.61	10.89	7.17	141.2	4.57	102.2
	SD	0.40	0.38	0.39	1.5	0.27	1.5
	N	10	10	10	10	10	10
2F	Mean	2.22	11.09	7.19	140.4	4.67	101.0
	SD	0.18	0.25	0.35	1.2	0.39	1.3
	N	10	10	10	10	10	10
	%Diff G1	-14.94	1.84	0.28	-0.6	2.19	-1.2
3F	Mean	2.17a	10.89	7.71d	140.6	4.65	100.3
	SD	0.12	0.29	0.45	1.2	0.35	1.5
	N	10	10	10	10	10	10
	%Diff G1	-16.86	0.00	7.53	-0.4	1.75	-1.9
4F	Mean	2.50	10.51d	7.33	140.5	4.72	101.6
	SD	0.46	0.33	0.63	1.5	0.33	3.0
	N	10	10	10	10	10	10
	%Diff G1	-4.21	-3.49	2.23	-0.5	3.28	-0.6

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 Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	103.2	43.0	133.6	2.0	623.6	0.044	17.2
	SD	14.8	6.4	40.0	0.0	206.8	0.030	1.3
	N	5	5	5	5	5	5	5
4M	Mean	116.6	47.6	146.4	2.0	802.0	0.050	17.8
	SD	28.8	6.7	39.5	0.0	359.0	0.012	2.8
	N	5	5	5	5	5	5	5
	%Diff G1	13.0	10.7	9.6	0.0	28.6	13.636	3.5

Table 7

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	Mean	0.36	224.8	71.4	90.6	5.54	3.82	1.72
	SD	0.05	23.1	17.8	20.3	0.18	0.25	0.19
	N	5	5	5	5	5	5	5
4M	Mean	0.32	189.8	69.4	71.2	5.54	3.86	1.68
	SD	0.04	31.2	9.2	22.6	0.18	0.11	0.15
	N	5	5	5	5	5	5	5
	%Diff G1	-11.11	-15.6	-2.8	-21.4	0.00	1.05	-2.33

Table 7

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	2.26	10.78	7.86	138.6	5.00	100.0
	SD	0.35	0.24	0.76	0.9	0.07	1.2
	N	5	5	5	5	5	5
4M	Mean	2.32	10.82	8.56	140.0a	5.34	100.4
	SD	0.22	0.26	0.78	1.0	0.47	1.7
	N	5	5	5	5	5	5
	%Diff G1	2.65	0.37	8.91	1.0	6.80	0.4

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 Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	86.0	41.0	93.0	2.0	446.6	0.022	16.4
	SD	32.3	9.1	36.8	0.0	355.5	0.030	3.0
	N	5	5	5	5	5	5	5
4F	Mean	96.2	43.8	119.8	2.0	509.4	0.036	14.4
	SD	17.9	7.2	28.6	0.0	318.5	0.023	1.7
	N	5	5	5	5	5	5	5
	%Diff G1	11.9	6.8	28.8	0.0	14.1	63.636	-12.2

Table 7

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	0.38	227.0	87.6	76.0	6.24	4.58	1.66
	SD	0.08	41.3	13.4	17.1	0.51	0.44	0.19
	N	5	5	5	5	5	5	5
4F	Mean	0.40	228.6	64.6a	56.2	5.86	4.38	1.48
	SD	0.00	30.4	10.2	14.9	0.40	0.34	0.11
	N	5	5	5	5	5	5	5
	%Diff G1	5.26	0.7	-26.3	-26.1	-6.09	-4.37	-10.84

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 Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.76	10.66	6.18	137.6	4.64	99.8
	SD	0.39	0.47	0.90	1.7	0.63	2.2
	N	5	5	5	5	5	5
4F	Mean	2.98	10.94	6.96	138.2	4.68	101.0
	SD	0.24	0.29	0.50	1.3	0.28	1.4
	N	5	5	5	5	5	5
	%Diff G1	7.97	2.63	12.62	0.4	0.86	1.2

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FINAL STUDY PLAN

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity 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

04 Oct 2016

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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:	05 Oct 2016
Experimental Completion Date:	15 Mar 2017
Animal Arrival:	05 Oct 2016
Initiation of Dosing:	20 Oct 2016 (Male) 21 Oct 2016 (Female)
Completion of In-life:	19 Nov 2016 (Main animals) 02 Dec 2016 (Recovery animals) (Last date of necropsy)
Unaudited Draft Report:	31 Jan 2017
Audited Draft Report:	08 Mar 2017
Final Report:	15 Mar 2017

3. GUIDELINES FOR STUDY DESIGN

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

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.
- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.

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

4. REGULATORY COMPLIANCE

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

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

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Stability testing of the supplied Test Item will be performed by the Sponsor or Sponsor subcontractor at a laboratory that follows FDA 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
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Management Contact

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

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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)

Analytical Chemistry
(Concentration and
Particle Size Analysis)

(b) (6)

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

Immunology
(Purity Analysis)

(b) (6)

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

Immunology
(Cytokine Analysis)

(b) (6)

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

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Tel: (b) (6)
E-mail: (b) (6)

Pathology Will be added by amendment

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

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

PI at Sponsor-designated Test Site

Anti-Therapeutic Antibody Analysis (b) (6)
Integrated BioTherapeutics, Inc.
21 Firstfield Road
Suite 100
Gaithersburg, MD 20878, 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: Will be added by amendment

Concentration: Will be added by amendment

Retest Date: 6 months after date of manufacture

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Physical Description:	To be added by amendment
Storage Conditions:	Kept in a refrigerator set to maintain 4°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, composition, and stability 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 and Reference 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, Particle size, and Encapsulation 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, a reserve sample (1 mL, 1 vial or 100 mg) 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 on ice pack (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
200 Technology Sq, 3rd Floor
Suite 300
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 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 discarded prior to report finalization.

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10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

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

N/A = Not applicable.

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 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 glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for

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

10.3.1.2. Stability Analysis

Stability data will be added by amendment.

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

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

11.1. Justification of Test System and Number of Animals

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

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

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

11.2. Animal Identification

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

11.3. Environmental Acclimation

A minimum acclimation period of 15 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

- = Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site will be alternated on each dosing occasion. 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.

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 two weeks during the predosing period.

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 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. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

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

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Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

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

14.5. Food Consumption

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

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 4 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

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

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

15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

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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 (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. Laboratory Investigations (Cytokine analysis)

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

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Sample Collection Schedule

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

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

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

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

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

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

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

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

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

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

16.1. Unscheduled Deaths

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

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters, cytokines 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 complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

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16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

17.3. Pathology Peer Review

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

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

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

18. CONSTRUCTED VARIABLES

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

19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokine Analysis	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

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

20. COMPUTERIZED SYSTEMS

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

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.

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Critical Computerized Systems

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

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

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

- Study Plan, study plan amendments, and deviations
- Study schedule

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- 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, cytokines and ATA sample collection and/or evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

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

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

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

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-MTL Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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TEST FACILITY APPROVAL

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

(b) (6)
(b) (6) Date: 04 Oct 2016

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

(b) (6)
(b) (6) Date: 04 OCT 2016

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SPONSOR APPROVAL

The Study Plan was approved by the Sponsor by email on 04 Oct 2016. The signature below confirms the approval of the Study Plan by the Sponsor Representative

(b) (6)

(b) (6) Date: 25Jan17

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ATTACHMENT A

Tissue Collection and Preservation

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

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the administration sites (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining administration sites (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 injection on Day 29
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 (nonprotocol tissues that may be present on a slide as a result of collection of protocol tissues) will be recorded when observed.

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STUDY PLAN AMENDMENT 1

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity 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: 04-Oct-2016

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: 18-Oct-2016**
7. RESPONSIBLE PERSONNEL	To update the conctact information for the PI assigned to the ATA analysis.
8.1. Test Item	To include the test item information as per the certificate of analysis.
10.1. Preparation of Reference Item	To clarify the storage for the aliquots.
14. IN LIFE PROCEDURES, OBSERVATIONS, AND MEASURMENTS	To remove unnecessary information.
14.5. Food Consumption	To remove unnecessary information.
15.2. Laboratory Investigations (Cytokine analysis)	To clarify that samples collected from the preterminally euthanized animals will be taken on recovery animals only.
15.3. Anti-therapeutic Antibody (ATA) Sample Collection, Processing, and Analysis	To update the conctact information for the shipment of the ATA samples for analysis.
ATTACHMENT A	To modify words in order to be in accordance with the OECD terminology and to clarify which lymph nodes will be processed to slides.

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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:	05 Oct 2016
Experimental Completion Date:	15 Mar 2017
Animal Arrival:	05 Oct 2016
Initiation of Dosing:	20 Oct 2016 (Male) 21 Oct 2016 (Female)
Completion of In-life:	19 Nov 2016 (Main animals) 02 Dec 2016 (Recovery animals) (Last date of necropsy)
Unaudited Draft Report:	31 Jan 2017
Audited Draft Report:	08 Mar 2017
Final Report:	15 Mar 2017

3. GUIDELINES FOR STUDY DESIGN

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

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.
- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.

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

4. REGULATORY COMPLIANCE

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

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

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Stability testing of the supplied Test Item will be performed by the Sponsor or Sponsor subcontractor at a laboratory that follows FDA 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
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Management Contact

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

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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)

Analytical Chemistry
(Concentration and
Particle Size Analysis)

(b) (6)

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

Immunology
(Purity Analysis)

(b) (6)

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

Immunology
(Cytokine Analysis)

(b) (6)

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

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Tel: (b) (6)
E-mail: (b) (6)

Pathology — Will be added by amendment

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

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

PI at Sponsor-designated Test Site

Anti-Therapeutic Antibody Analysis — (b) (6)
Integrated BioTherapeutics, Inc.
4 Research Court~~21 Firstfield Road~~
Suite 300~~Suite 100~~
Rockville, MD 20850~~Gaithersburg, MD 20878~~, 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: **MTDP16064~~Will be added by amendment~~**

Concentration: **1.7 mg/mL~~Will be added by amendment~~**

Retest Date: 6 months after date of manufacture

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Physical Description: **White to off-white lipid nanopacticle dispersion** ~~**To be added by amendment**~~

Storage Conditions: Kept in a refrigerator set to maintain 4°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, composition, and stability 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 and Reference 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, Particle size, and Encapsulation 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, a reserve sample (1 mL, 1 vial or 100 mg) 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 on ice pack (after completion of dosing).

Shipping Contact
(b) (6)
Moderna Therapeutics
200 Technology Sq, 3rd Floor
Suite 300
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** ~~**The aliquots**~~ 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.

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

10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

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

N/A = Not applicable.

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 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 glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of

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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

Stability data will be added by amendment.

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

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

11.1. Justification of Test System and Number of Animals

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

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

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

11.2. Animal Identification

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

11.3. Environmental Acclimation

A minimum acclimation period of 15 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

- = Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site will be alternated on each dosing occasion. 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.

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

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status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

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

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

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

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

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 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. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

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

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Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

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

14.5. Food Consumption

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

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 4 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

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

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

15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

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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 (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. Laboratory Investigations (Cytokine analysis)

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

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Sample Collection Schedule

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

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

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

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

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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~~21 Firstfield Road~~
Suite 300~~Suite 100~~
Rockville, MD 20850~~Gaithersburg, MD 20878~~, USA
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

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

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

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

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

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

16.1. Unscheduled Deaths

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

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters, cytokines 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 complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

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16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

17.3. Pathology Peer Review

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

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

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

18. CONSTRUCTED VARIABLES

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

19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokine Analysis	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

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

20. COMPUTERIZED SYSTEMS

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

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.

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Critical Computerized Systems

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

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

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

- Study Plan, study plan amendments, and deviations
- Study schedule

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- 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, cytokines and ATA sample collection and/or evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

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

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

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

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-MTL Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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AMENDMENT APPROVAL

(b) (6)

(b) (6) Date: 18 OCT 2016

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SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 18 Oct 2016.

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ATTACHMENT A

Tissue Collection and Preservation

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

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the administration sites **used on Day 29** (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining administration sites **used on Day 29** (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 injection on Day 29
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 (non**specified~~protocol~~** tissues **in the Study Plan** that may be present on a slide as a result of collection of **~~protocol~~Study Plan** tissues) will be recorded when observed.

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STUDY PLAN AMENDMENT 2

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity 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: 04-Oct-2016

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: 18-Oct-2016**
7. RESPONSIBLE PERSONNEL	To update the conctact information for the PI assigned to the ATA analysis.
8.1. Test Item	To include the test item information as per the certificate of analysis.
10.1. Preparation of Reference Item	To clarify the storage for the aliquots.
14. IN LIFE PROCEDURES, OBSERVATIONS, AND MEASURMENTS	To remove unnecessary information.
14.5. Food Consumption	To remove unnecessary information.
15.2. Laboratory Investigations (Cytokine analysis)	To clarify that samples collected from the preterminally euthanized animals will be taken on recovery animals only.
15.3. Anti-therapeutic Antibody (ATA) Sample Collection, Processing, and Analysis	To update the conctact information for the shipment of the ATA samples for analysis.
ATTACHMENT A	To modify words in order to be in accordance with the OECD terminology and to clarify which lymph nodes will be processed to slides.
Amendment 2	**Date: 16-Nov-2016**
5.2. Test Facility-designated Subcontractor(s)	To add histopathology as it will be performed at PAI-FDK.
7. RESPONSIBLE PERSONNEL	To assign a pathologist from PAI-FDK.
10.3.1.2. Stability Analysis	Section updated as no stability analysis will be performed; formulations were/will be prepared on each day of dosing.
17.2. Histopathology	To include that slides will be shipped to the pathologist.
17.3. Pathology Peer Review	To update as the pathology peer review will not be performed at the Test Facility.
ATTACHMENT A	To remove the histology and microscopic evaluation for the body nasal cavity since the olfactory bulb is already included in the examination of the seven levels of the brain.

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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:	05 Oct 2016
Experimental Completion Date:	15 Mar 2017
Animal Arrival:	05 Oct 2016
Initiation of Dosing:	20 Oct 2016 (Male) 21 Oct 2016 (Female)
Completion of In-life:	19 Nov 2016 (Main animals) 02 Dec 2016 (Recovery animals) (Last date of necropsy)
Unaudited Draft Report:	31 Jan 2017
Audited Draft Report:	08 Mar 2017
Final Report:	15 Mar 2017

3. GUIDELINES FOR STUDY DESIGN

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

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.
- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.

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

4. REGULATORY COMPLIANCE

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

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

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Stability testing of the supplied Test Item will be performed by the Sponsor or Sponsor subcontractor at a laboratory that follows FDA 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
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

The following study phases performed by Test Facility-designated subcontractors will be audited by the respective subcontractor QAP(s):

- **Histopathology**

For all study phase(s) inspected by subcontractor QAP(s), copies of each periodic inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility QAP.

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Appendix 1

Fax: (b) (6)
E-mail: (b) (6)

Management Contact

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

Analytical Chemistry
(Concentration and
Particle Size Analysis)

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

Immunology
(Purity Analysis)

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

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Immunology
(Cytokine Analysis) (b) (6)

Charles River Laboratories Montreal ULC
Sherbrooke Site (CR-SHB)
1580 Ida-Métivier
Sherbrooke, QC J1E 0B5
Canada
Tel: (b) (6)
E-mail: (b) (6)

~~**Pathology** **Will be added by amendment**~~

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

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

Principal Investigators (PI) at a Test Facility-designated Test Site

Pathology (b) (6)

Charles River Laboratories, Inc. (PAI-FDK)
15 Worman's Mill Ct., Suite I
Frederick, MD 21701, USA
Main Telephone: (b) (6)
Direct Telephone: (b) (6)
E-mail: (b) (6)

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

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

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PI at Sponsor-designated Test Site

Anti-Therapeutic
Antibody Analysis

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

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:	MTDP16064
Concentration:	1.7 mg/mL
Retest Date:	6 months after date of manufacture
Physical Description:	White to off-white lipid nanopacticle dispersion
Storage Conditions:	Kept in a refrigerator set to maintain 4°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

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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, composition, and stability 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 and Reference 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, Particle size, and Encapsulation 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, a reserve sample (1 mL, 1 vial or 100 mg) will be collected and maintained under the appropriate storage conditions by the Test Facility.

8.6. Test and Reference Item Inventory and Disposition

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

Shipping Contact
(b) (6)
Moderna Therapeutics
200 Technology Sq, 3rd Floor
Suite 300

Appendix 1

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 discarded prior to report finalization.

10.3. Sample Collection and Analysis

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

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Dose Formulation Sample Collection Schedule

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

N/A = Not applicable.

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 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 glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

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10.3.1.2. Stability Analysis

There will be no stability analysis performed for concentration used on this study.~~Stability data will be added by amendment.~~

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

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

11.1. Justification of Test System and Number of Animals

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

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

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

11.2. Animal Identification

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

11.3. Environmental Acclimation

A minimum acclimation period of 15 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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

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

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

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

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

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

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

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12.4. Water

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

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

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

12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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13. EXPERIMENTAL DESIGN

Experimental Design

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

- = Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site will be alternated on each dosing occasion. 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.

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. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

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14.1. Mortality/Moribundity Checks

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

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

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

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

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 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. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

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

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Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

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

14.5. Food Consumption

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

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 4 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

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.

Appendix 1

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

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

15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

Appendix 1

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 (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. Laboratory Investigations (Cytokine analysis)

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

Appendix 1

Sample Collection Schedule

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

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

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

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

Appendix 1

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

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

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters, cytokines 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 complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

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16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

The appropriate Charles River Laboratories, Pathology Associates Test Site will be contacted for the slide shipping address.

17.3. Pathology Peer Review

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

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

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

18. CONSTRUCTED VARIABLES

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

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19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokine Analysis	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

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

20. COMPUTERIZED SYSTEMS

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

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

Critical Computerized Systems

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

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

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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, cytokines and ATA sample collection and/or evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

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

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

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

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-MTL Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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AMENDMENT APPROVAL

(b) (6)

(b) (6)

Date: 16 November 2016

(b) (6)

(b) (6)

Date: 16 Nov 2016

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SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 15 Nov 2016.

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ATTACHMENT A

Tissue Collection and Preservation

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

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Inguinal	-	X	X	X	Lymph node draining the administration sites used on Day 29 (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining administration sites used on Day 29 (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 injection on Day 29
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

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STUDY PLAN AMENDMENT 3

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity 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: 04-Oct-2016

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: 18-Oct-2016**
7. RESPONSIBLE PERSONNEL	To update the conctact information for the PI assigned to the ATA analysis.
8.1. Test Item	To include the test item information as per the certificate of analysis.
10.1. Preparation of Reference Item	To clarify the storage for the aliquots.
14. IN LIFE PROCEDURES, OBSERVATIONS, AND MEASURMENTS	To remove unnecessary information.
14.5. Food Consumption	To remove unnecessary information.
15.2. Laboratory Investigations (Cytokine analysis)	To clarify that samples collected from the preterminally euthanized animals will be taken on recovery animals only.
15.3. Anti-therapeutic Antibody (ATA) Sample Collection, Processing, and Analysis	To update the conctact information for the shipment of the ATA samples for analysis.
ATTACHMENT A	To modify words in order to be in accordance with the OECD terminology and to clarify which lymph nodes will be processed to slides.
Amendment 2	**Date: 16-Nov-2016**
5.2. Test Facility-designated Subcontractor(s)	To add histopathology as it will be performed at PAI-FDK.
7. RESPONSIBLE PERSONNEL	To assign a pathologist from PAI-FDK.
10.3.1.2. Stability Analysis	Section updated as no stability analysis will be performed; formulations were/will be prepared on each day of dosing.
17.2. Histopathology	To include that slides will be shipped to the pathologist.
17.3. Pathology Peer Review	To update as the pathology peer review will not be performed at the Test Facility.
ATTACHMENT A	To remove the histology and microscopic evaluation for the body nasal cavity since the olfactory bulb is already included in the examination of the seven levels of the brain.
Amendment 3	**Date: 13-Dec-2016**
10.2. Preparation of Test Item	To include that all residual volume of formulated test item will be shipped to the sponsor for 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:	05 Oct 2016
Experimental Completion Date:	15 Mar 2017
Animal Arrival:	05 Oct 2016
Initiation of Dosing:	20 Oct 2016 (Male) 21 Oct 2016 (Female)
Completion of In-life:	19 Nov 2016 (Main animals) 02 Dec 2016 (Recovery animals) (Last date of necropsy)
Unaudited Draft Report:	31 Jan 2017
Audited Draft Report:	08 Mar 2017
Final Report:	15 Mar 2017

3. GUIDELINES FOR STUDY DESIGN

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

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.
- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.

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

4. REGULATORY COMPLIANCE

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

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

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Stability testing of the supplied Test Item will be performed by the Sponsor or Sponsor subcontractor at a laboratory that follows FDA 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
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

The following study phases performed by Test Facility-designated subcontractors will be audited by the respective subcontractor QAP(s):

- Histopathology

For all study phase(s) inspected by subcontractor QAP(s), copies of each periodic inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility QAP.

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Appendix 1

Fax: (b) (6)
E-mail: (b) (6)

Management Contact

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

Analytical Chemistry
(Concentration and
Particle Size Analysis)

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

Immunology
(Purity Analysis)

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

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Immunology
(Cytokine Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Sherbrooke Site (CR-SHB)
1580 Ida-Métivier
Sherbrooke, QC J1E 0B5
Canada
Tel: (b) (6)
E-mail: (b) (6)

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

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

Principal Investigators (PI) at a Test Facility-designated Test Site

Pathology

(b) (6)

Charles River Laboratories, Inc. (PAI-FDK)
15 Worman's Mill Ct., Suite I
Frederick, MD 21701, USA
Main Telephone: (b) (6)
Direct Telephone: (b) (6)
E-mail: (b) (6)

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

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

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PI at Sponsor-designated Test Site

Anti-Therapeutic
Antibody Analysis

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

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:	MTDP16064
Concentration:	1.7 mg/mL
Retest Date:	6 months after date of manufacture
Physical Description:	White to off-white lipid nanopacticle dispersion
Storage Conditions:	Kept in a refrigerator set to maintain 4°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

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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, composition, and stability 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 and Reference 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, Particle size, and Encapsulation 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, a reserve sample (1 mL, 1 vial or 100 mg) will be collected and maintained under the appropriate storage conditions by the Test Facility.

8.6. Test and Reference Item Inventory and Disposition

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

Shipping Contact
(b) (6)
Moderna Therapeutics
200 Technology Sq, 3rd Floor
Suite 300

Appendix 1

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 shipped on ice pack to the sponsor at the following address :~~discarded prior to report finalization.~~**

Shipping Contact
(b) (6)
Moderna Therapeutics
300 Technology Sq, 3rd Floor
Cambridge MA 02139
E-mail: (b) (6)

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Residual volumes of formulated Test Item will be analyzed for mRNA/lipid identity confirmation. Results will be provided to the Test Facility and will not be included in the report unless deemed appropriate 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[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 29	N/A	All groups	Dosing container

N/A = Not applicable.

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 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 glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.

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Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

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

11.1. Justification of Test System and Number of Animals

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

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

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

11.2. Animal Identification

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

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11.3. Environmental Acclimation

A minimum acclimation period of 15 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%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

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12.3. Food

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

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

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

12.4. Water

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

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

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

12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

13. EXPERIMENTAL DESIGN

Experimental Design

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

- = Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site will be alternated on each dosing occasion. 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.

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. During the study, additional evaluations to those described

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below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

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

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

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

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

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 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. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

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

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Severe edema	4

Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

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

Procedure: Animals will be individually weighed. A fasted weight will be recorded on the day of necropsy. Terminal body weights will not be collected from animals found dead or euthanized moribund.

14.5. Food Consumption

Frequency: Weekly, starting Day -7, throughout the dosing and recovery periods.

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

14.6. Ophthalmic Examinations

Frequency: Once prestudy and again toward the end of Week 4 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.

Procedure: All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.

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

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

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

15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

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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 (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. Laboratory Investigations (Cytokine analysis)

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

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Sample Collection Schedule

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

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

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

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

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

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

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters, cytokines 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 complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

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16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

The appropriate Charles River Laboratories, Pathology Associates Test Site will be contacted for the slide shipping address.

17.3. Pathology Peer Review

A pathology peer review will be conducted by:

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

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

18. CONSTRUCTED VARIABLES

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

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19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokine Analysis	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

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

20. COMPUTERIZED SYSTEMS

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

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

Critical Computerized Systems

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

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

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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, cytokines and ATA sample collection and/or evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

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

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

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

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-MTL 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: 13 DEC 2016

(b) (6)

Appendix 1

SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 13 Dec 2016.

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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 administration sites used on Day 29 (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining administration sites used on Day 29 (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 injection on Day 29
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

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STUDY PLAN AMENDMENT 4

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity 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: 04-Oct-2016

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: 18-Oct-2016**
7. RESPONSIBLE PERSONNEL	To update the conctact information for the PI assigned to the ATA analysis.
8.1. Test Item	To include the test item information as per the certificate of analysis.
10.1. Preparation of Reference Item	To clarify the storage for the aliquots.
14. IN LIFE PROCEDURES, OBSERVATIONS, AND MEASURMENTS	To remove unnecessary information.
14.5. Food Consumption	To remove unnecessary information.
15.2. Laboratory Investigations (Cytokine analysis)	To clarify that samples collected from the preterminally euthanized animals will be taken on recovery animals only.
15.3. Anti-therapeutic Antibody (ATA) Sample Collection, Processing, and Analysis	To update the conctact information for the shipment of the ATA samples for analysis.
ATTACHMENT A	To modify words in order to be in accordance with the OECD terminology and to clarify which lymph nodes will be processed to slides.
Amendment 2	**Date: 16-Nov-2016**
5.2. Test Facility-designated Subcontractor(s)	To add histopathology as it will be performed at PAI-FDK.
7. RESPONSIBLE PERSONNEL	To assign a pathologist from PAI-FDK.
10.3.1.2. Stability Analysis	Section updated as no stability analysis will be performed; formulations were/will be prepared on each day of dosing.
17.2. Histopathology	To include that slides will be shipped to the pathologist.
17.3. Pathology Peer Review	To update as the pathology peer review will not be performed at the Test Facility.
ATTACHMENT A	To remove the histology and microscopic evaluation for the body nasal cavity since the olfactory bulb is already included in the examination of the seven levels of the brain.
Amendment 3	**Date: 13-Dec-2016**
10.2. Preparation of Test Item	To include that all residual volume of formulated test item will be shipped to the sponsor for analysis.
Amendment 4	**Date: 25-Jan-2017**
4. REGULATORY COMPLIANCE	To remove the stability testing since an end-of-use analysis of the bulk Test Item will be conducted by the Test Facility to demonstrate the stability of the Test Item during the dosing period.
8.3. Test and Reference Item Characterization	To remove stability since an end-of-use analysis of the bulk Test Item will be conducted to demonstrate stability of the Test Item during the dosing period.
8.6. Test and Reference Item Inventory and Disposition	To update since remaining bulk Test Item will be discarded as per Sponsor request.

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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:	05 Oct 2016
Experimental Completion Date:	15 Mar 2017
Animal Arrival:	05 Oct 2016
Initiation of Dosing:	20 Oct 2016 (Male) 21 Oct 2016 (Female)
Completion of In-life:	19 Nov 2016 (Main animals) 02 Dec 2016 (Recovery animals) (Last date of necropsy)
Unaudited Draft Report:	31 Jan 2017
Audited Draft Report:	08 Mar 2017
Final Report:	15 Mar 2017

3. GUIDELINES FOR STUDY DESIGN

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

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.
- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.

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

4. REGULATORY COMPLIANCE

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

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

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- ~~**Stability testing of the supplied Test Item will be performed by the Sponsor or Sponsor subcontractor at a laboratory that follows FDA 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
Senneville Site (CR-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (b) (6)
E-mail: (b) (6)

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

The following study phases performed by Test Facility-designated subcontractors will be audited by the respective subcontractor QAP(s):

- Histopathology

For all study phase(s) inspected by subcontractor QAP(s), copies of each periodic inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility QAP.

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Appendix 1

Fax: (b) (6)
E-mail: (b) (6)

Management Contact

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

Analytical Chemistry
(Concentration and
Particle Size Analysis)

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

Immunology
(Purity Analysis)

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

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Immunology
(Cytokine Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Sherbrooke Site (CR-SHB)
1580 Ida-Métivier
Sherbrooke, QC J1E 0B5
Canada
Tel: (b) (6)
E-mail: (b) (6)

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

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

Principal Investigators (PI) at a Test Facility-designated Test Site

Pathology

(b) (6)

Charles River Laboratories, Inc. (PAI-FDK)
15 Worman's Mill Ct., Suite I
Frederick, MD 21701, USA
Main Telephone: (b) (6)
Direct Telephone: (b) (6)
E-mail: (b) (6)

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

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

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PI at Sponsor-designated Test Site

Anti-Therapeutic
Antibody Analysis

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

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:	MTDP16064
Concentration:	1.7 mg/mL
Retest Date:	6 months after date of manufacture
Physical Description:	White to off-white lipid nanopacticle dispersion
Storage Conditions:	Kept in a refrigerator set to maintain 4°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

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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~~ **and** composition~~, and stability~~ 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 and Reference 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, Particle size, and Encapsulation 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, a reserve sample (1 mL, 1 vial or 100 mg) 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 **discarded prior to report finalization.**~~**returned to the Sponsor on ice pack (after completion of dosing).**~~

~~**Shipping Contact**~~
(b) (6)
~~**Moderna Therapeutics**~~
~~**200 Technology Sq, 3rd Floor**~~
~~**Suite 300**~~

Appendix 1

~~**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 shipped on ice pack to the sponsor at the following address :

Shipping Contact
(b) (6)
Moderna Therapeutics
300 Technology Sq, 3rd Floor
Cambridge MA 02139
E-mail: (b) (6)

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Residual volumes of formulated Test Item will be analyzed for mRNA/lipid identity confirmation. Results will be provided to the Test Facility and will not be included in the report unless deemed appropriate 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[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 29	N/A	All groups	Dosing container

N/A = Not applicable.

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 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 glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.

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Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

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

11.1. Justification of Test System and Number of Animals

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

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

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

11.2. Animal Identification

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

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11.3. Environmental Acclimation

A minimum acclimation period of 15 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%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

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12.3. Food

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

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

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

12.4. Water

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

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

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

12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

13. EXPERIMENTAL DESIGN

Experimental Design

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

- = Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site will be alternated on each dosing occasion. 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.

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. During the study, additional evaluations to those described

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below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

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

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

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

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

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 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. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

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

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Severe edema	4

Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

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

Procedure: Animals will be individually weighed. A fasted weight will be recorded on the day of necropsy. Terminal body weights will not be collected from animals found dead or euthanized moribund.

14.5. Food Consumption

Frequency: Weekly, starting Day -7, throughout the dosing and recovery periods.

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

14.6. Ophthalmic Examinations

Frequency: Once prestudy and again toward the end of Week 4 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.

Procedure: All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.

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

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

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

15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

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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 (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. Laboratory Investigations (Cytokine analysis)

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

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Sample Collection Schedule

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

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

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

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

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

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

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters, cytokines 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 complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

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16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

The appropriate Charles River Laboratories, Pathology Associates Test Site will be contacted for the slide shipping address.

17.3. Pathology Peer Review

A pathology peer review will be conducted by:

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

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

18. CONSTRUCTED VARIABLES

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

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19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokine Analysis	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

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

20. COMPUTERIZED SYSTEMS

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

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

Critical Computerized Systems

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

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

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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, cytokines and ATA sample collection and/or evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

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

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

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

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-MTL Institutional Animal Care and Use Committee (IACUC). During the study, the care and use of animals will be conducted with guidance from the USA National Research Council and the Canadian Council on Animal Care (CCAC).

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AMENDMENT APPROVAL

(b) (6) _____ Date: 25 JAN 2017

(b) (6)

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SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 25 Jan 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	-
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 administration sites used on Day 29 (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining administration sites used on Day 29 (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 injection on Day 29
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

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STUDY PLAN AMENDMENT 5

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity 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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Appendix 1

SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 04-Oct-2016

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: 18-Oct-2016**
7. RESPONSIBLE PERSONNEL	To update the conctact information for the PI assigned to the ATA analysis.
8.1. Test Item	To include the test item information as per the certificate of analysis.
10.1. Preparation of Reference Item	To clarify the storage for the aliquots.
14. IN LIFE PROCEDURES, OBSERVATIONS, AND MEASURMENTS	To remove unnecessary information.
14.5. Food Consumption	To remove unnecessary information.
15.2. Laboratory Investigations (Cytokine analysis)	To clarify that samples collected from the preterminally euthanized animals will be taken on recovery animals only.
15.3. Anti-therapeutic Antibody (ATA) Sample Collection, Processing, and Analysis	To update the conctact information for the shipment of the ATA samples for analysis.
ATTACHMENT A	To modify words in order to be in accordance with the OECD terminology and to clarify which lymph nodes will be processed to slides.
Amendment 2	**Date: 16-Nov-2016**
5.2. Test Facility-designated Subcontractor(s)	To add histopathology as it will be performed at PAI-FDK.
7. RESPONSIBLE PERSONNEL	To assign a pathologist from PAI-FDK.
10.3.1.2. Stability Analysis	Section updated as no stability analysis will be performed; formulations were/will be prepared on each day of dosing.
17.2. Histopathology	To include that slides will be shipped to the pathologist.
17.3. Pathology Peer Review	To update as the pathology peer review will not be performed at the Test Facility.
ATTACHMENT A	To remove the histology and microscopic evaluation for the body nasal cavity since the olfactory bulb is already included in the examination of the seven levels of the brain.
Amendment 3	**Date: 13-Dec-2016**
10.2. Preparation of Test Item	To include that all residual volume of formulated test item will be shipped to the sponsor for analysis.
Amendment 4	**Date: 25-Jan-2017**
4. REGULATORY COMPLIANCE	To remove the stability testing since an end-of-use analysis of the bulk Test Item will be conducted by the Test Facility to demonstrate the stability of the Test Item during the dosing period.
8.3. Test and Reference Item Characterization	To remove stability since an end-of-use analysis of the bulk Test Item will be conducted to demonstrate stability of the Test Item during the dosing period.
8.6. Test and Reference Item Inventory and Disposition	To update since remaining bulk Test Item will be discarded as per Sponsor request.

Appendix 1

Item or Section(s)	Justification
Amendment 5	**Date: 16-Feb-2017**
8.4. Analysis of Test Item	To remove the encapsulation analysis since it will not be performed.
22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS	To clarify the Charles River archive site.

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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:	05 Oct 2016
Experimental Completion Date:	15 Mar 2017
Animal Arrival:	05 Oct 2016
Initiation of Dosing:	20 Oct 2016 (Male) 21 Oct 2016 (Female)
Completion of In-life:	19 Nov 2016 (Main animals) 02 Dec 2016 (Recovery animals) (Last date of necropsy)
Unaudited Draft Report:	31 Jan 2017
Audited Draft Report:	08 Mar 2017
Final Report:	15 Mar 2017

3. GUIDELINES FOR STUDY DESIGN

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

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.
- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.

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

4. REGULATORY COMPLIANCE

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

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

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines 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 assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

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

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

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

The following study phases performed by Test Facility-designated subcontractors will be audited by the respective subcontractor QAP(s):

- Histopathology

For all study phase(s) inspected by subcontractor QAP(s), copies of each periodic inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility QAP.

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Appendix 1

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)

Analytical Chemistry (Concentration and Particle Size Analysis)

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

Immunology (Purity Analysis)

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

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Immunology
(Cytokine Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Sherbrooke Site (CR-SHB)
1580 Ida-Métivier
Sherbrooke, QC J1E 0B5
Canada
Tel: (b) (6)
E-mail: (b) (6)

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

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

Principal Investigators (PI) at a Test Facility-designated Test Site

Pathology

(b) (6)

Charles River Laboratories, Inc. (PAI-FDK)
15 Worman's Mill Ct., Suite I
Frederick, MD 21701, USA
Main Telephone: (b) (6)
Direct Telephone: (b) (6)
E-mail: (b) (6)

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

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

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PI at Sponsor-designated Test Site

Anti-Therapeutic
Antibody Analysis

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

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:	MTDP16064
Concentration:	1.7 mg/mL
Retest Date:	6 months after date of manufacture
Physical Description:	White to off-white lipid nanopacticle dispersion
Storage Conditions:	Kept in a refrigerator set to maintain 4°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

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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 and Reference 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~~, and Encapsulation~~ 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, a reserve sample (1 mL, 1 vial or 100 mg) 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 discarded prior to report finalization.

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.

Appendix 1

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 shipped on ice pack to the sponsor at the following address :

Shipping Contact
(b) (6)
Moderna Therapeutics
300 Technology Sq, 3rd Floor
Cambridge MA 02139
E-mail: (b) (6)

Residual volumes of formulated Test Item will be analyzed for mRNA/lipid identity confirmation. Results will be provided to the Test Facility and will not be included in the report unless deemed appropriate 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.

Appendix 1

Dose Formulation Sample Collection Schedule

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

N/A = Not applicable.

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 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 glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

Appendix 1

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, 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 15 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.

Appendix 1

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).

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

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

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12.4. Water

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

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

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

12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

Appendix 1

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

- = Not applicable

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site will be alternated on each dosing occasion. 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.

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. 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.

Appendix 1

14.1. Mortality/Moribundity Checks

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

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

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

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

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 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. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

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

Appendix 1

Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

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

14.5. Food Consumption

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

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 4 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

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.

Appendix 1

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

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

15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

Appendix 1

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 (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. Laboratory Investigations (Cytokine analysis)

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

Appendix 1

Sample Collection Schedule

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

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

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

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

Appendix 1

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

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

Appendix 1

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

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

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

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

[b] Animals found dead or euthanized before the initiation of dosing.

16.1. Unscheduled Deaths

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

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters, cytokines 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 complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

Appendix 1

16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

The appropriate Charles River Laboratories, Pathology Associates Test Site will be contacted for the slide shipping address.

17.3. Pathology Peer Review

A pathology peer review will be conducted by:

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

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

18. CONSTRUCTED VARIABLES

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

Appendix 1

19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokine Analysis	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

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

20. COMPUTERIZED SYSTEMS

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

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

Critical Computerized Systems

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

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

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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, cytokines and ATA sample collection and/or evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

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

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

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

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-MTL 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: 16 Feb 2017

(b) (6)

Appendix 1

SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 16 Feb 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	-
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 administration sites used on Day 29 (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining administration sites used on Day 29 (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 injection on Day 29
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

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STUDY PLAN AMENDMENT 6

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity 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: 04-Oct-2016

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: 18-Oct-2016**
7. RESPONSIBLE PERSONNEL	To update the conctact information for the PI assigned to the ATA analysis.
8.1. Test Item	To include the test item information as per the certificate of analysis.
10.1. Preparation of Reference Item	To clarify the storage for the aliquots.
14. IN LIFE PROCEDURES, OBSERVATIONS, AND MEASURMENTS	To remove unnecessary information.
14.5. Food Consumption	To remove unnecessary information.
15.2. Laboratory Investigations (Cytokine analysis)	To clarify that samples collected from the preterminally euthanized animals will be taken on recovery animals only.
15.3. Anti-therapeutic Antibody (ATA) Sample Collection, Processing, and Analysis	To update the conctact information for the shipment of the ATA samples for analysis.
ATTACHMENT A	To modify words in order to be in accordance with the OECD terminology and to clarify which lymph nodes will be processed to slides.
Amendment 2	**Date: 16-Nov-2016**
5.2. Test Facility-designated Subcontractor(s)	To add histopathology as it will be performed at PAI-FDK.
7. RESPONSIBLE PERSONNEL	To assign a pathologist from PAI-FDK.
10.3.1.2. Stability Analysis	Section updated as no stability analysis will be performed; formulations were/will be prepared on each day of dosing.
17.2. Histopathology	To include that slides will be shipped to the pathologist.
17.3. Pathology Peer Review	To update as the pathology peer review will not be performed at the Test Facility.
ATTACHMENT A	To remove the histology and microscopic evaluation for the body nasal cavity since the olfactory bulb is already included in the examination of the seven levels of the brain.
Amendment 3	**Date: 13-Dec-2016**
10.2. Preparation of Test Item	To include that all residual volume of formulated test item will be shipped to the sponsor for analysis.
Amendment 4	**Date: 25-Jan-2017**
4. REGULATORY COMPLIANCE	To remove the stability testing since an end-of-use analysis of the bulk Test Item will be conducted by the Test Facility to demonstrate the stability of the Test Item during the dosing period.
8.3. Test and Reference Item Characterization	To remove stability since an end-of-use analysis of the bulk Test Item will be conducted to demonstrate stability of the Test Item during the dosing period.
8.6. Test and Reference Item Inventory and Disposition	To update since remaining bulk Test Item will be discarded as per Sponsor request.

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Item or Section(s)	Justification
Amendment 5	**Date: 16-Feb-2017**
8.4. Analysis of Test Item	To remove the encapsulation analysis since it will not be performed.
22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS	To clarify the Charles River archive site.
Amendment 6	**Date: 12-May-2017**
8.1. Test Item	To include clarification for TI concentration based on new Summary of Analysis (SoA) issued.
13. EXPERIMENTAL DESIGN	To include clarification to dose levels and dose concentrations based on new SoA issued

Appendix 1

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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:	05 Oct 2016
Experimental Completion Date:	15 Mar 2017
Animal Arrival:	05 Oct 2016
Initiation of Dosing:	20 Oct 2016 (Male) 21 Oct 2016 (Female)
Completion of In-life:	19 Nov 2016 (Main animals) 02 Dec 2016 (Recovery animals) (Last date of necropsy)
Unaudited Draft Report:	31 Jan 2017
Audited Draft Report:	08 Mar 2017
Final Report:	15 Mar 2017

3. GUIDELINES FOR STUDY DESIGN

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

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.
- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.

Appendix 1

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

4. REGULATORY COMPLIANCE

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

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

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines 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 assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

Appendix 1

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

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

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

The following study phases performed by Test Facility-designated subcontractors will be audited by the respective subcontractor QAP(s):

- Histopathology

For all study phase(s) inspected by subcontractor QAP(s), copies of each periodic inspection report will be made available to the Study Director, Test Facility Management, and the Test Facility QAP.

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Appendix 1

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)

Analytical Chemistry (Concentration and Particle Size Analysis)

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

Immunology (Purity Analysis)

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

Appendix 1

Immunology
(Cytokine Analysis)

(b) (6)

Charles River Laboratories Montreal ULC
Sherbrooke Site (CR-SHB)
1580 Ida-Métivier
Sherbrooke, QC J1E 0B5
Canada
Tel: (b) (6)
E-mail: (b) (6)

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

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

Principal Investigators (PI) at a Test Facility-designated Test Site

Pathology

(b) (6)

Charles River Laboratories, Inc. (PAI-FDK)
15 Worman's Mill Ct., Suite I
Frederick, MD 21701, USA
Main Telephone: (b) (6)
Direct Telephone: (b) (6)
E-mail: (b) (6)

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

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

Appendix 1

PI at Sponsor-designated Test Site

Anti-Therapeutic
Antibody Analysis

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

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:	MTDP16064
Concentration:	1.7 **/ 2.2*** mg/mL
Retest Date:	6 months after date of manufacture
Physical Description:	White to off-white lipid nanopacticle dispersion
Storage Conditions:	Kept in a refrigerator set to maintain 4°C

*** Concentration based on SoA released on 11 October 2016 / Concentration based on SoA released on 03 May 2017**

8.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Supplier:	Will be included in the Final Report

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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 and Reference 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, a reserve sample (1 mL, 1 vial or 100 mg) 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 discarded prior to report finalization.

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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 shipped on ice pack to the sponsor at the following address :

Shipping Contact
(b) (6)
Moderna Therapeutics
300 Technology Sq, 3rd Floor
Cambridge MA 02139
E-mail: (b) (6)

Residual volumes of formulated Test Item will be analyzed for mRNA/lipid identity confirmation. Results will be provided to the Test Facility and will not be included in the report unless deemed appropriate 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[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 29	N/A	All groups	Dosing container

N/A = Not applicable.

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 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 glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for

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

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	126 to 150 g (males) 101 to 125 g (females)

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

11.1. Justification of Test System and Number of Animals

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

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

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

11.2. Animal Identification

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

11.3. Environmental Acclimation

A minimum acclimation period of 15 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[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1706	10 **/ 13**	200	0.05 **/ 0.07**	10	10	-	-
3	mRNA-1706	50 **/ 65**	200	0.25 **/ 0.33**	10	10	-	-
4	mRNA-1706	100 **/ 129**	200	0.5 **/ 0.65**	10	10	5	5

- = Not applicable

[a] **Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.**

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site will be alternated on each dosing occasion. 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.

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. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

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14.1. Mortality/Moribundity Checks

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

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

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

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

Procedure: Animals removed from the cage for examination.

14.3. Local Irritation Assessment

Frequency: On days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 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. Observations will be scored according to the Local Irritation Assessment scoring table as follows:

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

Appendix 1

Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

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

14.5. Food Consumption

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

14.6. Ophthalmic Examinations

Frequency:	Once prestudy and again toward the end of Week 4 of the dosing period. During Week 2 of the recovery period if Test Item-related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be Atropine 0.126%.
Evaluation:	A report will be included as an appendix to the Final Report.

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.

Appendix 1

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

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

15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

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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 (Section 16.5). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. Laboratory Investigations (Cytokine analysis)

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

Appendix 1

Sample Collection Schedule

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

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

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

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

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

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

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters, cytokines 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 complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

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16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

The appropriate Charles River Laboratories, Pathology Associates Test Site will be contacted for the slide shipping address.

17.3. Pathology Peer Review

A pathology peer review will be conducted by:

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

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

18. CONSTRUCTED VARIABLES

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

Appendix 1

19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokine Analysis	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

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

20. COMPUTERIZED SYSTEMS

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

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

Critical Computerized Systems

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

21. AMENDMENTS AND DEVIATIONS

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

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

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred to CR-MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Appendix 1

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, cytokines and ATA sample collection and/or evaluation
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

23. REPORTING

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

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

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

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-MTL 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: 12 May 2017

(b) (6)

Appendix 1

SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 12 May 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	-
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-

Appendix 1

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 administration sites used on Day 29 (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining administration sites used on Day 29 (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 injection on Day 29
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

Appendix 1

DEVIATIONS

All deviations that occurred during the study have been authorized/acknowledged by the Study Director, assessed for impact, and documented in the study records. All study plan deviations and those SOP deviations that could have impacted the quality or integrity of the study are listed below.

None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

In-life Observations, Measurements, and Evaluations

- On Day 13 for males and Day 12 for females, the mortality/moribundity check was not performed in the AM. This deviation was considered to have had no impact on the animals health since animals were in good conditions during the PM mortality check.
- On Week 2 the food consumption could not be evaluated for animal Nos. 3004, 3005 and 3006. The food was dropped on the floor due to a technical oversight. This deviation was considered during data interpretation and therefore had no impact on the study integrity.
- For some animals, on Day 16, local irritation assessment for site 2 was performed 1 to 6 minutes before the 24 hours post dose due to a technical oversight. This had no impact on the study integrity since this was a minor time deviation.
- On Day 30, a hopper of food was found in the cage of female Nos. 2509 and 2510 and therefore, animals were not fasted prior to their terminal body weight measurement. This deviation was considered during data interpretation and therefore had no impact on the study integrity.

Laboratory Evaluations

- Samples for INF-α were analyzed with an ELISA kit which detects anti-IFN-α antibodies instead of the cytokine IFN-α. Error was due to an incorrectly recorded vendor kit identification during assay method development. The error was also propagated during transfer of the method to the site(s) approved Analytical Procedure and Laboratory Method (CAPA issued on 23 Aug 2017). Therefore, results could not be used for INF-α evaluation and there is no remaining samples to repeat the analysis with the appropriate assay reagents. Results were considered invalid and were not reported. The omission of IFN-α results on this study does not have an impact on the overall study integrity as the remaining safety endpoints on this study are sufficient for safety evaluation.

Appendix 1

- Some ATA blood samples were allowed to clot less than 20 minutes or more than 60 minutes prior to centrifugation:
    - Sample from animal No. 1003 allowed to clot at room temperature for 19 minutes prior centrifugation.
    - Sample from animal No. 2009 allowed to clot at room temperature for 16 minutes prior centrifugation.
    - Sample from animal No. 4009 allowed to clot at room temperature for 19 minutes prior centrifugation.
    - Sample from animal Nos. 1501 and 1502 allowed to clot at room temperature for 63 minutes prior centrifugation.

  This deviation had no impact on the samples integrity since this was a minor time deviation.

Postmortem and Pathology

- Tissues that were supposed to be microscopically evaluated were not available on slides and therefore, were not evaluated. Tissues are listed in the Individual Animal Data of the Pathology report as not present. This deviation had no impact on the study integrity since sufficient tissues were examined.

Appendix 2

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-7788

eurofins | Advantar

Summary of Analysis ***DATE: 11 October 2016***

Part 1 Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0001.00 (CPR12213)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion	
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button	
ASSAY (TEST METHOD)	**TARGET RANGE**	**TEST DATE**	**RESULTS**
RNA Content (mg/mL) (MRA-C0000-GTM0011.00)	(b) (4)	10/07/2016	(b) (4)
Bacterial Endotoxins (USP<85>)		08/30/2016	
Bioburden (USP<61>)		09/06/2016	

The data generated at Eurofins Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Eurofins Advantar has archived the raw data.

(b) (6)

Oct. 11, 2016
Date

Appendix 2

Eurofins Advantar Laboratories, Inc.
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Summary of Analysis ***DATE: 30 November 2016***

Part 2, Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0002.00 (CPR12558)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button

ASSAY (TEST METHOD)	TARGET RANGE	TEST DATE	RESULTS
Appearance (MRA-C0000-GTM0016.00)	White to off-white dispersion, no visible particulates	09/23/2016	Conforms (CPR12206 Page 7)
Identification (MRA-C0000-GTM0019.00)	Matches migration rate of standard	09/19/2016	Conforms (CPR12207 Page 12)
Purity (MRA-C0000-GTM0019.00)	(b) (4)	09/19/2016	(b) (4)
Related Impurities (MRA-C0000-GTM0019.00)	Report % Pre-main peak and % Post main peak areas	09/19/2016	
Encapsulated %RNA (MRA-C0000-GTM0014.00)	(b) (4)	10/06/2016	
Mean Particle Size (nm) (MRA-C0000-GTM0015.01)	Report result	09/28/2016	
Polydispersity (MRA-C0000-GTM0015.01)	(b) (4)	09/28/2016	
Lipid Identification (b) (4)		10/14/2016	
Cholesterol	Matches retention time of standard		Matches retention time of standard
DSPC	Matches retention time of standard		Matches retention time of standard
PEG2000-DMG	Matches retention time of standard		Matches retention time of standard
(UHPLC-CAD)	Matches retention time of standard		Matches retention time of standard (CPR12206 ADR B1)
Lipid Content (mg/mL) (b) (4)	Lipid (mg/mL) (b) (4)	10/14/2016	(b) (4)
Cholesterol			
DSPC			
PEG2000-DMG			
(UHPLC-CAD)			

Appendix 2

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Summary of Analysis ***DATE: 30 November 2016***

Part 2, Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0002.00 (CPR12558)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion	
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button	
ASSAY (TEST METHOD)	**TARGET RANGE**	**TEST DATE**	**RESULTS**
Lipid Process and Degradation Impurities	Report total % Area and RRT	10/14/2016	(b) (4)
pH (MRA-C0000-GTM0017.00)	Report result	09/23/2016	
Osmolality (mOsm/kg) (USP <785>)	Report result	09/23/2016	
Particulate matter (USP<788> Method 2)	(b) (4)	08/29/2016	
Residual solvents from formulation: Ethanol (MRA-C0000-GTM0018.01) (USP <467>)		09/16/2016	

Appendix 2

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Summary of Analysis ***DATE: 30 November 2016***

Part 2, Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0002.00 (CPR12558)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion	
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button	
ASSAY (TEST METHOD)	**TARGET RANGE**	**TEST DATE**	**RESULTS**
Elemental Impurities (ICP-OES)	Report Results	09/16/2016	(b) (4)

[1] Lyso-PEG-01 & RRT 0.390/0.395 co-elute, peak skimming/splitting was used to integrate.

The data generated at Eurofins Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Eurofins Advantar has archived the raw data.

(b) (6)

Nov. 30, 2016
Date

Appendix 2

Eurofins Advantar Laboratories, Inc.
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[1]Revised Summary of Analysis ***DATE: 3 May 2017***

Part 1 Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.01 **Document Number:** MRA-C0019-RTR0001.01 (CPR15236)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button

ASSAY (TEST METHOD)	TARGET RANGE	TEST DATE	RESULTS
RNA Content (mg/mL) (MRA-C0000-GTM0011.00)	(b) (4)	10/07/2016	(b) (4)
Bacterial Endotoxins (USP<85>)		08/30/2016	
Bioburden (USP<61>)		09/06/2016	

(b) (4)

The data generated at Eurofins Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Eurofins Advantar has archived the raw data.

(b) (6)

03MAY2017
Date

Appendix 2

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

From: (b) (6)

Cc: (b) (6)

Date: 10May2017

Subject: DPAD-TM-00051.01
Revised mRNA concentration of mRNA-1706 Lot MTDP16064

Summary

The concentration of the test article for mRNA-1706 Lot MTDP16064 captured in the release summary of analysis, CPR12213, was changed from 1.7 mg/mL to 2.2 mg/mL due to the change in the concentration of the reference material (Lot MTDS16004) used in the mRNA concentration determination.

All toxicology studies (5002045, 5002097 and 9800399) affected by this concentration change will be updated accordingly.

Background Information

The initial concentration of the reference standard for mRNA-1706 concentration determination, lot MTDS16004, was determined using a standard intact mRNA UV absorbance method (260nm) and reported as 1.84 mg/mL[1]. A revised methodology[2] was subsequently developed employing sodium hydroxide digestion of the mRNA into individual nucleoside monophosphates and used to determine the mRNA concentration in the reference standard. (b) (4)

(b) (4)

(b) (4) The updated mRNA concentration of the reference standard lot MTDS16004 was determined to be 2.15 mg/mL[3] using this new method.

The mRNA concentration of the test article lot MTDP16064, reported as 1.7 mg/mL[4] was determined using the original concentration of the reference standard. It is re-calculated factoring in the new concentration of the reference standard as well as correction on peak integration to include shoulder peak. The revised total mRNA concentration is reported as 2.2 mg/mL[5].

The changes in the mRNA concentration of the reference standard and test article are summarized in Table 1.

Appendix 2

Table 1: Revised mRNA concentration of reference standard and test article

Lot Number	Original mRNA Concentration, mg/mL	Revised mRNA Concentration, mg/mL
Reference Standard Lot MTDS16004	1.84[1]	2.15[3]
Test Article Lot MTDP16064	1.7[4]	2.2[5]

Based on the revised mRNA concentration of the test article, the actual dose used in the GLP toxicology studies 5002045, 5002097 and 9800399 will be updated as summarized in Table 2. The percentage change in mRNA concentration of MTDP16064 based on the original and revised mRNA concentrations presented in Table 1 is calculated to be 29% (increase).

Table 2: Revised toxicology dose levels

GLP Toxicology Study	Original Dose	Revised Dose
5002045	10 µg	13 µg
	50 µg	65 µg
	100 µg	129 µg
5002097	100 µg	129 µg
9800399	0.5 mg/kg	0.6 mg/kg
	1 mg/kg	1.3 mg/kg
	2 mg/kg	2.6 mg/kg
	3 mg/kg	3.9 mg/kg
	4 mg/kg	5.2 mg/kg
	8 mg/kg	10.3 mg/kg

References

[1] Original SOA of the reference standard lot MTDS16004

[2] Sodium Hydroxide Digest Method: 2017_03_23-014- (b) (6)

[3] Revised SOA of the reference standard lot MTDS16004

[4] Original SOA of the test article lot MTDP16064

[5] Revised SOA of the test article lot MTDP16064

Appendix 2

Approvals

Name/Title/Company/Role	Signature	Date
(b) (6) (b) (6) Drug Product-Analytical Development *Indicates authorship of memo*	(b) (6)	10May2017
(b) (6) (b) (6) Non-Clinical Sciences Moderna Therapeutics *Indicates second person review of verifiable facts and calculation*	(b) (6)	10May17

Appendix 3

FINAL REPORT

Study Phase: Analytical Chemistry

Test Facility Study No. 5002045

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

Page 1 of 33

Appendix 3

TABLE OF CONTENTS

Appendix 3

LIST OF TABLES

LIST OF APPENDICES

Appendix 3

1. SUMMARY

Dose formulation samples have been analyzed by Ion Exchange High Performance Liquid Chromatography (IEX-HPLC) for the determination of mRNA-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 5002045.

For the work detailed in this report, the analytical phase experimental start date was 19 Oct 2016, and the analytical phase experimental completion date was 20 Dec 2016.

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 all Test Item Groups for concentration and homogeneity verification and from the middle strata for the control group. On Day 29 of the study, duplicate samples were collected from the middle strata of all Groups for concentration verification. The samples were analyzed on the day of preparation on Day 1 and stored for 3 days refrigerated prior to analysis on Day 29.

3.2. Bulk Test Item End of Use 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:	mRNA-1325 (API)
Physical Description:	Clear, colorless solution
Batch/Lot No.:	MTDS16004
Concentration:	1.84 mg/mL / 2.15 mg/mL*
Retest Date:	Apr 2017
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

* Updated concentration as per SoA issued on 25 Apr 2017.

4.1.2. Reference Material (Bulk Test Item)

Identification:	mRNA-1706 (in lipid nanoparticles)
Physical Description:	White to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP16064
Concentration:	1.7 mg/mL (used for calculations) / 2.2 mg/mL**
Date of manufacture:	25 Aug 2016
Retest Date:	25 Aug 2017 (1 year after date of manufacture)
Storage Conditions:	Kept in a refrigeratorezer set to maintain 4°C
Supplier:	Moderna Therapeutics, Inc.

** Re-calculated concentration as per SoA issued on 03 May 2017.

4.1.3. Characterization of Reference Standard and Reference Material

The Sponsor provided the documentation for the identity, strength, purity, composition, and stability for the reference standard and reference material. Copies of the supplied Certificates of Analysis or equivalent documentation are presented in Appendix 2.

Appendix 3

4.1.4. Inventory and Disposition of Reference Standard and Reference Material

Records of the receipt, distribution, and storage of the reference standard and reference material were maintained. All unused Sponsor-supplied reference standard and reference material were retained for use on subsequent studies for the Sponsor.

4.2. Methods

4.2.1. Analytical Procedure

The method of analysis is documented in Analytical Procedure AP.5002045.SP.02 (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.

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 (M7)	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

5. RESULTS AND DISCUSSIONS

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

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.

Appendix 3

For homogeneity, the RSD of concentrations for all samples in each group tested was within the acceptance criteria of ≤ 5%. Results are presented in Table 1.

5.2. End of Use Bulk Test Item Analysis

The concentration and the particle size was measured. Concentration and particle size results were consistent with the initial Certificate of Analysis provided by the Sponsor. For the particle size analysis, an additional vial was shipped by the Sponsor since precise values, % difference within 5% between replicates, were not obtained during the initial analysis of the vial transferred from the Testing Facility. The reason for the variation in the particle size values is unknown, values were between 63.6 and 54.4 which is trending with the Certificate of Analysis. All the results from the initial analysis were maintained in the raw data.

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 end of use bulk Test Item concentration and particle size analysis demonstrated that the test item was suitable for use during the study period.

Appendix 3

7. REPORT APPROVAL

(b) (6)

(b) (6) Date: 01 Nov 2017

Appendix 3

Table 1 Study Samples - Concentration and Homogeneity

Occasion (Sampling Date)	Group	Theoretical Concentration (mg/mL)	Sampling Location	Measured Concentration (mg/mL) [b]	Percent of Theoretical [b]	RSD (%)
Day 1 (20 Oct 2016)	1	(b) (4)	Middle	ND	-	-
				ND	-	
			Mean	ND	-	-
	2		Top	(b) (4)	(b) (4)	(b) (4)
			Middle			
			Bottom			
			Mean			
	3		Top			
			Middle			
			Bottom			
			Mean			
	4		Top			
			Middle			
			Bottom			
			Mean			-
Day 29 (18 Nov 2016)	1		Middle			-
			Mean			-
	2		Middle			-
			Mean			-
	3		Middle			-
			Mean			-
	4		Middle			-
			Mean			-

ND = None detected
[a] Re-calculated theoretical dose concentration as per SoA issued on 03 May 2017.
[b] Calculations as per initial SoA.

Appendix 3

Table 2 Bulk Test Item - Concentration

Occasion (Analysis Date)	Theoretical Concentration (mg/mL)	Measured Concentration (mg/mL)	Percent of Theoretical	Mean Measured Concentration (mg/mL)
End of use (07 Dec 2016)	(b) (4)			

[a] Based on initial SoA issued on 11 October 2016.

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 use (20 Dec 2016)	(b) (4)				

Appendix 3

Appendix 1
Analytical Procedure

Appendix 3

Analytical Procedure (AP.5002045.SP.02)

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	mRNA-1325 (API)*
Description	Clear colorless solution
Lot number	MTDS16004
Concentration	1.84 mg/mL
Reference Material	mRNA-1706
Description	White to off-white lipid nanoparticle dispersion
Lot number	MTDP16064
Concentration	1.7 mg/mL (to be used for calculations)
Vehicle	Phosphate-buffered Saline (PBS) pH 7.2

* mRNA-1325 and mRNA-1706 have the same mRNA constructs.

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 analytical method was previously validated under study 1801737 and sample concentration stability was conducted under study 2100442.

Appendix 3

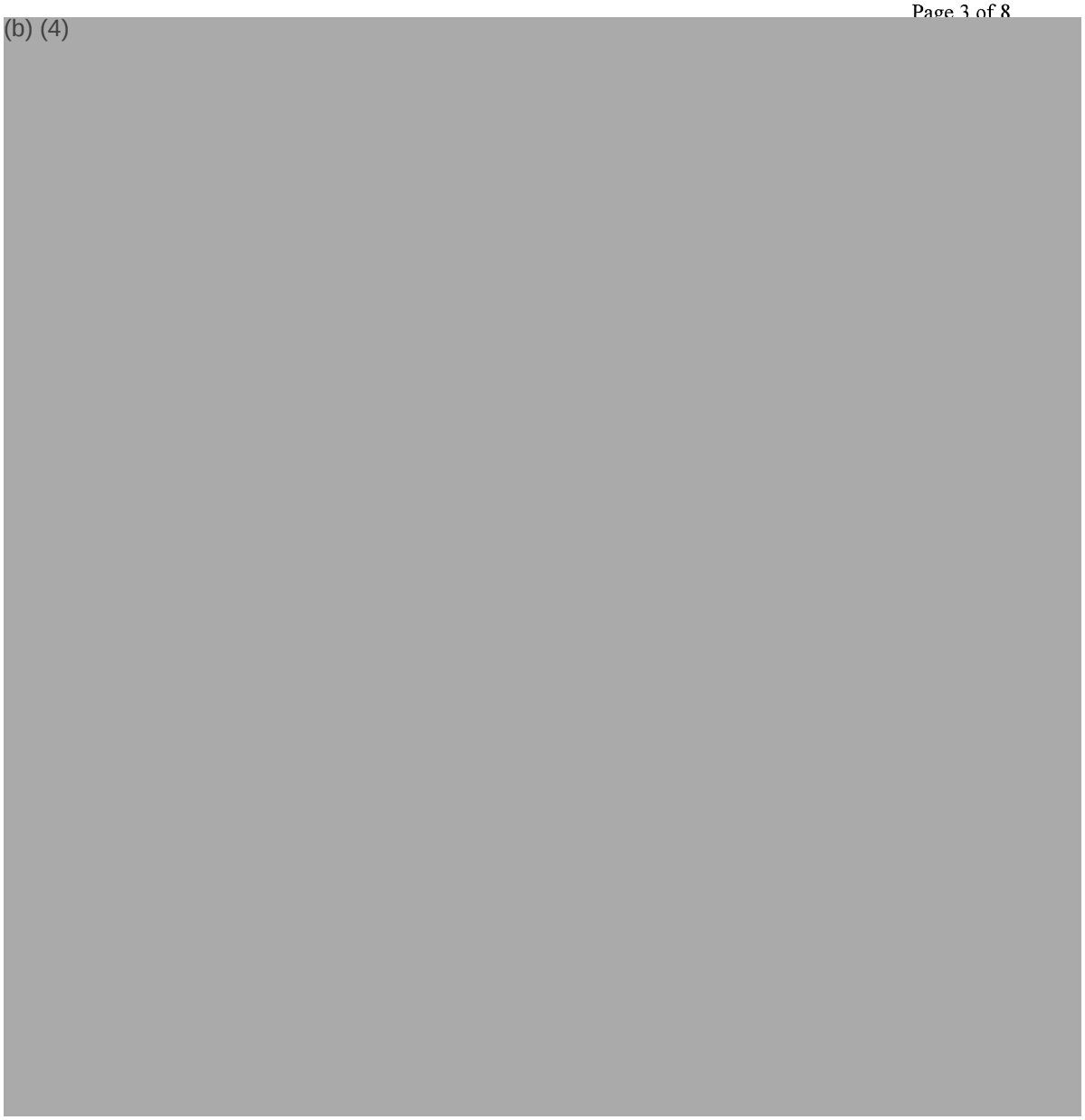
Analytical Procedure (AP.5002045.SP.02)

(b) (4)

Appendix 3

Analytical Procedure (AP.5002045.SP.02)

(b) (4)



Appendix 3

Analytical Procedure (AP.5002045.SP.02)

(b) (4)

Appendix 3

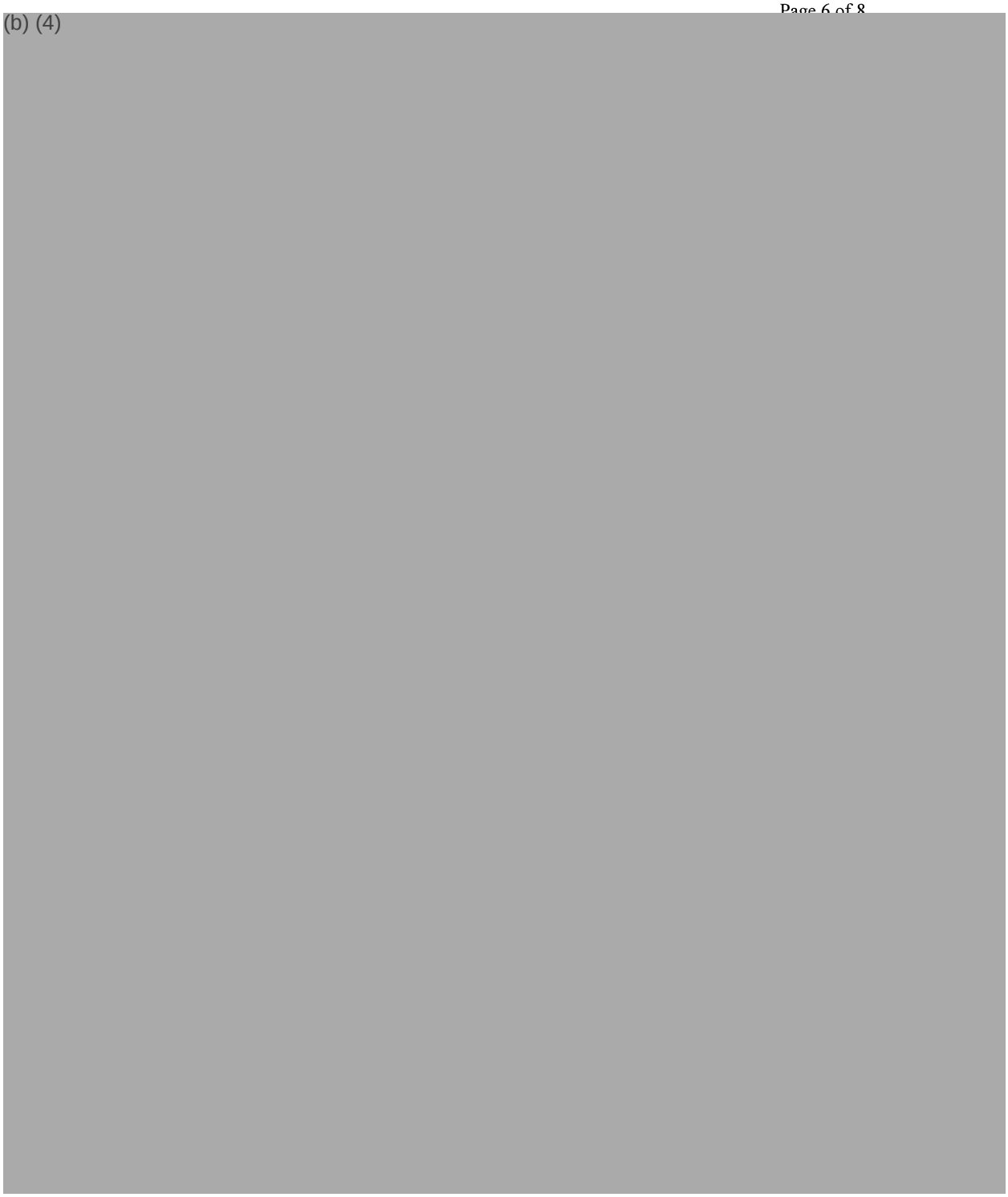
Analytical Procedure (AP.5002045.SP.02)

(b) (4)

Appendix 3

Analytical Procedure (AP.5002045.SP.02)

(b) (4)



Appendix 3

Analytical Procedure (AP.5002045.SP.02)

(b) (4)

Appendix 3

Analytical Procedure (AP.5002045.SP.02)

Acceptance criteria

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

AP Version Control

First update:
- Included missing expiry periods.
- Included reference study for sample concentration stability.
- Included analysis of bulk test item sample.

Verified by (b) (6) Date 29 Nov 2016

Approved by (b) (6) Date 29 Nov 2016.

Authorized by (b) (6) Date 29 Nov. 2016

Scientific Director ☑

Appendix 3

Analytical Procedure (AP.5002045.DLS.02)

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 to off-white lipid nanoparticle dispersion
Lot number	MTDP16064
Concentration	1.7 mg/mL (to be used for calculations)

For storage conditions for test item supplied by the Sponsor, refer to the corresponding log sheets.

NOTES:

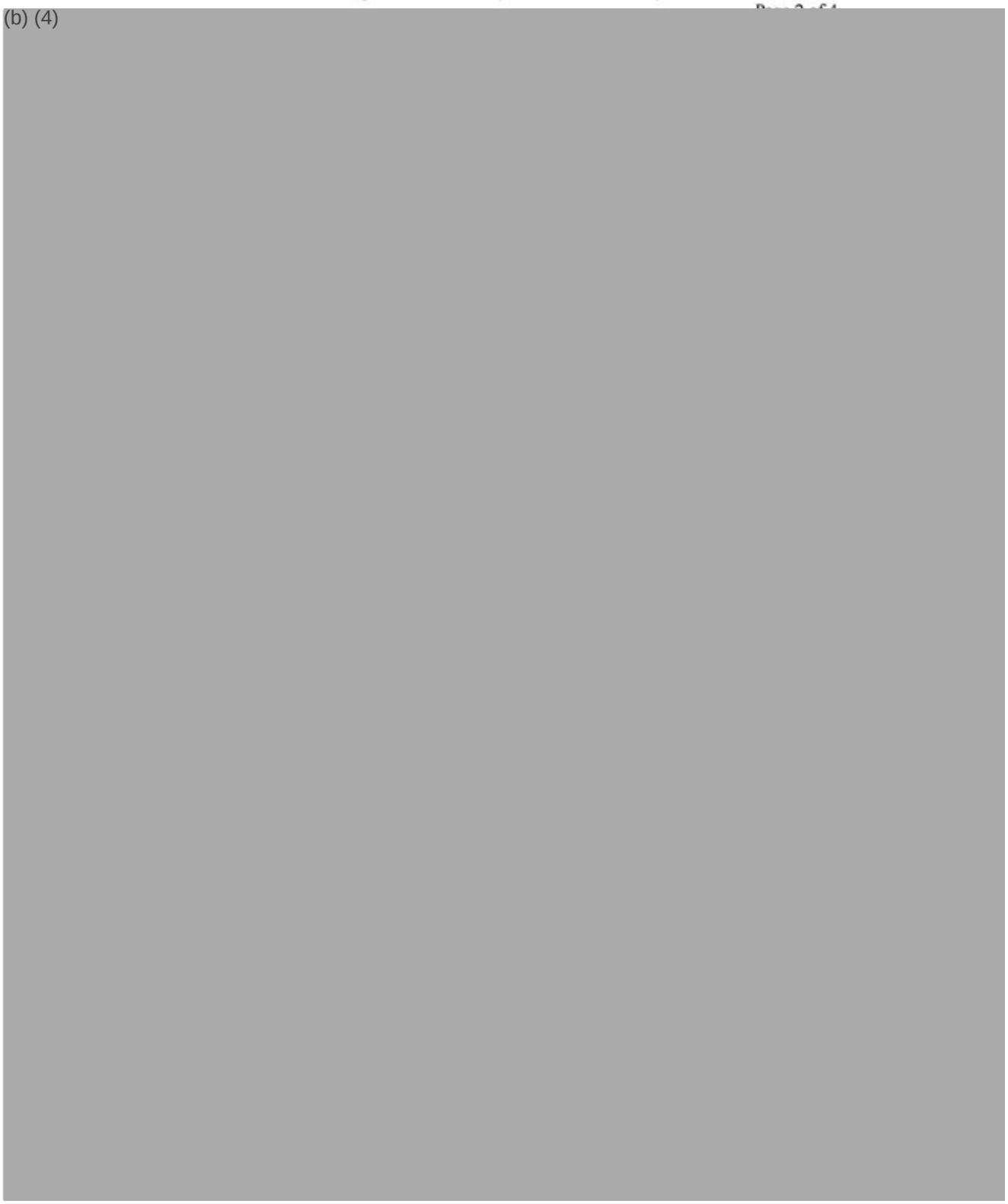
- ❑ Solution volumes throughout this AP may be scaled up or down as long as the final concentration remains the same as specified in the procedure.
- ❑ Any changes made are to be documented in the raw data of the run.
- ❑ Unless otherwise indicated, information relating to the time of mixing/stirring, 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

Analytical Procedure (AP.5002045.DLS.02)

(b) (4)



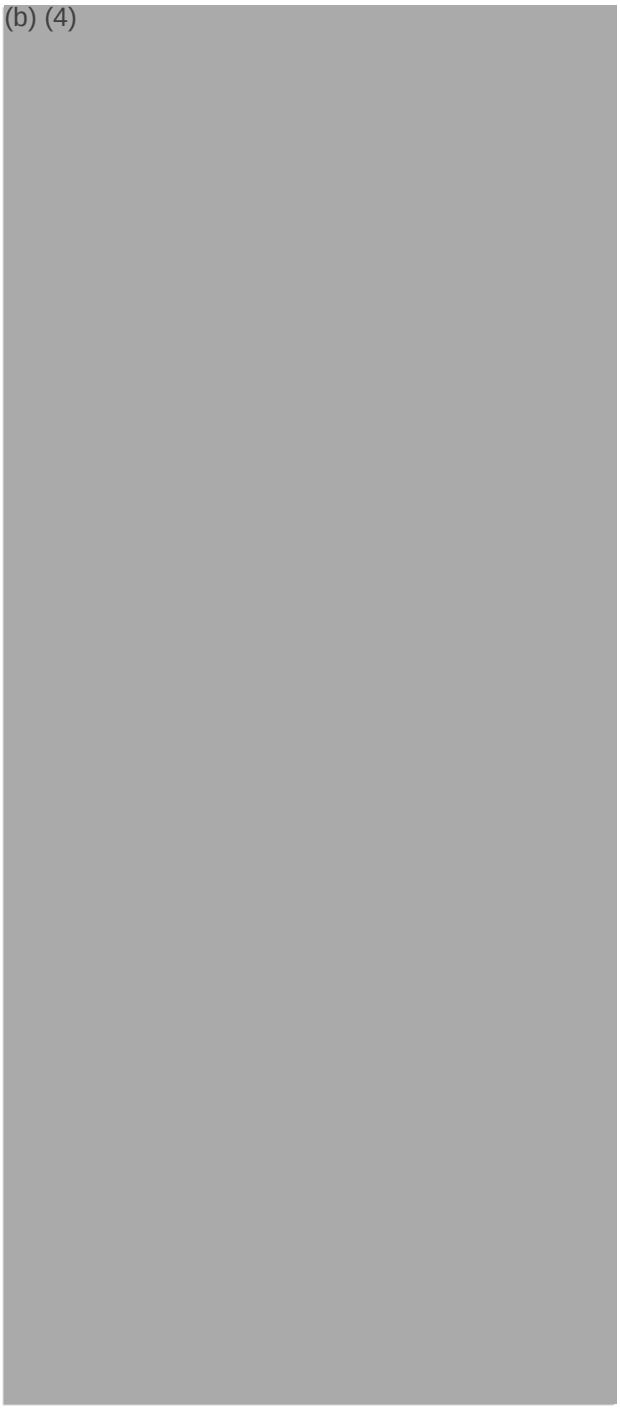
Appendix 3

Analytical Procedure (AP.5002045.DLS.02)

Instrument Parameters for Sample Reading

Save all settings as a preset on location D:\Dynamics\Projects\5002045.

(b) (4)



Appendix 3

(b) (4)

AP Version Control

First update:
• Included hand corrections for scaled up sample volume/dilution on Page 2.

Verified by (b) (6) Date 14 Feb 2017

Approved by Date 14 Feb 2017

Authorized by Date 14 Feb. 2017

Scientific Director ☑

Appendix 3

Appendix 2
Certificates of Analysis

Appendix 3

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-7788

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[1]Revised Summary of Analysis *DATE: 3 May 2017*

Part 1 Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.01 **Document Number:** MRA-C0019-RTR0001.01 (CPR15236)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion
Time point: Time Zero **Storage Condition:** 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button

ASSAY (TEST METHOD)	TARGET RANGE	TEST DATE	RESULTS
RNA Content (mg/mL) (MRA-C0000-GTM0011.00)	(b) (4)	10/07/2016	(b) (4)
Bacterial Endotoxins (USP<85>)		08/30/2016	
Bioburden (USP<61>)		09/06/2016	

(b) (4)

The data generated at Eurofins Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Eurofins Advantar has archived the raw data.

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

03MAY2017
Date

Appendix 3

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-7788

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Summary of Analysis ***DATE: 11 October 2016***

Part 1 Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0001.00 (CPR12213)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button

ASSAY (TEST METHOD)	TARGET RANGE	TEST DATE	RESULTS
RNA Content (mg/mL) (MRA-C0000-GTM0011.00)	(b) (4)	10/07/2016	(b) (4)
Bacterial Endotoxins (USP<85>)		08/30/2016	
Bioburden (USP<61>)		09/06/2016	

The data generated at Eurofins Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Eurofins Advantar has archived the raw data.

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

Oct. 11, 2016
Date

MRA-C0019-RTR0001.00 Confidential – Eurofins Advantar Laboratories, Inc. Page 1 of 1

Appendix 3

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San Diego, CA 92121
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Summary of Analysis ***DATE: 30 November 2016***

Part 2, Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0002.00 (CPR12558)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion	
Time point: Time Zero **Storage Condition:** 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button	
ASSAY (TEST METHOD)	**TARGET RANGE**	**TEST DATE**	**RESULTS**
Appearance (MRA-C0000-GTM0016.00)	White to off-white dispersion, no visible particulates	09/23/2016	Conforms (CPR12206 Page 7)
Identification (MRA-C0000-GTM0019.00)	Matches migration rate of standard	09/19/2016	Conforms (CPR12207 Page 12)
Purity (MRA-C0000-GTM0019.00)	(b) (4)	09/19/2016	(b) (4)
Related Impurities (MRA-C0000-GTM0019.00)	Report % Pre-main peak and % Post main peak areas	09/19/2016	
Encapsulated %RNA (MRA-C0000-GTM0014.00)	(b) (4)	10/06/2016	
Mean Particle Size (nm) (MRA-C0000-GTM0015.01)	Report result	09/28/2016	
Polydispersity (MRA-C0000-GTM0015.01)	(b) (4)	09/28/2016	
Lipid Identification		10/14/2016	
(b) (4)	Matches retention time of standard		Matches retention time of standard
Cholesterol	Matches retention time of standard		Matches retention time of standard
DSPC	Matches retention time of standard		Matches retention time of standard
PEG2000-DMG	Matches retention time of standard		Matches retention time of standard
(UHPLC-CAD)			(CPR12206 ADR B1)
Lipid Content (mg/mL)	Lipid (mg/mL)	10/14/2016	(b) (4)
(b) (4)	(b) (4)		
Cholesterol			
DSPC			
PEG2000-DMG			
(UHPLC-CAD)			

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Summary of Analysis ***DATE: 30 November 2016***

Part 2, Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0002.00 (CPR12558)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion	
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button	
ASSAY (TEST METHOD)	**TARGET RANGE**	**TEST DATE**	**RESULTS**
Lipid Process and Degradation Impurities	Report total % Area and RRT	10/14/2016	(b) (4)
pH (MRA-C0000-GTM0017.00)	Report result	09/23/2016	
Osmolality (mOsm/kg) (USP <785>)	Report result	09/23/2016	
Particulate matter (USP<788> Method 2)	(b) (4)	08/29/2016	
Residual solvents from formulation: Ethanol (MRA-C0000-GTM0018.01) (USP <467>)		09/16/2016	

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Summary of Analysis ***DATE: 30 November 2016***

Part 2, Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0002.00 (CPR12558)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button

ASSAY (TEST METHOD)	TARGET RANGE	TEST DATE	RESULTS
Elemental Impurities (ICP-OES)	Report Results	09/16/2016	(b) (4)

[1] Lyso-PEG-01 & RRT 0.390/0.395 co-elute, peak skimming/splitting was used to integrate.

The data generated at Eurofins Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Eurofins Advantar has archived the raw data.

(b) (6)

Nov. 30, 2016
Date

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
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	(b) (4)	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) — Date: 25 Apr 17

(b) (6)
Reviewed by: (b) (6) — Date: 25 APR 2017

CX-000171 Page 2 of 2 version 03

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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

Si (b) (6)
Generated by: (b) (6)
29 APR 2016
Date:
(b) (6)
Reviewed by: (b) (6)
29 APR 2016
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
NR	Not recorded	TE or TERM	Terminal euthanasia
		UE or UNSC	Unscheduled euthanasia

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Removal Time represents the time the removal was entered into the Provantis system and may not be representative of the time of death.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 4

Individual Animal Mortality

5002045

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	18NOV2016	11:15	.	.	TERM
			1002	1001	30	5	18NOV2016	11:15	.	.	TERM
			1003	1001	30	5	18NOV2016	12:25	.	.	TERM
			1104	1104	30	5	18NOV2016	12:24	.	.	TERM
			1005	1104	30	5	18NOV2016	15:21	.	.	TERM
			1006	1104	30	5	18NOV2016	14:48	.	.	TERM
			1007	1007	30	5	18NOV2016	16:39	.	.	TERM
			1008	1007	30	5	18NOV2016	15:55	.	.	TERM
			1009	1009	30	5	18NOV2016	17:55	.	.	TERM
			1010	1009	30	5	18NOV2016	17:04	.	.	TERM
			1011	1011	43	7	01DEC2016	8:50	.	.	REC
			1012	1011	43	7	01DEC2016	9:50	.	.	REC
			1013	1011	43	7	01DEC2016	10:41	.	.	REC
			1014	1014	43	7	01DEC2016	11:30	.	.	REC
			1015	1014	43	7	01DEC2016	13:52	.	.	REC
1	0 ug/dose	Female	1501	1501	30	5	19NOV2016	10:52	.	.	TERM
			1502	1501	30	5	19NOV2016	10:52	.	.	TERM
			1503	1501	30	5	19NOV2016	11:54	.	.	TERM
			1504	1504	30	5	19NOV2016	11:53	.	.	TERM
			1505	1504	30	5	19NOV2016	12:50	.	.	TERM
			1506	1504	30	5	19NOV2016	12:49	.	.	TERM
			1507	1507	30	5	19NOV2016	15:02	.	.	TERM
			1508	1507	30	5	19NOV2016	14:58	.	.	TERM
			1509	1509	30	5	19NOV2016	16:00	.	.	TERM
			1510	1509	30	5	19NOV2016	15:55	.	.	TERM
			1511	1511	43	7	02DEC2016	8:52	.	.	REC
			1512	1511	43	7	02DEC2016	10:00	.	.	REC
			1513	1511	43	7	02DEC2016	11:07	.	.	REC
			1514	1514	43	7	02DEC2016	13:16	.	.	REC
			1515	1514	43	7	02DEC2016	13:56	.	.	REC
2	13 ug/dose	Male	2001	2001	30	5	18NOV2016	12:09	.	.	TERM
			2002	2001	30	5	18NOV2016	12:08	.	.	TERM
			2003	2001	30	5	18NOV2016	14:59	.	.	TERM
			2004	2004	30	5	18NOV2016	14:15	.	.	TERM
			2005	2004	30	5	18NOV2016	16:22	.	.	TERM

Appendix 4

Individual Animal Mortality

5002045

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
2	13 ug/dose	Male	2006	2004	30	5	18NOV2016	15:38	.	.	TERM
			2007	2007	30	5	18NOV2016	17:39	.	.	TERM
			2008	2007	30	5	18NOV2016	16:49	.	.	TERM
			2009	2009	30	5	18NOV2016	18:13	.	.	TERM
			2010	2009	30	5	18NOV2016	17:53	.	.	TERM
2	13 ug/dose	Female	2501	2501	30	5	19NOV2016	11:39	.	.	TERM
			2502	2501	30	5	19NOV2016	11:38	.	.	TERM
			2503	2501	30	5	19NOV2016	12:36	.	.	TERM
			2504	2504	30	5	19NOV2016	12:37	.	.	TERM
			2505	2504	30	5	19NOV2016	13:30	.	.	TERM
			2506	2504	30	5	19NOV2016	14:42	.	.	TERM
			2507	2507	30	5	19NOV2016	15:46	.	.	TERM
			2508	2507	30	5	19NOV2016	15:41	.	.	TERM
			2509	2509	30	5	19NOV2016	16:42	.	.	TERM
			2510	2509	30	5	19NOV2016	16:38	.	.	TERM
3	65 ug/dose	Male	3001	3001	30	5	18NOV2016	11:52	.	.	TERM
			3002	3001	30	5	18NOV2016	11:49	.	.	TERM
			3003	3001	30	5	18NOV2016	12:58	.	.	TERM
			3004	3004	30	5	18NOV2016	12:57	.	.	TERM
			3005	3004	30	5	18NOV2016	16:04	.	.	TERM
			3006	3004	30	5	18NOV2016	15:21	.	.	TERM
			3007	3007	30	5	18NOV2016	17:19	.	.	TERM
			3008	3007	30	5	18NOV2016	16:31	.	.	TERM
			3009	3009	30	5	18NOV2016	18:28	.	.	TERM
			3010	3009	30	5	18NOV2016	17:36	.	.	TERM
3	65 ug/dose	Female	3501	3501	30	5	19NOV2016	11:23	.	.	TERM
			3502	3501	30	5	19NOV2016	11:22	.	.	TERM
			3503	3501	30	5	19NOV2016	12:21	.	.	TERM
			3504	3504	30	5	19NOV2016	12:23	.	.	TERM
			3505	3504	30	5	19NOV2016	13:16	.	.	TERM
			3506	3504	30	5	19NOV2016	13:16	.	.	TERM
			3507	3507	30	5	19NOV2016	15:32	.	.	TERM
			3508	3507	30	5	19NOV2016	15:25	.	.	TERM
			3509	3509	30	5	19NOV2016	16:29	.	.	TERM

Appendix 4

Individual Animal Mortality

5002045

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
3	65 ug/dose	Female	3510	3509	30	5	19NOV2016	16:24	.	.	TERM
4	129 ug/dose	Male	4001	4001	30	5	18NOV2016	11:34	.	.	TERM
			4002	4001	30	5	18NOV2016	11:30	.	.	TERM
			4003	4001	30	5	18NOV2016	12:42	.	.	TERM
			4004	4004	30	5	18NOV2016	12:39	.	.	TERM
			4105	4004	30	5	18NOV2016	15:37	.	.	TERM
			4006	4004	30	5	18NOV2016	15:04	.	.	TERM
			4007	4007	30	5	18NOV2016	16:58	.	.	TERM
			4008	4007	30	5	18NOV2016	16:11	.	.	TERM
			4009	4009	30	5	18NOV2016	18:11	.	.	TERM
			4010	4009	30	5	18NOV2016	17:19	.	.	TERM
			4011	4011	43	7	01DEC2016	9:22	.	.	REC
			4012	4011	43	7	01DEC2016	10:15	.	.	REC
			4013	4011	43	7	01DEC2016	11:05	.	.	REC
			4014	4014	43	7	01DEC2016	13:25	.	.	REC
			4015	4014	43	7	01DEC2016	14:18	.	.	REC
4	129 ug/dose	Female	4501	4501	30	5	19NOV2016	11:08	.	.	TERM
			4502	4501	30	5	19NOV2016	11:06	.	.	TERM
			4503	4501	30	5	19NOV2016	12:07	.	.	TERM
			4504	4504	30	5	19NOV2016	12:08	.	.	TERM
			4505	4504	30	5	19NOV2016	13:02	.	.	TERM
			4506	4504	30	5	19NOV2016	13:01	.	.	TERM
			4507	4507	30	5	19NOV2016	15:19	.	.	TERM
			4508	4507	30	5	19NOV2016	15:11	.	.	TERM
			4509	4509	30	5	19NOV2016	16:15	.	.	TERM
			4510	4509	30	5	19NOV2016	16:08	.	.	TERM
			4511	4511	43	7	02DEC2016	9:31	.	.	REC
			4512	4511	43	7	02DEC2016	10:31	.	.	REC
			4513	4511	43	7	02DEC2016	11:34	.	.	REC
			4514	4514	43	7	02DEC2016	13:38	.	.	REC
			4515	4514	43	7	02DEC2016	14:13	.	.	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 #	Observation during dosing	Unsc #	Unscheduled examination
Vet Aid	Anything observed by Vet Aid	#	Number to avoid using the same timeslot/animal/day

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Only animals with findings are presented in this appendix.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 5

Individual Clinical Observations

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	14 DE	21 DE	28 DE	30 DE	42 DE	43 DE
1	m	1001	Skin, Scab	Hindlimb, Right	.	X	.	.	.	.
		1002	Fur, Staining, Red	Dorsal Thoracic	.	.	X	.	.	.
		1007	Skin, Scab	Tail	X	X	X	X	.	.
		1009	Skin, Scab	Tail	X	X	X	.	.	.
		1011	Skin, Scab	Hindlimb, Right	.	.	.	.	X	X
		1012	Skin, Scab	Hindlimb, Right	.	.	.	.	X	X
		1014	Skin, Scab	Cranium	.	.	.	.	X	X

Severity Codes: X = Present

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	21 DE	28 DE	30 DE
2	m	2003	Skin, Scab	Pinna, Left	X	.	.	.
		2004	Skin, Red	Hindlimb, Right	.	X	.	.
			Skin, Red	Hindlimb, Left	.	X	.	.
			Skin, Scab	Tail	.	.	.	X
		2005	Fur, Thin Cover	Cranium	.	.	X	.
		2007	Skin, Scab	Tail	.	X	.	.

Severity Codes: X = Present

Group 2 - 13 ug/dose

Appendix 5

Individual Clinical Observations

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-14 Vet Aid	-1 DE	7 DE
3	m	3001	Skin, Scab	Pinna, Right	.	X	X
		3006	Fur, Erected		X	.	.
		3009	Fur, Thin Cover	Cranium	.	X	.
		3010	Fur, Thin Cover	Cranium	.	X	.

Severity Codes: X = Present

Group 3 - 65 ug/dose

Appendix 5

Individual Clinical Observations

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-14 Vet Aid	-1 DE	7 DE	14 DE	21 DE	28 DE
4	m	4003	Skin, Scab	Cranium	.	.	X	X	.	.
			Fur, Thin Cover	Cranium	.	X	X	X	.	.
		4004	Skin, Scab	Inguinal, Left	.	.	.	.	.	X
			Skin, Scab	Cranium	.	.	.	.	.	X
			Fur, Thin Cover	Inguinal, Left	.	.	.	.	.	X
			Fur, Thin Cover	Cranium	.	.	.	.	.	X
		4105	Nictitating MembraneProtruding	Right	X	.	.	.	.	.
		4006	Skin, Scab	Cranium	.	.	.	.	.	X
			Fur, Thin Cover	Cranium	.	X	.	.	.	X
		4007	Fur, Thin Cover	Cranium	.	X	.	.	.	.
		4009	Skin, Scab	Tail	.	.	.	.	X	X
		4011	Fur, Staining, Brown	Urogenital	.	.	.	.	.	.
			Fur, Staining, Red	Forelimb, Right	.	.	.	.	X	X
			Fur, Thin Cover	Cranium	.	X	.	.	.	.
		4013	Skin, Scab	Dorsal Cervical	.	X	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	X	.	.	.	.
		4014	Skin, Scab	Tail	.	.	.	X	.	.
			Skin, Scab	Pinna, Right	.	.	.	.	.	.
			Skin, Scab	Pinna, Left	.	.	.	.	.	X

Severity Codes: X = Present

Group 4 - 129 ug/dose

Appendix 5

Individual Clinical Observations

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30 DE	42 DE	43 DE
4	m	4003	Skin, Scab	Cranium	.	.	.
			Fur, Thin Cover	Cranium	.	.	.
		4004	Skin, Scab	Inguinal, Left	X	.	.
			Skin, Scab	Cranium	X	.	.
			Fur, Thin Cover	Inguinal, Left	X	.	.
			Fur, Thin Cover	Cranium	X	.	.
		4105	Nictitating MembraneProtruding	Right	.	.	.
		4006	Skin, Scab	Cranium	X	.	.
			Fur, Thin Cover	Cranium	X	.	.
		4007	Fur, Thin Cover	Cranium	.	.	.
		4009	Skin, Scab	Tail	X	.	.
		4011	Fur, Staining, Brown	Urogenital	.	.	X
			Fur, Staining, Red	Forelimb, Right	.	.	.
			Fur, Thin Cover	Cranium	.	.	.
		4013	Skin, Scab	Dorsal Cervical	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.
		4014	Skin, Scab	Tail	.	.	.
			Skin, Scab	Pinna, Right	.	X	X
			Skin, Scab	Pinna, Left	.	.	.

Severity Codes: X = Present

Group 4 - 129 ug/dose

Appendix 5

Individual Clinical Observations

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	3 Unsc	7 DE	14 DE	21 DE	28 DE	30 DE	35 DE	42 DE	43 DE
1	f	1501	Skin, Scab	Hindlimb, Right	.	.	.	.	.	X	.	.	.	.
		1502	Skin, Scab	Tail	.	.	.	X	.	X	X	.	.	.
			Skin, Scab	Interscapular	X	.	X	.	X	.	.	.	.	.
			Fur, Thin Cover	Interscapular	X	.	X	X	X	.	X	.	.	.
			Tail, Sloughing		.	.	.	.	.	X	X	.	.	.
		1503	Skin, Scab	Tail	.	.	X	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Right	.	.	X	.	.	.	.	.	.	.
		1504	Skin, Lesion	Hindlimb, Left	.	1	.	.	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Left	.	.	X	.	.	.	.	.	.	.
		1505	Skin, Scab	Pinna, Right	.	.	X	.	.	.	.	.	.	.
		1510	Skin, Scab	Scapular, Right	.	.	X	.	.	.	.	.	.	.
			Skin, Scab	Dorsal Cervical	.	.	X	.	.	.	.	.	.	.
		1513	Caught in Cage	Tail	.	.	X	.	.	.	.	.	.	.
			Skin, Lesion	Tail	.	.	1	.	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	X	X	.	.	.	.	.
		1514	Skin, Red	Hindlimb, Right	.	.	.	.	.	.	.	.	X	X
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	.	.	X	X
			Skin, Dry	Hindlimb, Right	.	.	.	.	.	.	.	.	X	X
			Skin, Dry	Hindlimb, Left	.	.	.	.	.	.	.	.	X	X
			Skin, Scab	Forepaw, Right	.	.	.	X	X	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	.	.	X
			Pinna Partly Missing	Left	.	.	X	X	X	X	.	X	X	X
			Nail Missing	Forepaw, Right	.	.	.	X	X	X	.	.	.	.

Severity Codes: X = Present; 1 = Slight

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	7 DE	14 DE
2	f	2506	Skin, Scab	Dorsal Thoracic	X	X	X
			Fur, Thin Cover	Dorsal Thoracic	X	X	X

Severity Codes: X = Present

Group 2 - 13 ug/dose

Appendix 5

Individual Clinical Observations

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 Unsc PostRx	7 DE	14 DE	21 DE	28 DE	30 DE
3	f	3501	Pinna Partly Missing	Right	.	.	X	X	X	X
		3504	Skin, Lesion	Hindlimb, Right	1	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	X	.	.	.	.
		3509	Skin, Scab	Tail	.	.	.	.	X	X
		3510	Skin, Scab	Tail	.	.	X	.	.	.

Severity Codes: X = Present; 1 = Slight

Group 3 - 65 ug/dose

Appendix 5

Individual Clinical Observations

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-1 DE	2 Unsc	7 DE	14 DE	21 DE	28 DE	30 DE	35 DE	42 DE	43 DE
4	f	4501	Warm to Touch		.	X	.	.	.	.	.	.	.	.
			Skin, Red	Periorbital, Right	.	.	.	.	.	.	X	.	.	.
			Fur, Staining, Red	Periorbital, Right	.	.	.	.	.	.	X	.	.	.
		4502	Warm to Touch		.	X	.	.	.	.	.	.	.	.
		4503	Warm to Touch		.	X	.	.	.	.	.	.	.	.
		4504	Dehydrated Suspected		.	1	.	.	.	.	.	.	.	.
			Warm to Touch		.	X	.	.	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	X	X	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.	X	.	.	.
		4505	Warm to Touch		.	X	.	.	.	.	.	.	.	.
			Skin, Scab	Tail	.	.	.	.	.	X	.	.	.	.
		4506	Warm to Touch		.	X	.	.	.	.	.	.	.	.
			Skin, Scab	Urogenital	.	.	.	X	.	.	.	.	.	.
			Fur, Thin Cover	Urogenital	.	.	.	.	X	.	.	.	.	.
		4507	Warm to Touch		.	X	.	.	.	.	.	.	.	.
		4508	Warm to Touch		.	X	.	.	.	.	.	.	.	.
		4509	Warm to Touch		.	X	.	.	.	.	.	.	.	.
			Pinna Partly Missing	Right	.	.	X	X	X	X	X	.	.	.
		4510	Warm to Touch		.	X	.	.	.	.	.	.	.	.
		4511	Warm to Touch		.	X	.	.	.	.	.	.	.	.
		4512	Warm to Touch		.	X	.	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	X	.	X	X	X
		4513	Vocalization Increased		X	.	.	.	.	.	.	.	.	.
			Warm to Touch		.	X	.	.	.	.	.	.	.	.
			Skin, Scab	Urogenital	.	.	.	X	.	.	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	X	.	.	.	.
			Skin, Scab	Hindlimb, Left	.	.	.	.	.	X	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	.	.	.	.	.	X
		4514	Warm to Touch		.	X	.	.	.	.	.	.	.	.
		4515	Warm to Touch		.	X	.	.	.	.	.	.	.	.
			Skin, Scab	Pinna, Right	.	.	.	.	.	.	.	X	X	X

Severity Codes: X = Present; 1 = Slight

Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment Explanation Page

Score	Erythema (Redness) Description
0	No erythema
1	Very slight erythema
2	Mild erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness to slight eschar formation, injuries in depth)
M	Notable dermal lesions (maximized)

Score	Edema (Swelling) Description
0	No edema
1	Very slight edema
2	Slight edema
3	Moderate edema
4	Severe edema

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
AVS	Suspected aberrant value	Post Rx	Observation Post dosing
NR	Not recorded	PreRx	Observation predosing
OA	Omitted activity		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
1	m	1001	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1002	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1003	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1104	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1005	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1006	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1007	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1008	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
1	m	1009	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1010	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1011	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
		1012	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
		1013	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
		1014	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
		1015	Erythema	Treatment Site No.02	0	.	0	0	0	0	1	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
2	m	2001	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	1	.	.
		2002	Erythema	Treatment Site No.02	.	.	.	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	.	.	.	1	1	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
		2003	Erythema	Treatment Site No.02	.	.	.	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	.	.	.	1	1	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
		2004	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	3	.	.
		2005	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	1	.	.
		2006	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		2007	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	2	.	.
		2008	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	0	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
2	m	2009	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	3	.	.
		2010	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	2	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
3	m	3001	Erythema	Treatment Site No.02	0	.	0	0	1	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	3	.	.
		3002	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	2	.	.
		3003	Erythema	Treatment Site No.02	0	.	0	0	1	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	3	.	.
		3004	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	3	.	.
		3005	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	3	.	.
		3006	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	3	.	.
		3007	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	3	0	0	0	.	0	4	.	.
		3008	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	3	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
3	m	3009	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	1	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	2	1	0	0	.	0	3	.	.
		3010	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	3	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
4	m	4001	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	.
			Edema	Treatment Site No.01	3	0	0	0	.	0	4	.	.
		4002	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	2	1	0	0	.	0	3	.	.
		4003	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Erythema	Treatment Site No.01	1	2	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	3	.	.
		4004	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	1	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	3	.	.
		4105	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	3	.	.
		4006	Erythema	Treatment Site No.02	0	.	0	1	2	0	0	.	.
			Erythema	Treatment Site No.01	1	1	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	4	.	.
		4007	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	1	1	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	0	.	.
		4008	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	1	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	3	1	0	0	.	0	3	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
4	m	4009	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	.
			Edema	Treatment Site No.01	3	0	0	0	.	0	4	.	.
		4010	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	.
			Edema	Treatment Site No.01	2	1	0	0	.	0	3	.	.
		4011	Erythema	Treatment Site No.02	0	.	0	0	1	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	1	0
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	0
			Edema	Treatment Site No.01	2	1	0	0	.	0	4	1	0
		4012	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	1	0
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	0
			Edema	Treatment Site No.01	2	1	0	0	.	0	3	1	0
		4013	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	0
			Edema	Treatment Site No.01	2	0	0	0	.	0	3	0	0
		4014	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	1	0
			Edema	Treatment Site No.02	0	.	0	3	1	0	0	.	0
			Edema	Treatment Site No.01	3	1	0	0	.	0	3	1	0
		4015	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	3	2	0	0	.	0
			Edema	Treatment Site No.01	3	0	0	0	.	0	3	0	0

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
1	f	1501	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1502	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1503	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1504	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1505	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1506	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1507	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1508	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
1	f	1509	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1510	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
		1511	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
		1512	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
		1513	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
		1514	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	1	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
		1515	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	0	0
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	0
			Edema	Treatment Site No.01	0	0	0	0	.	0	0	0	0

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
2	f	2501	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	1	.	.
		2502	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
		2503	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
		2504	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
		2505	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	0	.	.
		2506	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	1	.	.
		2507	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	1	.	.
		2508	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	0	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
2	f	2509	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	1	.	.
		2510	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	1	0	0	0	.	0	1	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
3	f	3501	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	0	1	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	3	.	.
		3502	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
			Edema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Edema	Treatment Site No.01	2	2	0	0	.	0	3	.	.
		3503	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	.	.
		3504	Erythema	Treatment Site No.02	0	.	0	0	1	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	1	3	0	0	.	0	2	.	.
		3505	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	0	3	0	0	.	0	2	.	.
		3506	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	1	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	1	3	0	0	.	0	3	.	.
		3507	Erythema	Treatment Site No.02	0	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	0	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	1	3	0	0	.	0	2	.	.
		3508	Erythema	Treatment Site No.02	.	.	0	0	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
			Edema	Treatment Site No.02	.	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	2	2	0	0	.	0	3	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
3	f	3509	Erythema	Treatment Site No.02	.	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	.	.	0	2	0	0	0	.	.
			Edema	Treatment Site No.01	2	2	0	0	.	0	3	.	.
		3510	Erythema	Treatment Site No.02	0	.	0	0	2	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
			Edema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Edema	Treatment Site No.01	2	0	0	0	.	0	2	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
4	f	4501	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Erythema	Treatment Site No.01	2	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	.	.
		4502	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	.	.
		4503	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	.	.
		4504	Erythema	Treatment Site No.02	0	.	0	1	2	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	.	.
		4505	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	.	.
		4506	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	1	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	.	.
		4507	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	.	.
		4508	Erythema	Treatment Site No.02	0	.	0	0	1	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	.	.

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	4	9	16	18	23	30	32	37
4	f	4509	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	2	2	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	4	.	.
		4510	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	.
			Erythema	Treatment Site No.01	1	0	0	0	.	0	0	.	.
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	.
			Edema	Treatment Site No.01	2	3	0	0	.	0	4	.	.
		4511	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	0
			Erythema	Treatment Site No.01	1	0	0	0	.	0	1	0	0
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	0
			Edema	Treatment Site No.01	2	3	0	0	.	0	4	1	0
		4512	Erythema	Treatment Site No.02	0	.	0	1	2	0	0	.	0
			Erythema	Treatment Site No.01	2	0	0	0	.	0	1	1	0
			Edema	Treatment Site No.02	0	.	0	1	1	0	0	.	0
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	2	0
		4513	Erythema	Treatment Site No.02	0	.	0	1	1	0	0	.	0
			Erythema	Treatment Site No.01	1	0	0	0	.	0	1	1	0
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	0
			Edema	Treatment Site No.01	2	2	0	0	.	0	3	1	0
		4514	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	0
			Erythema	Treatment Site No.01	1	1	0	0	.	0	0	1	0
			Edema	Treatment Site No.02	0	.	0	2	0	0	0	.	0
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	1	0
		4515	Erythema	Treatment Site No.02	0	.	0	1	0	0	0	.	0
			Erythema	Treatment Site No.01	1	0	0	0	.	0	1	1	0
			Edema	Treatment Site No.02	0	.	0	2	1	0	0	.	0
			Edema	Treatment Site No.01	2	3	0	0	.	0	3	1	0

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

Group 1 - 0 ug/dose Group 2 - 13 ug/dose Group 3 - 65 ug/dose Group 4 - 129 ug/dose

Appendix 7

Individual Body Weights Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	TERR	Technical error
AVS	Suspected aberrant value	UPTD	Unable to perform due to technical difficulty
OA	Omitted activity	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day -9	-1	7	14	21	28	35	42
1M	1001	189	256	317	372	427	481	--	--
	1002	203	270	323	375	418	452	--	--
	1003	211	291	347	400	448	497	--	--
	1104	216	291	351	408	455	504	--	--
	1005	185	240	291	344	382	431	--	--
	1006	183	246	301	358	401	450	--	--
	1007	193	274	354	407	465	520	--	--
	1008	211	294	374	444	501	561	--	--
	1009	196	262	334	393	448	490	--	--
	1010	199	277	354	433	486	536	--	--
	1011	205	277	331	381	426	476	496	519
	1012	185	242	297	343	388	436	464	495
	1013	207	284	355	419	471	525	556	581
	1014	195	262	321	380	427	480	490	526
	1015	200	267	326	377	421	458	473	504

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day -9	-1	7	14	21	28	35	42
2M	2001	199	281	350	409	466	527	--	--
	2002	191	258	315	369	419	478	--	--
	2003	187	262	328	391	447	500	--	--
	2004	202	270	334	389	433	478	--	--
	2005	197	260	316	371	405	453	--	--
	2006	195	253	307	363	405	450	--	--
	2007	192	268	333	395	442	487	--	--
	2008	200	270	328	381	423	474	--	--
	2009	200	275	326	389	429	475	--	--
	2010	206	285	344	395	435	473	--	--

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day -9	-1	7	14	21	28	35	42
3M	3001	205	279	333	389	422	474	--	--
	3002	188	264	314	378	412	472	--	--
	3003	189	258	309	365	399	456	--	--
	3004	191	260	313	379	411	463	--	--
	3005	200	272	325	381	419	462	--	--
	3006	193	273	336	399	443	495	--	--
	3007	200	272	322	387	422	478	--	--
	3008	202	278	329	388	425	464	--	--
	3009	199	281	334	413	455	518	--	--
	3010	197	269	320	383	412	453	--	--

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day -9	-1	7	14	21	28	35	42
4M	4001	197	264	297	360	391	447	--	--
	4002	189	257	293	353	379	429	--	--
	4003	183	260	290	353	374	437	--	--
	4004	209	285	336	405	451	518	--	--
	4105	187	262	314	383	410	481	--	--
	4006	202	284	323	392	432	490	--	--
	4007	197	263	312	373	416	463	--	--
	4008	212	298	336	406	428	486	--	--
	4009	201	266	310	370	404	454	--	--
	4010	187	259	299	358	382	429	--	--
	4011	199	265	310	376	406	456	467	515
	4012	191	254	289	342	374	416	428	470
	4013	195	270	318	387	424	483	500	537
	4014	209	291	350	430	482	557	586	627
	4015	207	289	335	400	428	485	497	538

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day -10	-1	7	14	21	28	35	42
1F	1501	180	229	248	265	291	298	--	--
	1502	193	237	270	295	319	327	--	--
	1503	177	212	239	260	268	271	--	--
	1504	174	214	238	263	289	304	--	--
	1505	178	230	250	277	308	327	--	--
	1506	171	213	235	252	275	291	--	--
	1507	186	231	263	284	303	323	--	--
	1508	179	213	238	253	273	282	--	--
	1509	171	204	220	237	245	268	--	--
	1510	175	204	226	247	259	270	--	--
	1511	189	221	248	268	287	302	360	328
	1512	181	229	250	271	294	306	322	342
	1513	184	213	254	283	308	329	357	378
	1514	183	218	235	244	264	275	285	293
	1515	192	226	249	269	284	301	319	329

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day -10	-1	7	14	21	28	35	42
2F	2501	179	233	259	288	315	323	--	--
	2502	185	215	242	254	267	269	--	--
	2503	176	218	238	256	278	291	--	--
	2504	181	222	248	280	300	319	--	--
	2505	185	231	264	294	312	327	--	--
	2506	176	207	238	256	269	277	--	--
	2507	178	220	246	274	289	304	--	--
	2508	189	230	259	281	293	303	--	--
	2509	182	225	247	275	289	301	--	--
	2510	183	222	244	265	279	301	--	--

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day -10	-1	7	14	21	28	35	42
3F	3501	185	234	261	293	306	332	--	--
	3502	188	233	255	277	293	316	--	--
	3503	179	220	236	254	275	288	--	--
	3504	176	214	232	256	272	292	--	--
	3505	184	221	245	269	292	304	--	--
	3506	180	228	252	285	299	319	--	--
	3507	177	222	247	295	297	323	--	--
	3508	182	235	263	297	329	351	--	--
	3509	182	229	238	251	265	280	--	--
	3510	176	210	225	241	250	266	--	--

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day -10	-1	7	14	21	28	35	42
4F	4501	181	221	245	273	281	305	--	--
	4502	187	239	260	292	300	320	--	--
	4503	183	233	239	275	291	302	--	--
	4504	169	200	215	234	250	265	--	--
	4505	178	225	236	256	286	299	--	--
	4506	177	215	254	292	291	309	--	--
	4507	193	242	253	279	305	319	--	--
	4508	173	204	216	231	248	267	--	--
	4509	190	239	260	293	315	338	--	--
	4510	188	246	261	292	313	334	--	--
	4511	180	218	240	270	281	297	311	329
	4512	172	217	233	262	275	290	293	316
	4513	185	210	211	220	257	285	297	318
	4514	180	220	228	252	259	275	279	301
	4515	175	225	240	265	277	293	307	329

Appendix 8

Individual Body Weight Gains Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	TERR	Technical error
AVS	Suspected aberrant value	UPTD	Unable to perform due to technical difficulty
NC	Not calculable	X	Excluded from mean
OA	Omitted activity		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day Change -9 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1M	1001	67	61	55	55	54	--	--
	1002	67	53	52	43	34	--	--
	1003	80	56	53	48	49	--	--
	1104	75	60	57	47	49	--	--
	1005	55	51	53	38	49	--	--
	1006	63	55	57	43	49	--	--
	1007	81	80	53	58	55	--	--
	1008	83	80	70	57	60	--	--
	1009	66	72	59	55	42	--	--
	1010	78	77	79	53	50	--	--
	1011	72	54	50	45	50	20	23
	1012	57	55	46	45	48	28	31
	1013	77	71	64	52	54	31	25
	1014	67	59	59	47	53	10	36
	1015	67	59	51	44	37	15	31

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day Change -9 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
2M	2001	82	69	59	57	61	--	--
	2002	67	57	54	50	59	--	--
	2003	75	66	63	56	53	--	--
	2004	68	64	55	44	45	--	--
	2005	63	56	55	34	48	--	--
	2006	58	54	56	42	45	--	--
	2007	76	65	62	47	45	--	--
	2008	70	58	53	42	51	--	--
	2009	75	51	63	40	46	--	--
	2010	79	59	51	40	38	--	--

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day Change -9 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
3M	3001	74	54	56	33	52	--	--
	3002	76	50	64	34	60	--	--
	3003	69	51	56	34	57	--	--
	3004	69	53	66	32	52	--	--
	3005	72	53	56	38	43	--	--
	3006	80	63	63	44	52	--	--
	3007	72	50	65	35	56	--	--
	3008	76	51	59	37	39	--	--
	3009	82	53	79	42	63	--	--
	3010	72	51	63	29	41	--	--

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day Change -9 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
4M	4001	67	33	63	31	56	--	--
	4002	68	36	60	26	50	--	--
	4003	77	30	63	21	63	--	--
	4004	76	51	69	46	67	--	--
	4105	75	52	69	27	71	--	--
	4006	82	39	69	40	58	--	--
	4007	66	49	61	43	47	--	--
	4008	86	38	70	22	58	--	--
	4009	65	44	60	34	50	--	--
	4010	72	40	59	24	47	--	--
	4011	66	45	66	30	50	11	48
	4012	63	35	53	32	42	12	42
	4013	75	48	69	37	59	17	37
	4014	82	59	80	52	75	29	41
	4015	82	46	65	28	57	12	41

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day Change -10 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1F	1501	49	19	17	26	7	--	--
	1502	44	33	25	24	8	--	--
	1503	35	27	21	8	3	--	--
	1504	40	24	25	26	15	--	--
	1505	52	20	27	31	19	--	--
	1506	42	22	17	23	16	--	--
	1507	45	32	21	19	20	--	--
	1508	34	25	15	20	9	--	--
	1509	33	16	17	8	23	--	--
	1510	29	22	21	12	11	--	--
	1511	32	27	20	19	15	58	-32
	1512	48	21	21	23	12	16	20
	1513	29	41	29	25	21	28	21
	1514	35	17	9	20	11	10	8
	1515	34	23	20	15	17	18	10

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day Change -10 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
2F	2501	54	26	29	27	8	--	--
	2502	30	27	12	13	2	--	--
	2503	42	20	18	22	13	--	--
	2504	41	26	32	20	19	--	--
	2505	46	33	30	18	15	--	--
	2506	31	31	18	13	8	--	--
	2507	42	26	28	15	15	--	--
	2508	41	29	22	12	10	--	--
	2509	43	22	28	14	12	--	--
	2510	39	22	21	14	22	--	--

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day Change -10 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
3F	3501	49	27	32	13	26	--	--
	3502	45	22	22	16	23	--	--
	3503	41	16	18	21	13	--	--
	3504	38	18	24	16	20	--	--
	3505	37	24	24	23	12	--	--
	3506	48	24	33	14	20	--	--
	3507	45	25	48	2	26	--	--
	3508	53	28	34	32	22	--	--
	3509	47	9	13	14	15	--	--
	3510	34	15	16	9	16	--	--

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	Day Change -10 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
4F	4501	40	24	28	8	24	--	--
	4502	52	21	32	8	20	--	--
	4503	50	6	36	16	11	--	--
	4504	31	15	19	16	15	--	--
	4505	47	11	20	30	13	--	--
	4506	38	39	38	-1	18	--	--
	4507	49	11	26	26	14	--	--
	4508	31	12	15	17	19	--	--
	4509	49	21	33	22	23	--	--
	4510	58	15	31	21	21	--	--
	4511	38	22	30	11	16	14	18
	4512	45	16	29	13	15	3	23
	4513	25	1	9	37	28	12	21
	4514	40	8	24	7	16	4	22
	4515	50	15	25	12	16	14	22

Appendix 9

Individual Food Consumption Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	OA	Omitted activity
AFE	Animal found with no food during measurement interval-Exclude	ONEG	Original value negative, animal did not eat
AFNF	Animal found with no food during measurement interval	POWF	Powdered food
ANH	Animal found with no hopper during measurement interval	REHO	Animal rehoused during measurement interval
ANIC	Animal not in cage or in incorrect cage during measurement	REPL	Animal replaced during measurement interval
ANW	Animal found with no water access during measurement intervals	SPIL	Spilled food (by animal)
ANWB	Animal found with no water bottle during measurement interval	TERR	Technical error
AVS	Suspected aberrant value	UPTD	Unable to perform due to technical difficulty
AWE	Animal found with no water in bottle during measurement interval-Exclude	WAFE	Water added to food during measurement interval
FSG	Food supplementation given during interval, included in feed weight	WAFI	Water added to food during measurement interval, included
FSNC	Food supplementation given during interval, value not calculable	WETF	Wet or contaminated food (in container)
NC	Not calculable	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	28.8	30.5	31.6	33.0	33.0	--	--
	1002	28.8	30.5	31.6	33.0	33.0	--	--
	1003	28.8	30.5	31.6	33.0	33.0	--	--
	1104	30.6	29.2	30.3	30.8	32.0	--	--
	1005	25.4	29.2	30.3	30.8	32.0	--	--
	1006	25.4	29.2	30.3	30.8	32.0	--	--
	1007	32.8	35.2	35.9	36.9	37.9	--	--
	1008	32.8	35.2	35.9	36.9	37.9	--	--
	1009	31.9	34.1	36.1	36.3	36.1	--	--
	1010	31.9	34.1	36.1	36.3	36.1	--	--
	1011	28.4	30.0	31.2	32.0	32.7	32.4	33.7
	1012	28.4	30.0	31.2	32.0	32.7	32.4	33.7
	1013	28.4	30.0	31.2	32.0	32.7	32.4	33.7
	1014	28.3	28.7	30.6	30.4	31.4	30.4	31.6
	1015	28.3	28.7	30.6	30.4	31.4	30.4	31.6

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	29.0	30.7	33.8	34.0	36.0	--	--
	2002	29.0	30.7	33.8	34.0	36.0	--	--
	2003	29.0	30.7	33.8	34.0	36.0	--	--
	2004	26.4	28.6	31.1	30.3	32.6	--	--
	2005	26.4	28.6	31.1	30.3	32.6	--	--
	2006	26.4	28.6	31.1	30.3	32.6	--	--
	2007	27.3	29.5	32.3	31.8	33.2	--	--
	2008	27.3	29.5	32.3	31.8	33.2	--	--
	2009	29.1	30.0	33.1	32.6	33.2	--	--
	2010	29.1	30.0	33.1	32.6	33.2	--	--

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	28.0	27.5	32.1	28.2	32.6	--	--
	3002	28.0	27.5	32.1	28.2	32.6	--	--
	3003	28.0	27.5	32.1	28.2	32.6	--	--
	3004	27.5	28.1	--TERR	29.1	32.0	--	--
	3005	27.5	28.1	--TERR	29.1	32.0	--	--
	3006	27.5	28.1	--TERR	29.1	32.0	--	--
	3007	28.4	27.9	31.4	28.6	31.8	--	--
	3008	28.4	27.9	31.4	28.6	31.8	--	--
	3009	29.3	27.9	33.7	31.5	35.1	--	--
	3010	29.3	27.9	33.7	31.5	35.1	--	--

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	26.8	24.1	30.9	26.1	33.0	--	--
	4002	26.8	24.1	30.9	26.1	33.0	--	--
	4003	26.8	24.1	30.9	26.1	33.0	--	--
	4004	--REHO	28.1	35.2	31.3	36.9	--	--
	4105	--REHO	28.1	35.2	31.3	36.9	--	--
	4006	--REHO	28.1	35.2	31.3	36.9	--	--
	4007	30.5	28.6	35.6	31.9	36.4	--	--
	4008	30.5	28.6	35.6	31.9	36.4	--	--
	4009	30.1	27.4	32.8	29.0	33.2	--	--
	4010	30.1	27.4	32.8	29.0	33.2	--	--
	4011	27.6	25.6	32.0	28.9	33.7	30.4	35.4
	4012	27.6	25.6	32.0	28.9	33.7	30.4	35.4
	4013	27.6	25.6	32.0	28.9	33.7	30.4	35.4
	4014	31.3	31.4	38.7	35.9	41.6	38.1	42.3
	4015	31.3	31.4	38.7	35.9	41.6	38.1	42.3

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	22.0	21.9	24.2	23.7	23.7	--	--
	1502	22.0	21.9	24.2	23.7	23.7	--	--
	1503	22.0	21.9	24.2	23.7	23.7	--	--
	1504	20.0	20.5	21.9	23.3	24.5	--	--
	1505	20.0	20.5	21.9	23.3	24.5	--	--
	1506	20.0	20.5	21.9	23.3	24.5	--	--
	1507	19.6	21.6	22.9	23.9	24.2	--	--
	1508	19.6	21.6	22.9	23.9	24.2	--	--
	1509	18.6	20.6	21.3	21.9	22.9	--	--
	1510	18.6	20.6	21.3	21.9	22.9	--	--
	1511	21.0	23.8	26.0	25.8	26.4	27.4	26.6
	1512	21.0	23.8	26.0	25.8	26.4	27.4	26.6
	1513	21.0	23.8	26.0	25.8	26.4	27.4	26.6
	1514	21.4	21.4	22.8	21.9	24.6	26.0	24.7
	1515	21.4	21.4	22.8	21.9	24.6	26.0	24.7

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	21.1	21.0	22.9	22.0	22.9	--	--
	2502	21.1	21.0	22.9	22.0	22.9	--	--
	2503	21.1	21.0	22.9	22.0	22.9	--	--
	2504	21.0	23.0	24.4	24.0	24.9	--	--
	2505	21.0	23.0	24.4	24.0	24.9	--	--
	2506	21.0	23.0	24.4	24.0	24.9	--	--
	2507	20.6	21.1	23.0	22.0	22.9	--	--
	2508	20.6	21.1	23.0	22.0	22.9	--	--
	2509	19.4	20.6	21.8	21.5	23.4	--	--
	2510	19.4	20.6	21.8	21.5	23.4	--	--

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	21.4	21.6	23.9	22.9	25.4	--	--
	3502	21.4	21.6	23.9	22.9	25.4	--	--
	3503	21.4	21.6	23.9	22.9	25.4	--	--
	3504	21.5	21.6	23.5	24.0	25.7	--	--
	3505	21.5	21.6	23.5	24.0	25.7	--	--
	3506	21.5	21.6	23.5	24.0	25.7	--	--
	3507	22.9	24.0	28.9	26.6	29.0	--	--
	3508	22.9	24.0	28.9	26.6	29.0	--	--
	3509	21.2	19.4	21.0	19.4	23.6	--	--
	3510	21.2	19.4	21.0	19.4	23.6	--	--

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	21.2	20.1	24.2	23.0	25.0	--	--
	4502	21.2	20.1	24.2	23.0	25.0	--	--
	4503	21.2	20.1	24.2	23.0	25.0	--	--
	4504	20.3	20.3	23.2	21.5	23.6	--	--
	4505	20.3	20.3	23.2	21.5	23.6	--	--
	4506	20.3	20.3	23.2	21.5	23.6	--	--
	4507	20.9	19.6	21.4	21.3	22.6	--	--
	4508	20.9	19.6	21.4	21.3	22.6	--	--
	4509	23.9	21.2	24.2	23.2	26.6	--	--
	4510	23.9	21.2	24.2	23.2	26.6	--	--
	4511	20.2	19.3	21.3	22.5	24.6	21.9	24.8
	4512	20.2	19.3	21.3	22.5	24.6	21.9	24.8
	4513	20.2	19.3	21.3	22.5	24.6	21.9	24.8
	4514	21.9	20.1	22.7	20.5	23.4	21.1	24.9
	4515	21.9	20.1	22.7	20.5	23.4	21.1	24.9

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		
- 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

Appendix 10

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
--	Not required for veterinary monitoring / No findings / Not scheduled to be performed/Dead	OOS	Sample analysed outside of established stability, results for information only
ADQ	Adequate	QNS	Quantity not sufficient
AVS	Suspected aberrant value	RSV	Refer to source data
CLOT	Sample clotted	SAMU	Large number of smudge cells
COMM	Comment added	SND	Stability not documented
DEC	Decreased	SNR	Sample not received
INC	Increased	Unsc	Unscheduled bleed
MDIFF	Manual differential	UPTD	Unable to perform due to technical difficulty
NA	Not applicable	UTD	Unable to determine
NAF	No abnormal findings	UTDM	Unable to determine, not confirmed by microscopy
NRBC	WBC corrected for presence of nucleated RBC	UTDR	Unable to determine, results not reproducible
NSCH	Not scheduled to be performed	Vet	Bleed for veterinary monitoring
OA	Omitted activity	VNC	Value not calculable
		X	Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Note: Additional morphology for flagged samples has been reported for the following animals: 2009, 2010, 3006, 3008, 4002, 4105, 4006, 4010, 3507, 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)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	9.47	0.94	8.19	0.21	0.06	0.02	0.05
	1002	8.00	0.69	7.07	0.13	0.05	0.01	0.06
	1003	7.61	0.79	6.48	0.12	0.14	0.01	0.05
	1104	8.95	1.04	7.59	0.16	0.09	0.02	0.05
	1005	5.76	0.86	4.61	0.17	0.04	0.00	0.08
	1006	7.83	0.45	7.16	0.12	0.03	0.02	0.05
	1007	7.68	0.72	6.68	0.15	0.06	0.02	0.06
	1008	10.08	0.98	8.70	0.20	0.09	0.02	0.08
	1009	7.25	0.55	6.47	0.13	0.05	0.01	0.04
	1010	7.36	0.92	6.11	0.19	0.09	0.01	0.05
2M	2001	14.33	6.68	6.82	0.23	0.14	0.02	0.42
	2002	14.55	7.29	6.25	0.40	0.16	0.02	0.43
	2003	12.98	6.76	5.39	0.26	0.07	0.02	0.48
	2004	16.49	8.77	6.76	0.41	0.16	0.03	0.35
	2005	12.12	6.56	4.80	0.19	0.11	0.01	0.44
	2006	12.92	7.93	4.25	0.27	0.24	0.02	0.21
	2007	15.89	6.57	8.48	0.43	0.11	0.04	0.25
	2008	10.89	5.22	4.95	0.23	0.15	0.01	0.33
	2009	10.92	5.35	5.46	0.00	0.11	0.00	--MDIFF
	2010	10.27	3.88	5.76	0.22	0.22	0.02	0.16

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	1001	7.83	15.0	44.1	56.4	19.2	34.0	11.9
	1002	7.49	14.0	42.2	56.3	18.7	33.1	12.9
	1003	7.80	14.3	43.0	55.1	18.4	33.4	12.3
	1104	8.15	14.5	42.7	52.5	17.7	33.8	12.5
	1005	7.75	14.6	44.1	56.8	18.8	33.0	11.9
	1006	7.88	14.3	41.8	53.1	18.1	34.1	11.7
	1007	7.61	14.2	42.1	55.4	18.7	33.8	12.2
	1008	8.13	14.5	42.5	52.2	17.8	34.1	13.2
	1009	7.51	14.9	43.6	58.0	19.9	34.2	11.9
	1010	7.55	13.8	40.3	53.4	18.2	34.1	12.9
2M	2001	7.78	14.0	41.8	53.8	18.0	33.5	12.9
	2002	7.84	14.7	43.2	55.1	18.8	34.1	12.6
	2003	7.48	14.1	41.3	55.1	18.8	34.1	12.6
	2004	7.91	14.7	43.6	55.2	18.6	33.7	13.0
	2005	7.95	14.4	42.3	53.1	18.1	34.1	12.9
	2006	8.14	14.4	42.2	51.9	17.6	34.0	13.1
	2007	8.10	15.4	45.6	56.2	19.0	33.7	12.8
	2008	8.01	14.3	42.0	52.4	17.9	34.0	12.8
	2009	7.94	14.8	43.9	55.2	18.7	33.8	13.2
	2010	8.53	15.9	46.0	53.9	18.6	34.5	12.1

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	PLATELET CLUMPS	WBC MORPH
1M	1001	920	232.4	--	--	--	--	--
	1002	1177	349.1	--	--	--	--	--
	1003	1147	252.8	--	--	--	--	--
	1104	965	246.1	--	--	--	--	--
	1005	955	282.2	--	--	--	--	--
	1006	1156	223.4	--	--	--	--	--
	1007	1274	237.1	--	--	--	--	--
	1008	1189	251.2	--	--	--	--	--
	1009	940	253.0	--	--	--	--	--
	1010	1454	248.6	--	--	--	--	--
2M	2001	1381	195.9	--	--	--	--	--
	2002	866	218.7	--	--	--	--	--
	2003	1084	214.9	--	--	--	--	--
	2004	1268	222.0	--	--	--	--	--
	2005	1096	193.1	--	--	--	--	--
	2006	1251	210.8	--	--	--	--	--
	2007	905	195.7	--	--	--	--	--
	2008	1134	168.6	--	--	--	--	--
	2009	624	187.2	1+	--	NAF	--	NAF
	2010	663	176.8	1+	--	NAF	--	NAF

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	17.56	10.86	5.94	0.18	0.34	0.03	0.20
	3002	21.47	13.89	6.92	0.21	0.27	0.04	0.13
	3003	17.50	12.88	4.04	0.18	0.17	0.02	0.22
	3004	17.07	12.17	4.21	0.25	0.20	0.02	0.23
	3005	16.06	8.37	6.84	0.20	0.25	0.02	0.40
	3006	17.21	9.85	6.73	0.18	0.22	0.04	0.20
	3007	14.07	9.00	4.49	0.10	0.17	0.02	0.29
	3008	18.41	9.57	8.65	0.18	0.00	0.00	--MDIFF
	3009	19.77	13.51	5.33	0.53	0.09	0.04	0.27
	3010	22.13	12.05	9.16	0.52	0.18	0.05	0.17
4M	4001	10.29	7.42	2.49	0.23	0.03	0.01	0.11
	4002	11.96	9.86	1.80	0.13	0.11	0.00	0.05
	4003	13.77	10.67	2.75	0.17	0.03	0.02	0.13
	4004	13.29	8.66	4.21	0.13	0.11	0.02	0.15
	4105	18.88	7.93	10.38	0.19	0.38	0.00	--MDIFF
	4006	19.21	10.76	8.07	0.19	0.19	0.00	--MDIFF
	4007	15.81	11.16	3.89	0.17	0.32	0.01	0.25
	4008	13.25	9.44	3.15	0.33	0.14	0.02	0.17
	4009	15.23	9.78	4.90	0.26	0.18	0.02	0.10
	4010	10.43	6.88	3.23	0.31	0.00	0.00	--MDIFF

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
3M	3001	7.95	13.6	41.1	51.7	17.1	33.1	12.8
	3002	7.95	15.0	44.4	55.8	18.9	33.8	12.9
	3003	7.85	14.8	43.7	55.7	18.8	33.8	14.0
	3004	7.94	14.5	42.7	53.8	18.3	34.1	12.8
	3005	7.70	13.5	41.6	54.0	17.5	32.5	13.5
	3006	7.20	13.7	39.9	55.5	19.1	34.4	12.9
	3007	7.39	13.6	39.9	54.0	18.4	34.0	13.0
	3008	8.10	14.6	42.5	52.5	18.0	34.3	13.3
	3009	8.35	15.8	47.2	56.5	19.0	33.5	13.0
	3010	7.62	15.0	43.3	56.8	19.7	34.7	13.0
4M	4001	7.69	15.0	43.5	56.5	19.4	34.4	13.8
	4002	8.38	14.9	44.2	52.7	17.8	33.8	13.4
	4003	8.48	16.1	47.4	56.0	18.9	33.9	13.6
	4004	7.54	15.4	44.8	59.4	20.4	34.3	13.9
	4105	7.71	14.5	42.8	55.5	18.8	33.9	14.1
	4006	7.74	14.3	42.7	55.2	18.4	33.4	13.2
	4007	7.93	14.4	44.0	55.5	18.2	32.8	13.6
	4008	8.12	15.0	44.3	54.6	18.5	33.9	14.4
	4009	7.90	15.2	43.9	55.5	19.3	34.7	13.1
	4010	8.16	15.2	44.5	54.6	18.6	34.2	12.7

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	PLATELET CLUMPS	WBC MORPH
3M	3001	1062	193.9	--	--	--	--	--
	3002	766	194.0	--	--	--	--	--
	3003	1136	213.0	--	--	--	--	--
	3004	1210	168.8	--	--	--	--	--
	3005	1072	192.0	--	--	--	--	--
	3006	1191	158.6	1+	--	NAF	--	NAF
	3007	1085	166.4	--	--	--	--	--
	3008	1074	141.7	1+	--	NAF	--	NAF
	3009	935	147.4	--	--	--	--	--
	3010	764	170.7	--	--	--	--	--
4M	4001	1124	193.4	--	--	--	--	--
	4002	873	193.6	1+	1+	NAF	--	NAF
	4003	895	198.5	--	--	--	--	--
	4004	991	221.4	--	--	--	--	--
	4105	927	145.9	1+	--	NAF	--	NAF
	4006	687	142.5	1+	1+	NAF	--	NAF
	4007	1348	119.2	--	--	--	--	--
	4008	818	208.3	--	--	--	--	--
	4009	927	198.0	--	--	--	--	--
	4010	906	143.4	1+	--	NAF	--	NAF

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	1501	7.72	1.39	6.09	0.12	0.09	0.01	0.03
	1502	7.37	0.79	6.34	0.14	0.06	0.01	0.04
	1503	6.54	0.86	5.27	0.28	0.08	0.01	0.04
	1504	5.30	0.54	4.61	0.07	0.05	0.01	0.03
	1505	5.94	0.69	4.98	0.18	0.05	0.01	0.03
	1506	6.70	1.25	5.20	0.16	0.05	0.00	0.04
	1507	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	1508	6.49	0.53	5.67	0.15	0.05	0.01	0.07
	1509	7.59	0.46	6.72	0.22	0.05	0.01	0.13
	1510	9.90	0.71	8.75	0.25	0.04	0.02	0.11
2F	2501	13.45	6.33	6.10	0.25	0.35	0.02	0.40
	2502	7.14	3.30	3.52	0.05	0.21	0.01	0.05
	2503	6.52	3.49	2.62	0.10	0.23	0.01	0.06
	2504	7.34	3.72	3.24	0.10	0.22	0.01	0.05
	2505	7.34	3.52	3.50	0.12	0.12	0.01	0.06
	2506	11.22	5.75	4.90	0.13	0.24	0.02	0.17
	2507	12.42	4.28	7.42	0.16	0.33	0.04	0.20
	2508	10.51	5.61	4.35	0.19	0.14	0.01	0.20
	2509	11.86	4.35	6.60	0.24	0.32	0.02	0.34
	2510	10.95	3.62	6.78	0.13	0.16	0.02	0.24

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	7.83	14.4	41.1	52.4	18.4	35.1	10.8
	1502	7.26	14.2	39.2	54.0	19.6	36.3	11.2
	1503	8.12	14.9	41.7	51.3	18.3	35.6	10.7
	1504	7.82	13.6	39.5	50.5	17.4	34.5	10.7
	1505	7.40	14.2	39.7	53.6	19.1	35.7	11.2
	1506	7.69	13.6	38.8	50.4	17.7	35.2	10.9
	1507	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	1508	7.93	14.2	40.6	51.1	17.9	35.0	10.4
	1509	8.32	14.9	42.7	51.3	17.9	34.9	11.0
	1510	7.68	14.2	40.2	52.4	18.5	35.4	10.6
2F	2501	7.15	13.4	37.5	52.5	18.8	35.8	10.9
	2502	7.80	14.3	40.3	51.7	18.3	35.4	10.7
	2503	7.13	13.5	37.9	53.2	18.9	35.6	11.1
	2504	7.56	14.8	40.8	54.0	19.6	36.3	11.1
	2505	8.08	14.9	42.7	52.8	18.4	34.8	10.8
	2506	8.39	15.5	44.1	52.6	18.5	35.2	11.2
	2507	8.60	15.1	43.5	50.5	17.6	34.8	11.4
	2508	8.79	16.0	46.1	52.5	18.1	34.6	11.3
	2509	7.83	14.1	40.2	51.3	18.0	35.1	11.0
	2510	7.33	13.3	38.2	52.2	18.1	34.7	11.5

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	PLATELET CLUMPS	WBC MORPH
1F	1501	1069	191.3	--	--	--	--	--
	1502	1154	199.0	--	--	--	--	--
	1503	1005	184.8	--	--	--	--	--
	1504	1276	197.7	--	--	--	--	--
	1505	1166	193.6	--	--	--	--	--
	1506	1109	221.7	--	--	--	--	--
	1507	--CLOT	--CLOT	--	--	--	--	--
	1508	1257	142.1	--	--	--	--	--
	1509	1114	265.4	--	--	--	--	--
	1510	1162	158.5	--	--	--	--	--
2F	2501	1222	149.1	--	--	--	--	--
	2502	1122	131.4	--	--	--	--	--
	2503	1195	145.9	--	--	--	--	--
	2504	891	177.7	--	--	--	--	--
	2505	1051	151.0	--	--	--	--	--
	2506	1221	125.2	--	--	--	--	--
	2507	1094	173.5	--	--	--	--	--
	2508	917	139.8	--	--	--	--	--
	2509	1231	166.1	--	--	--	--	--
	2510	1214	149.4	--	--	--	--	--

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
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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	7.58	5.04	2.17	0.11	0.18	0.00	0.07
	3502	8.84	6.35	2.10	0.06	0.28	0.00	0.04
	3503	8.25	6.43	1.53	0.08	0.13	0.00	0.07
	3504	5.29	3.79	1.10	0.07	0.28	0.00	0.05
	3505	9.74	6.01	3.26	0.10	0.26	0.01	0.10
	3506	12.51	6.74	5.28	0.08	0.33	0.02	0.07
	3507	12.02	6.49	5.17	0.36	0.00	0.00	--MDIFF
	3508	8.79	5.53	2.91	0.09	0.19	0.01	0.06
	3509	7.63	5.00	2.40	0.08	0.06	0.00	0.10
	3510	8.66	6.19	2.21	0.11	0.07	0.01	0.07
4F	4501	4.49	2.07	2.02	0.04	0.30	0.01	0.06
	4502	12.02	7.51	3.96	0.19	0.22	0.02	0.13
	4503	12.51	10.21	1.60	0.19	0.34	0.01	0.15
	4504	3.92	2.61	1.07	0.05	0.17	0.00	0.02
	4505	8.76	5.60	2.58	0.15	0.26	0.01	0.16
	4506	7.70	5.44	1.96	0.06	0.18	0.01	0.05
	4507	8.71	5.96	2.34	0.13	0.11	0.01	0.15
	4508	5.82	3.84	1.86	0.06	0.06	0.00	--MDIFF
	4509	10.04	6.72	2.64	0.21	0.25	0.01	0.21
	4510	9.19	5.80	3.05	0.08	0.17	0.01	0.08

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Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	8.14	15.8	44.6	54.7	19.4	35.4	11.4
	3502	7.72	14.7	42.4	54.9	19.1	34.7	12.5
	3503	8.26	15.4	42.7	51.7	18.6	36.0	11.5
	3504	7.74	14.9	41.9	54.2	19.3	35.6	11.9
	3505	7.49	14.3	40.3	53.8	19.2	35.6	11.7
	3506	7.72	15.1	41.5	53.8	19.6	36.4	11.7
	3507	7.70	15.0	42.3	54.9	19.5	35.6	12.4
	3508	8.79	15.8	45.1	51.3	18.0	35.1	11.9
	3509	7.89	14.5	40.8	51.7	18.4	35.6	12.0
	3510	8.30	14.4	41.7	50.2	17.4	34.7	12.1
4F	4501	7.71	14.5	41.1	53.3	18.8	35.2	12.2
	4502	8.54	15.5	44.1	51.6	18.2	35.2	12.1
	4503	7.73	14.4	40.1	51.9	18.6	35.9	12.3
	4504	7.95	15.5	43.7	55.0	19.4	35.4	12.9
	4505	8.50	16.2	45.6	53.7	19.0	35.5	11.5
	4506	8.25	15.5	43.9	53.2	18.8	35.3	11.7
	4507	8.60	15.8	44.8	52.1	18.3	35.1	12.2
	4508	8.46	15.3	43.9	51.8	18.1	34.9	12.6
	4509	8.16	14.7	42.2	51.8	18.1	34.9	12.2
	4510	7.30	14.2	39.4	54.0	19.5	36.0	12.5

Appendix 10

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	PLATELET CLUMPS	WBC MORPH
3F	3501	774	164.7	--	--	--	--	--
	3502	1058	189.7	--	--	--	--	--
	3503	986	170.5	--	--	--	--	--
	3504	965	232.2	--	--	--	--	--
	3505	1031	134.2	--	--	--	--	--
	3506	1124	135.6	--	--	--	--	--
	3507	962	208.0	1+	1+	--	2+	NAF
	3508	880	211.9	--	--	--	--	--
	3509	1037	150.2	--	--	--	--	--
	3510	1133	172.7	--	--	--	--	--
4F	4501	930	154.3	--	--	--	--	--
	4502	876	171.3	--	--	--	--	--
	4503	970	186.3	--	--	--	--	--
	4504	665	243.1	--	--	--	--	--
	4505	852	175.0	--	--	--	--	--
	4506	930	194.0	--	--	--	--	--
	4507	1152	224.9	--	--	--	--	--
	4508	711	227.9	1+	--	--	3+	NAF
	4509	766	136.4	--	--	--	--	--
	4510	810	208.8	--	--	--	--	--

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	10.95	0.94	9.70	0.14	0.10	0.03	0.03
	1012	6.91	0.72	5.82	0.20	0.07	0.01	0.09
	1013	9.99	1.46	8.07	0.33	0.06	0.01	0.06
	1014	8.90	1.46	7.07	0.22	0.10	0.01	0.03
	1015	12.82	1.44	10.97	0.17	0.17	0.02	0.04
4M	4011	8.70	1.20	7.13	0.26	0.07	0.02	0.02
	4012	4.99	1.06	3.73	0.15	0.03	0.01	0.02
	4013	8.01	1.46	6.28	0.13	0.08	0.01	0.04
	4014	9.63	2.37	6.64	0.48	0.11	0.02	0.02
	4015	9.80	1.19	8.37	0.17	0.04	0.02	0.02

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	1011	7.47	13.8	42.1	56.3	18.4	32.7	11.4
	1012	7.48	13.2	39.9	53.3	17.6	33.0	12.4
	1013	7.75	13.3	40.0	51.6	17.1	33.2	12.4
	1014	7.23	12.8	39.0	53.9	17.8	33.0	13.9
	1015	7.97	13.5	40.9	51.3	16.9	33.0	12.7
4M	4011	7.52	13.3	40.6	54.0	17.7	32.9	14.9
	4012	7.15	13.3	40.1	56.1	18.6	33.1	13.4
	4013	7.26	13.0	40.8	56.2	18.0	32.0	13.4
	4014	7.60	13.8	41.9	55.1	18.2	32.9	13.1
	4015	7.55	13.2	40.2	53.3	17.4	32.7	13.5

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	PLATELET CLUMPS	WBC MORPH
1M	1011	845	196.2	--	--	--	--	--
	1012	1094	204.3	--	--	--	--	--
	1013	1370	238.5	--	--	--	--	--
	1014	1282	257.4	--	--	--	--	--
	1015	884	211.4	--	--	--	--	--
4M	4011	885	242.3	--	--	--	--	--
	4012	1253	224.4	--	--	--	--	--
	4013	1087	237.7	--	--	--	--	--
	4014	1083	221.8	--	--	--	--	--
	4015	1265	303.2	--	--	--	--	--

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	7.23	0.49	6.53	0.10	0.05	0.01	0.05
	1512	4.17	0.52	3.46	0.12	0.05	0.00	0.02
	1513	5.76	0.48	5.11	0.07	0.06	0.01	0.02
	1514	7.79	0.67	6.85	0.09	0.10	0.01	0.06
	1515	9.10	1.16	7.55	0.22	0.08	0.02	0.06
4F	4511	4.92	0.60	4.14	0.12	0.04	0.00	0.02
	4512	6.51	0.56	5.77	0.08	0.05	0.01	0.03
	4513	3.16	0.41	2.64	0.05	0.04	0.00	0.02
	4514	9.34	1.16	7.86	0.17	0.07	0.01	0.08
	4515	8.38	1.05	7.08	0.14	0.05	0.02	0.04

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	6.90	12.1	37.2	53.9	17.6	32.6	11.3
	1512	7.40	13.4	39.9	53.9	18.0	33.5	11.1
	1513	8.22	14.4	42.4	51.6	17.5	34.0	11.2
	1514	7.26	13.0	38.2	52.6	17.9	34.0	11.4
	1515	7.62	13.6	40.8	53.5	17.9	33.4	11.4
4F	4511	7.12	12.7	38.6	54.3	17.8	32.7	12.7
	4512	6.88	12.6	38.5	56.0	18.3	32.7	13.7
	4513	6.96	12.9	39.2	56.3	18.5	32.9	13.0
	4514	6.91	12.8	39.1	56.5	18.5	32.7	12.8
	4515	7.43	13.1	39.4	53.0	17.6	33.3	13.6

Appendix 10

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POIK	PLT MORPH	PLATELET CLUMPS	WBC MORPH
1F	1511	1144	151.5	--	--	--	--	--
	1512	1179	218.6	--	--	--	--	--
	1513	1040	109.1	--	--	--	--	--
	1514	1072	156.2	--	--	--	--	--
	1515	1065	196.9	--	--	--	--	--
4F	4511	1186	208.3	--	--	--	--	--
	4512	1426	255.8	--	--	--	--	--
	4513	1166	194.0	--	--	--	--	--
	4514	1076	241.9	--	--	--	--	--
	4515	1301	227.3	--	--	--	--	--

Appendix 11

Individual Coagulation Values Explanation Page

ACL Advance

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Activated Partial Thromboplastin Time	APTT	sec	Turbidimetric
Fibrinogen	FIB	mg/dL	Turbidimetric
Prothrombin Time	PT	sec	Turbidimetric
Thrombin Time	TT	sec	Turbidimetric

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
NA	Not applicable	UPTD	Unable to perform due to technical difficulty
NCD	No clot detected	UTD	Unable to determine
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 information only	VNC	Value not calculable
QNS	Quantity not sufficient	X	Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 11

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1001	16.5	14.3	263	N
	1002	17.5	15.2	276	N
	1003	12.9	15.8	267	N
	1104	13.7	15.8	332	N
	1005	15.1	15.3	313	N
	1006	15.0	16.7	285	N
	1007	14.9	15.5	304	N
	1008	13.8	16.5	354	N
	1009	15.9	15.2	303	N
	1010	15.9	15.4	311	N
2M	2001	14.4	18.8	608	N
	2002	14.4	18.3	667	N
	2003	13.5	18.5	667	N
	2004	14.5	18.1	725	N
	2005	13.0	17.0	695	N
	2006	13.8	18.3	587	N
	2007	13.8	18.8	746	N
	2008	13.5	18.4	655	N
	2009	13.6	19.2	659	N
	2010	14.1	17.3	611	N

Appendix 11

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3M	3001	13.3	20.5	695	N
	3002	13.7	19.8	725	N
	3003	12.5	20.4	676	N
	3004	12.6	19.9	763	N
	3005	12.8	19.9	705	N
	3006	13.2	18.2	787	N
	3007	12.1	20.1	676	N
	3008	12.7	20.6	826	N
	3009	12.1	20.5	813	N
	3010	12.9	19.6	757	N
4M	4001	20.1	12.5	690	N
	4002	19.9	12.4	700	N
	4003	21.4	12.5	655	N
	4004	18.1	12.1	714	N
	4105	19.0	12.5	725	N
	4006	20.3	11.3	672	N
	4007	21.6	12.2	826	N
	4008	14.8	13.2	781	N
	4009	20.3	12.0	714	N
	4010	22.3	13.0	800	N

Appendix 11

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1501	14.7	16.0	240	N
	1502	15.2	14.2	269	N
	1503	15.1	15.6	248	N
	1504	15.8	15.0	218	N
	1505	14.9	16.0	243	N
	1506	14.0	15.8	257	N
	1507	--CLOT	--CLOT	--CLOT	--CLOT
	1508	14.7	15.7	212	N
	1509	15.0	16.9	205	N
	1510	16.0	15.6	235	N
2F	2501	15.5	17.3	460	N
	2502	14.8	21.1	488	N
	2503	13.9	18.8	514	N
	2504	14.7	17.0	462	N
	2505	15.7	19.2	519	N
	2506	15.0	19.3	470	N
	2507	15.8	18.2	456	N
	2508	15.0	19.2	446	N
	2509	17.3	18.7	481	N
	2510	15.6	18.8	490	N

Appendix 11

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3F	3501	15.2	18.8	530	N
	3502	15.3	20.8	472	N
	3503	15.5	18.6	492	N
	3504	15.4	20.0	474	N
	3505	15.0	17.6	533	N
	3506	14.4	18.6	517	N
	3507	15.4	19.6	488	N
	3508	14.8	18.6	519	N
	3509	16.0	20.0	568	N
	3510	15.9	19.1	512	N
4F	4501	17.0	20.6	405	N
	4502	16.3	19.7	472	N
	4503	17.6	20.2	441	N
	4504	17.0	20.2	402	N
	4505	17.7	20.5	446	N
	4506	15.7	20.8	490	N
	4507	14.8	18.9	464	N
	4508	16.1	21.6	458	N
	4509	17.4	20.0	502	N
	4510	14.9	20.3	495	N

Appendix 11

Individual Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1011	18.2	16.0	261	N
	1012	17.2	16.0	263	N
	1013	16.2	15.3	285	N
	1014	17.3	17.0	256	N
	1015	16.2	15.5	291	N
4M	4011	16.9	15.6	265	N
	4012	17.8	15.6	230	N
	4013	18.6	15.7	271	N
	4014	16.4	16.6	253	N
	4015	--CLOT	--CLOT	--CLOT	--CLOT

Appendix 11

Individual Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1511	17.7	15.3	207	N
	1512	16.2	15.4	211	N
	1513	17.0	15.4	240	N
	1514	17.7	15.4	222	N
	1515	17.1	15.9	254	N
4F	4511	17.7	16.2	219	N
	4512	17.2	15.4	232	N
	4513	17.5	15.9	184	N
	4514	18.6	16.3	191	N
	4515	17.5	16.2	206	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
NA	Not applicable	UTDL	Unable to determine due to marked lipemia
NSCH	Not scheduled to be performed	UTDR	Unable to determine, results not reproducible
OA	Omitted activity	VARR	Assigned value above reportable range
OOS	Sample analysed outside of established stability, results for information only	VBRR	Assigned value below reportable range
QNS	Quantity not sufficient	Vet	Bleed for veterinary monitoring
RSV	Refer to source data	VNC	Value not calculable
SND	Stability not documented	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)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 12

Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	64	37	162	2VBRR	284	0.04	13
	1002	63	38	195	2VBRR	229	0.06	16
	1003	109	65	218	2VBRR	718	0.08	15
	1104	92	38	148	2VBRR	588	0.06	13
	1005	55	48	159	2VBRR	182	0.08	18
	1006	60	53	212	2VBRR	195	0.09	12
	1007	63	37	151	2VBRR	149	0.09	14
	1008	63	39	151	2VBRR	302	0.05	12
	1009	68	40	87	2VBRR	374	0.07	15
	1010	82	34	127	2VBRR	444	0.08	10
2M	2001	59	41	208	2VBRR	210	0.08	15
	2002	69	46	173	2VBRR	288	0.09	17
	2003	109	50	155	2VBRR	880	0.07	15
	2004	83	49	207	2VBRR	473	0.13	14
	2005	96	47	150	2VBRR	708	0.12	15
	2006	89	41	175	2VBRR	546	0.07	18
	2007	128	43	156	2VBRR	1406	0.08	21
	2008	120	58	146	2VBRR	1000	0.06	22
	2009	63	33	140	2VBRR	204	0.06	20
	2010	92	33	109	2VBRR	602	0.11	18

Appendix 12

Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	0.3	149	67	89	5.7	4.1	1.6
	1002	0.3	303	56	65	5.3	3.8	1.5
	1003	0.3	214	70	57	5.6	3.9	1.7
	1104	0.3	179	74	38	5.6	3.7	1.9
	1005	0.3	255	86	67	5.4	3.9	1.5
	1006	0.3	260	72	83	5.6	3.8	1.8
	1007	0.3	173	110	60	5.5	3.9	1.6
	1008	0.3	180	115	125	5.8	3.8	2.0
	1009	0.3	219	57	58	5.8	3.8	2.0
	1010	0.3	178	77	196	6.0	3.9	2.1
2M	2001	0.3	236	89	91	5.6	3.5	2.1
	2002	0.4	152	63	92	5.6	3.5	2.1
	2003	0.3	136	75	52	5.9	3.6	2.3
	2004	0.3	227	55	49	5.7	3.4	2.3
	2005	0.4	151	64	51	6.0	3.6	2.4
	2006	0.4	162	68	32	5.9	3.6	2.3
	2007	0.4	201	66	52	6.0	3.5	2.5
	2008	0.4	172	67	60	6.0	3.5	2.5
	2009	0.4	194	48	30	5.3	3.2	2.1
	2010	0.3	145	60	47	5.8	3.5	2.3

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	2.6	10.6	7.8	144	5.3	104	N
	1002	2.5	10.6	9.7	140	5.0	102	N
	1003	2.3	10.6	9.9	140	5.1	99	N
	1104	1.9	10.5	7.8	142	5.2	103	N
	1005	2.6	10.2	9.1	139	5.4	101	N
	1006	2.1	10.2	8.5	138	4.7	99	N
	1007	2.4	10.5	8.1	141	4.6	102	N
	1008	1.9	10.5	8.7	140	5.3	101	N
	1009	1.9	10.7	8.2	140	5.0	100	N
	1010	1.9	10.5	8.8	140	4.8	101	N
2M	2001	1.7	11.2	8.5	138	5.1	98	N
	2002	1.7	10.7	8.5	140	5.0	101	N
	2003	1.6	11.2	7.7	139	5.5	101	N
	2004	1.5	11.1	9.1	138	5.8	100	N
	2005	1.5	10.9	9.2	139	6.3	99	N
	2006	1.6	10.8	8.5	138	5.7	100	N
	2007	1.4	10.6	8.4	140	5.9	98	N
	2008	1.4	10.9	7.7	141	5.9	101	N
	2009	1.5	10.4	8.5	140	5.2	101	N
	2010	1.5	10.9	8.6	141	5.5	101	N

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	94	47	167	2VBRR	581	0.11	21
	3002	94	43	161	2VBRR	631	0.06	19
	3003	64	32	189	2VBRR	157	0.09	13
	3004	56	38	172	2VBRR	152	0.12	13
	3005	79	39	138	2VBRR	355	0.14	18
	3006	70	32	125	2VBRR	425	0.10	15
	3007	92	44	191	2VBRR	503	0.11	20
	3008	74	37	191	2VBRR	389	0.08	19
	3009	64	39	140	2VBRR	207	0.10	19
	3010	101	38	173	2VBRR	709	0.06	18
4M	4001	92	61	305	2VBRR	300	0.09	17
	4002	96	56	236	2VBRR	334	0.09	16
	4003	86	52	259	2VBRR	218	0.13	14
	4004	105	41	177	2VBRR	802	0.09	15
	4105	92	29	182	2VBRR	466	0.09	24
	4006	113	36	204	2VBRR	753	0.07	14
	4007	84	32	184	2VBRR	547	0.08	19
	4008	137	41	197	2VBRR	1117	0.17	18
	4009	79	37	179	2VBRR	351	0.11	17
	4010	77	40	199	2VBRR	322	0.10	15

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	199	77	89	5.7	3.5	2.2
	3002	0.4	153	75	55	5.9	3.5	2.4
	3003	0.4	161	70	47	5.8	3.7	2.1
	3004	0.4	168	68	85	6.0	3.8	2.2
	3005	0.3	148	70	54	5.9	3.4	2.5
	3006	0.5	186	117	46	6.0	3.6	2.4
	3007	0.4	212	72	39	5.4	3.4	2.0
	3008	0.5	176	56	50	5.8	3.5	2.3
	3009	0.4	168	66	72	6.1	3.6	2.5
	3010	0.5	167	61	71	5.9	3.5	2.4
4M	4001	0.4	167	63	65	5.7	3.5	2.2
	4002	0.4	198	96	134	5.9	3.6	2.3
	4003	0.3	122	59	44	5.8	3.8	2.0
	4004	0.4	192	101	94	6.1	3.6	2.5
	4105	0.5	133	84	44	5.8	3.5	2.3
	4006	0.4	127	79	84	5.8	3.5	2.3
	4007	0.4	208	101	52	6.3	3.7	2.6
	4008	0.4	151	60	52	5.7	3.4	2.3
	4009	0.4	190	71	62	5.3	3.4	1.9
	4010	0.4	145	59	65	5.9	3.5	2.4

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	1.6	10.8	9.1	139	6.0	100	N
	3002	1.5	10.6	8.1	140	5.5	101	N
	3003	1.8	10.9	8.6	138	5.4	101	N
	3004	1.7	10.8	8.8	139	5.1	101	N
	3005	1.4	11.3	10.4	140	6.1	100	N
	3006	1.5	11.5	9.5	141	5.2	100	N
	3007	1.7	10.3	8.2	140	6.0	101	N
	3008	1.5	10.9	8.3	138	5.6	99	N
	3009	1.4	11.1	8.4	140	5.6	100	N
	3010	1.5	10.6	8.8	140	6.0	101	N
4M	4001	1.6	10.3	9.3	138	5.6	99	N
	4002	1.6	10.8	10.7	141	5.6	100	N
	4003	1.9	10.5	9.3	140	5.2	102	N
	4004	1.4	11.0	8.2	140	5.6	100	N
	4105	1.5	10.8	8.6	141	5.6	101	N
	4006	1.5	10.9	9.1	141	6.0	102	N
	4007	1.4	10.7	9.8	140	6.8	100	N
	4008	1.5	10.7	9.6	140	5.9	100	N
	4009	1.8	10.3	9.4	139	5.6	99	N
	4010	1.5	10.6	9.1	141	5.9	102	N

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	123	42	99	2VBRR	726	0.06	16
	1502	150	44	107	2VBRR	1071	0.08	12
	1503	100	35	85	2VBRR	667	0.05	16
	1504	106	31	140	2VBRR	659	0.06	15
	1505	84	26	88	2VBRR	552	0.10	15
	1506	105	31	87	2VBRR	522	0.05	17
	1507	79	28	70	2VBRR	351	0.07	14
	1508	73	30	82	2VBRR	238	0.10	15
	1509	58	27	74	2VBRR	143	0.11	16
	1510	97	35	122	2VBRR	326	0.07	15
2F	2501	71	55	91	2VBRR	110	0.12	22
	2502	120	78	65	2VBRR	106	0.09	14
	2503	107	58	64	2VBRR	714	0.04	19
	2504	133	36	82	2VBRR	906	0.11	19
	2505	70	40	71	2VBRR	225	0.10	17
	2506	184	114	75	2VBRR	574	0.11	17
	2507	103	36	100	2VBRR	715	0.10	17
	2508	118	35	94	2VBRR	865	0.07	15
	2509	71	42	129	2VBRR	193	0.10	12
	2510	72	45	98	2VBRR	162	0.08	16

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	119	83	65	7.0	4.9	2.1
	1502	0.5	113	103	46	6.4	4.7	1.7
	1503	0.4	120	67	105	6.1	4.3	1.8
	1504	0.4	141	67	39	5.8	4.3	1.5
	1505	0.3	162	77	59	6.3	4.4	1.9
	1506	0.5	149	65	32	6.4	4.4	2.0
	1507	0.4	119	79	40	6.3	4.3	2.0
	1508	0.4	122	75	33	6.4	4.9	1.5
	1509	0.4	133	85	43	6.6	5.0	1.6
	1510	0.4	114	64	39	5.8	4.2	1.6
2F	2501	0.4	135	90	54	6.2	4.4	1.8
	2502	0.4	180	78	30	6.6	4.6	2.0
	2503	0.4	128	102	41	6.5	4.4	2.1
	2504	0.4	115	102	41	6.2	4.1	2.1
	2505	0.4	137	72	80	6.7	4.5	2.2
	2506	0.4	113	62	68	6.5	4.5	2.0
	2507	0.4	137	76	39	6.0	4.3	1.7
	2508	0.4	129	84	49	6.3	4.4	1.9
	2509	0.3	184	81	39	5.9	4.1	1.8
	2510	0.4	240	109	53	6.4	4.3	2.1

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1F	1501	2.3	10.6	6.7	141	4.2	102	N
	1502	2.8	10.5	6.8	142	5.0	103	N
	1503	2.4	11.0	7.6	141	4.6	102	N
	1504	2.9	10.6	7.5	142	4.7	103	N
	1505	2.3	11.3	7.2	138	4.6	99	N
	1506	2.2	10.3	6.5	141	4.4	102	N
	1507	2.2	11.3	7.5	141	4.7	101	N
	1508	3.3	11.4	7.6	142	4.9	104	N
	1509	3.1	11.0	7.1	140	4.2	102	N
	1510	2.6	10.9	7.2	144	4.4	104	N
2F	2501	2.4	11.1	6.7	140	4.2	100	N
	2502	2.3	10.9	7.0	141	4.1	103	N
	2503	2.1	11.2	7.6	141	4.6	101	N
	2504	2.0	10.8	7.1	138	5.1	99	N
	2505	2.0	11.6	7.9	140	4.7	101	N
	2506	2.3	11.0	7.1	142	4.4	100	N
	2507	2.5	10.9	7.0	140	4.9	100	N
	2508	2.3	11.1	7.1	142	5.4	101	N
	2509	2.3	10.9	7.4	140	4.6	103	N
	2510	2.0	11.4	7.0	140	4.7	102	N

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	78	49	91	2VBRR	200	0.07	19
	3502	151	117	130	2VBRR	273	0.08	20
	3503	83	35	111	2VBRR	150	0.10	16
	3504	139	88	93	2VBRR	141	0.10	22
	3505	86	58	113	2VBRR	122	0.08	19
	3506	79	45	101	2VBRR	134	0.13	14
	3507	130	32	129	2VBRR	1191	0.09	15
	3508	123	31	94	2VBRR	915	0.11	15
	3509	125	33	100	2VBRR	613	0.13	15
	3510	127	25	133	2VBRR	858	0.09	18
4F	4501	300	73	112	2VBRR	907	0.12	18
	4502	159	49	120	2VBRR	1131	0.10	17
	4503	126	40	136	2VBRR	677	0.13	15
	4504	98	37	132	2VBRR	201	0.11	13
	4505	118	46	179	2VBRR	158	0.11	12
	4506	81	37	110	2VBRR	194	0.08	14
	4507	114	52	124	2VBRR	126	0.14	11
	4508	122	29	121	2VBRR	181	0.08	16
	4509	129	32	120	2VBRR	771	0.16	16
	4510	79	22	110	2VBRR	116	0.12	16

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	133	97	94	6.1	4.2	1.9
	3502	0.5	112	122	53	6.7	4.7	2.0
	3503	0.5	146	93	64	6.2	4.3	1.9
	3504	0.5	150	108	46	6.6	4.4	2.2
	3505	0.4	160	88	49	6.1	4.2	1.9
	3506	0.4	137	79	57	6.3	4.4	1.9
	3507	0.5	125	61	70	5.8	3.9	1.9
	3508	0.4	186	144	113	6.5	4.4	2.1
	3509	0.3	153	69	28	6.1	4.1	2.0
	3510	0.4	147	62	37	5.8	4.0	1.8
4F	4501	0.5	131	82	59	5.4	4.1	1.3
	4502	0.5	145	79	58	6.1	4.3	1.8
	4503	0.4	133	54	43	5.7	4.1	1.6
	4504	0.4	131	59	34	5.7	4.4	1.3
	4505	0.4	127	84	62	5.7	4.0	1.7
	4506	0.4	141	73	33	6.1	4.1	2.0
	4507	0.4	166	90	64	6.5	4.6	1.9
	4508	0.4	138	66	44	5.9	4.1	1.8
	4509	0.5	155	35	48	5.8	4.0	1.8
	4510	0.4	165	71	59	5.8	3.9	1.9

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	2.2	11.0	7.4	140	5.0	101	N
	3502	2.3	10.8	7.8	141	5.0	99	N
	3503	2.3	10.8	7.5	141	4.2	102	N
	3504	2.0	11.0	8.2	141	4.2	99	N
	3505	2.2	11.0	7.9	139	4.3	99	N
	3506	2.3	11.1	7.6	143	4.4	102	N
	3507	2.1	10.3	7.7	141	4.8	100	N
	3508	2.1	11.4	8.1	140	5.1	98	N
	3509	2.0	10.7	6.7	139	4.6	101	N
	3510	2.2	10.8	8.2	141	4.9	102	N
4F	4501	3.2	10.1	6.2	139	4.5	100	N
	4502	2.4	10.5	6.5	139	5.1	98	N
	4503	2.6	10.7	7.8	139	4.5	101	N
	4504	3.4	10.2	7.0	141	4.5	105	N
	4505	2.4	10.7	7.3	140	4.6	100	N
	4506	2.0	10.2	7.1	143	5.0	105	N
	4507	2.4	11.2	8.0	142	4.4	102	N
	4508	2.3	10.5	7.9	142	5.4	106	N
	4509	2.2	10.7	7.9	139	4.6	97	N
	4510	2.1	10.3	7.6	141	4.6	102	N

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Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	98	48	142	2VBRR	745	0.03	15
	1012	111	43	133	2VBRR	821	0.07	18
	1013	106	47	135	2VBRR	648	0.07	18
	1014	81	32	73	2VBRR	282	0.00VBRR	18
	1015	120	45	185	2VBRR	622	0.05	17
4M	4011	128	56	166	2VBRR	1142	0.06	16
	4012	73	40	118	2VBRR	256	0.06	15
	4013	112	53	197	2VBRR	736	0.03	22
	4014	118	45	97	2VBRR	764	0.05	19
	4015	152	44	154	2VBRR	1112	0.05	17

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Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	234	72	90	5.3	3.6	1.7
	1012	0.3	258	68	81	5.5	4.0	1.5
	1013	0.4	223	98	125	5.8	4.0	1.8
	1014	0.4	197	48	72	5.5	3.5	2.0
	1015	0.3	212	71	85	5.6	4.0	1.6
4M	4011	0.4	202	74	77	5.6	3.9	1.7
	4012	0.3	163	63	43	5.4	3.9	1.5
	4013	0.3	239	83	105	5.3	3.7	1.6
	4014	0.3	174	60	68	5.7	4.0	1.7
	4015	0.3	171	67	63	5.7	3.8	1.9

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Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1M	1011	2.1	10.5	6.5	139	4.9	100	N
	1012	2.7	10.6	8.3	139	5.1	101	N
	1013	2.2	11.1	8.1	137	5.0	98	N
	1014	1.8	10.8	8.2	139	5.0	100	N
	1015	2.5	10.9	8.2	139	5.0	101	N
4M	4011	2.3	10.6	7.4	139	5.6	100	N
	4012	2.6	10.5	8.3	140	4.8	103	N
	4013	2.3	10.9	9.4	139	5.2	99	N
	4014	2.4	11.1	8.6	141	6.0	101	N
	4015	2.0	11.0	9.1	141	5.1	99	N

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Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	96	36	89	2VBRR	646	0.00VBRR	16
	1512	62	30	52	2VBRR	140	0.05	13
	1513	73	47	84	2VBRR	302	0.00VBRR	15
	1514	138	53	153	2VBRR	972	0.00VBRR	21
	1515	61	39	87	2VBRR	173	0.06	17
4F	4511	97	41	145	2VBRR	518	0.04	14
	4512	78	56	155	2VBRR	192	0.06	12
	4513	83	42	110	2VBRR	283	0.00VBRR	14
	4514	99	43	91	2VBRR	542	0.03	16
	4515	124	37	98	2VBRR	1012	0.05	16

Appendix 12

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	203	82	58	5.5	3.9	1.6
	1512	0.3	246	76	97	6.3	4.7	1.6
	1513	0.3	234	103	91	6.7	4.7	2.0
	1514	0.4	172	76	64	6.0	4.5	1.5
	1515	0.4	280	101	70	6.7	5.1	1.6
4F	4511	0.4	223	63	78	5.7	4.3	1.4
	4512	0.4	252	69	55	5.9	4.3	1.6
	4513	0.4	206	50	39	5.3	3.9	1.4
	4514	0.4	267	78	62	6.0	4.6	1.4
	4515	0.4	195	63	47	6.4	4.8	1.6

Appendix 12

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	2.4	10.2	5.3	138	4.6	101	N
	1512	2.9	10.9	5.6	139	4.1	102	N
	1513	2.3	11.1	6.7	137	4.2	98	N
	1514	3.0	10.1	5.8	139	5.7	101	N
	1515	3.2	11.0	7.5	135	4.6	97	N
4F	4511	3.1	10.6	7.4	138	4.7	102	N
	4512	2.7	11.0	7.0	137	4.8	100	N
	4513	2.8	10.7	6.1	140	4.2	103	N
	4514	3.3	11.3	7.2	139	4.9	100	N
	4515	3.0	11.1	7.1	137	4.8	100	N

Appendix 13

Ophthalmology Report

Clarification

Following issuance of a new certificate of analysis, the dose levels/dose concentrations used during the study were updated as per table below.

Group No.	Test Material	Dose Level[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)
1	Reference Item	0	200	0
2	mRNA-1706	10 /13	200	0.05 / 0.07
3	mRNA-1706	50 / 65	200	0.25 / 0.33
4	mRNA-1706	100 / 129	200	0.5 / 0.65

[a] Values based on summary of analysis (SoA) issued on 11 Oct 2016 / Values based on SoA issued on 03 May 2017.

Doses were not updated in the ophthalmology report.

Appendix 13

FINAL REPORT

Study Phase: Ophthalmology Evaluation

Test Facility Study No. 5002045

TEST FACILITY:
Charles River Laboratories Montreal ULC
Senneville Site (CR MTL)

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Appendix 13

LIST OF APPENDICES

Appendix 13

1. INTRODUCTION

This report presents the ophthalmology evaluations for the study entitled *ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity Study of mRNA-1706 in Sprague-Dawley Rats with a 2-Week Recovery Period* (Study No. 5002045).

For the work detailed in this report, the ophthalmology phase start date was 10 Oct 2016, and the ophthalmology phase completion date was 16 Nov 2016.

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

- = Not applicable

2.1. Ophthalmic Examinations

Frequency: Examinations were performed once prestudy and again toward the end of Week 4 of the dosing period on main study and recovery study animals.

Procedure: All animals were subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used was 0.126% atropine.

2.2. Computerized Systems

The following critical computerized system was used by the Test Facility in the generation of this report (Text Table 2).

Text Table 2
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	8	Ophthalmic evaluations

Appendix 13

3. RESULTS AND DISCUSSION

(Appendix 1)

3.1. Pretreatment Evaluation

A few minor background findings were recorded; however, all animals were considered appropriate for assignment to the study.

3.2. Week 4 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 for 1 month (3 doses) to 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)

(b) (6)

Date: 03 MAR 2017

Appendix 13

Appendix 1
Individual Ophthalmic Findings

Appendix 13

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	Vac	Vacuole
Hemo	Hemmorhage	Var Rx	Variation from dosing
Hyper	HyperPigmentation	Vasc	Vascularization
Hyperpl	Hyperplasia	V	Visualize
Hypo	HypoPigmentation	Visu	Visualized
OD	Right Eye	OS	Left Eye
OU	Both Eyes		

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

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11	-10	27	28
1	m	1001	Cornea, Op, Multi, Pinpoint	Left	.	.	.	1
		1002	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		1003	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		1005	Lens Op, Cortex, Ant, Focal	Left Supero-Nasal	.	1	.	1
		1006	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
		1008	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	1
		1009	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	1
		1010	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
		1011	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
			Lens,Op ,Nucleus	Right	.	2	.	2
		1012	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		1013	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		1014	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		1015	Lens Op, Cortex, Ant, Focal	Right	.	.	.	1
			Lens Op, Cortex, Ant, Multi	Left	.	.	.	1

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

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

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11	-10	27	28
2	m	2001	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	1
		2002	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		2003	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		2004	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		2006	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		2008	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

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

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11	-10	27	28
3	m	3001	Vitreous, Hemorrhage	Left	.	.	.	2
		3002	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		3004	Lens Op, Cortex, Ant, Multi	Left	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		3005	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		3006	Lens,Op ,Nucleus	Right	.	2	.	2
		3007	Lens Op, Cortex, Ant, Focal	Left Supero-Nasal	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	1
		3008	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		3010	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11	-10	27	28
4	m	4002	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		4003	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		4004	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	.	.	2
		4105	Lens Op, Cortex, Ant, Multi	Right	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
			Lens,Op ,Nucleus	Right	.	1	.	2
		4006	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		4008	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4009	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		4010	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		4011	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		4012	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
			Lens,Op ,Nucleus	Right	.	2	.	2
		4013	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
			Lens,Op ,Nucleus	Left	.	2	.	2
		4014	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		4015	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
			Retina, Fold	Right	.	X	.	X
			Retina, Fold	Left	.	X	.	X

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

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

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11	-10	27	28
1	f	1502	Adnexa,Disch,Chromodacryorrhea	Left	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		1503	Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1504	Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1505	Cornea, Op, Multi, Pinpoint	Right	.	.	2	.
			Lens,Op ,Nucleus	Right	.	.	1	.
		1506	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1507	Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1508	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
			Lens,Op ,Nucleus	Left	2	.	2	.
		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	.
		1511	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		1512	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1513	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
			Lens,Op ,Nucleus	Right	1	.	1	.
			Lens,Op ,Nucleus	Left	1	.	2	.
		1515	Cornea, Op, Multi, Pinpoint	Left	1	.	1	.

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11	-10	27	28
2	f	2501	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	1	.
		2502	Vitreous, Hemorrhage	Left	1	.	.	.
			Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		2503	Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
		2505	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		2506	Lens Op, Cortex, Ant, Focal	Right	.	.	1	.
		2507	Lens Op, Cortex, Ant, Focal	Right	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		2508	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		2509	Vitreous, Hemorrhage	Right	1	.	.	.
			Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		2510	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
			Lens,Op ,Nucleus	Left	1	.	2	.

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

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

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11	-10	27	28
3	f	3501	Cornea, Op, Multi, Pinpoint	Right	.	.	1	.
		3502	Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
			Lens,Op ,Nucleus	Right	2	.	1	.
			Lens,Op ,Nucleus	Left	1	.	1	.
		3503	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		3505	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		3506	Lens Op, Cortex, Ant, Focal	Left Supero-Nasal	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3507	Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
		3508	Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
			Lens,Op ,Nucleus	Right	1	.	1	.
		3510	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 13
Appendix 1

Individual Ophthalmic Findings

5002045

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-11	-10	27	28
4	f	4501	Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	2	.
			Lens,Op ,Nucleus	Right	1	.	.	.
			Lens,Op ,Nucleus	Left	.	.	1	.
		4503	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		4504	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
			Lens,Op ,Nucleus	Right	1	.	1	.
		4505	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	1	.
		4506	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		4507	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
			Lens,Op ,Nucleus	Right	2	.	2	.
		4508	Lens Op, Cortex, Ant, Focal	Left Supero-Temporal	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		4509	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		4511	Cornea, Op, Multi, Pinpoint	Right	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	.	.	1	.

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 100 ug/dose

Appendix 14

NON-GLP FINAL REPORT

Study Phase: Immunology Cytokines

Test Facility Study No. 5002045

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

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Appendix 14

LIST OF TABLES

LIST OF APPENDICES

Appendix 14

1. INTRODUCTION

This report describes the evaluation of Cytokines in rat plasma (EDTA) or serum samples from Study No. 5002045 titled "ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity Study of mRNA-1706 in Sprague-Dawley Rats with a 2-Week Recovery Period".

For the work detailed in this report, the phase experimental start date was 05 Dec 2016, and the phase experimental completion date was 16 Dec 2016.

1.1. Materials and Methods

The methodology and materials used for the analyses were detailed in their respective analytical procedures (only the latest version is appended) listed in the table below:

Analyte	Analytical Procedure(s) no.
IL-1β, IL-6, IP-10, MCP-1, MIP-1α and TNF-α	AP.5002045.Cyt.02

The methods were not validated.

For the IFN-α analysis, a rat anti-IFN-α antibody ELISA kit was used instead of a rat IFN-α antibody kit. IFN-α results are considered invalid.

1.2. Computerized Systems

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

Text Table 1
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Softmax Pro GxP	5.4.6	Data collection and analysis/regression
Bio Plex Manager (Bio-Rad)	Version 6.1	Data collection and analysis/regression
Watson LIMS	7.4.2 SP1	Sample tracking
Microsoft Excel	2007	Descriptive statistics
Microsoft Word	2007	Data reporting
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 4.0.4	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

Appendix 14

2. RESULTS AND DISCUSSIONS

2.1. Standards and Quality Control Samples for Cytokine Panel

Standard, Quality control (QC) preparation and acceptance criteria are described in the latest version of the analytical procedure (Appendix 2). Standard curve and quality control specifications are presented in (Text Table 2).

Text Table 2
Cytokine Standard Curves and Quality Controls Specifications

Cytokine Panel	Range of the Curve (pg/mL)	LLOQ (pg/mL)	ULOQ (pg/mL)	HQC (pg/mL)	MQC (pg/mL)	LQC (pg/mL)
IL-1β	11.7 to 1500	11.7	1500	1200	150	15.6
IL-6	352 to 45000	352	45000	36000	4500	469
IP-10	11.7 to 1500	11.7	1500	1200	150	15.6
MCP-1	141 to 18000	141	18000	14400	1800	188
MIP-1α	11.7 to 1500	11.7	1500	1200	150	15.6
TNF-α	2.93 to 375	2.93	375	300	37.5	7.81

A total of 7 cytokine analysis assays were performed and 71.4% met the method acceptance criteria. All results were reported from the assays that met the acceptance criteria or from assays considered acceptable as for MIP-1α analyzed under assay Cyt-03. This assay was considered acceptable even if the HQC were not within acceptance criteria because all samples results from this assay were below the LLOQ.

2.2. Standards and Quality Control Samples for IFN-α

A rat anti-IFN-α antibody ELISA kit was used instead of a rat IFN-α antibody kit. IFN-α results are considered invalid.

2.3. Cytokines

The study samples were analyzed in duplicate and results are presented in Table 1 and Appendix 3.

IL-1β

Following dosing with the reference item, IL-1β concentrations were observed in 3 out of 5 males and females. A range of concentrations between 35.62 and 1058.29 pg/mL was observed in males and between 29.49 and 179.81 pg/mL in females. IL-1β concentrations in males dosed with mRNA-1706 at 129 µg/dose were within or lower the control group range. Higher concentrations were observed in dosed females due to animal 4511 which showed higher IL-1β concentrations than the control range at almost all time points. These changes were not statistically significant and are not considered test item related.

Appendix 14

IL-6

For all males from the reference item group, at all time points, the IL-6 concentrations observed were below the LLOQ. IL-6 concentrations above the LLOQ were observed in 2 out of 5 females from the control group on Day 15 and 29, 6 hours post-dose and in one female on Day 29, 6 hours post-dose (ranging from 725.91 to 976.55 pg/mL). In the test item group, IL-6 concentrations slightly above the LLOQ were observed in 3 out of 5 males. IL-6 concentrations above the LLOQ were observed in 2 out of 5 females on Day 15, 6 hours post-dose but concentrations were comparable to the control group range. These changes were not statistically significant and are not considered test item related.

TNF-α

TNF-α concentrations in the control groups were all below or similar to the LLOQ. Concentrations close to the LLOQ were observed in dosed females with mRNA-1706 at 129 µg/dose. Statistically significant increases were however observed in dosed males on Day 15, 6 hours post-dose. However, TNF-α concentrations were back to LLOQ level on Day 43. These changes are considered test item related.

IP-10

IP-10 concentrations ranging from 56.59 to 393.28 pg/mL in males and 39.97 to 170.22 pg/mL in female were observed in reference item dosed animals. Higher IP-10 concentrations were observed in all dosed males and females when compared to the control group, with the highest concentrations generally being observed on Day 29, 6 hours post-dose in males and on Day 1, 6 hours post-dose in females.

An increase of around 4.20 to 8.16-fold in males and 11.15 to 14.82-fold in females were observed when compared to the mean IP-10 concentration detected in the control group at the same time point (excluding Day 43). Higher fold increases were observed on Day 29, 6 hours post-dose in both genders.

These changes, considered test item related, were statistically significant when compared to the reference item group concentrations at all time points (except Day 43) in both genders.

IP-10 concentrations were back to the control range on Day 43 in males and females.

Appendix 14

MIP-1α

MIP-1α concentrations in the control groups were all below the LLOQ. In males, concentrations from dosed groups at all time points were below or similar to the LLOQ. However, higher MIP-1α concentrations were detected in all dosed female, generally peaking on Day 29, 6 hours post-dose.

An increase of around 2.59 to 3.53-fold in females were observed when compared to the mean MIP-1α concentration detected in the control group at the same time point (excluding Day 43). Higher fold increases were observed on Day 29, 6 hours post-dose.

In females, the MIP-1α changes observed on Day 15 and Day 29, 6 hours post-dose were statistically significant and are considered test item related.

MIP-1α concentrations were back to the control range on Day 43 in males and females.

MCP-1

MCP-1 concentrations found to be above the LLOQ ranging from 286.37 to 547.74 pg/mL were observed in control males and from 305.82 to 630.19 pg/mL in control females. Higher MCP-1 concentrations were observed following dosing with mRNA-1706 129 µg/dose when compared to the control group.

An increase of around 1.56 to 2.28-fold in males and 2.18 to 3.65-fold in females were observed when compared to the mean MCP-1 concentration detected in the control group at the same time point (excluding Day 43). Higher fold increases were generally observed on Day 29, 6 hours post-dose in both genders.

These changes, considered test item related, were statistically significant when compared to the reference item group concentrations at all time points (except Day 43) in both genders.

MCP-1 concentrations were back to the control range on Day 43 in males and females.

IFN-α

A rat anti-IFN-α antibody ELISA kit was used instead of a rat IFN-α antibody kit. IFN-α results are considered invalid.

Appendix 14

3. CONCLUSION

Increases in IP-10, MIP-1α (in females), MCP-1 and TNF-α (in males) concentrations were observed in animal dosed with mRNA-1706 at 129 µg/dose. Concentrations were generally back to level similar to the control group on Day 43.

IL-1β, IL-6 and concentrations in animals dosed with mRNA-1706 at 129 µg/dose were similar to the control animals.

A rat anti-IFN-α antibody ELISA kit was used instead of a rat IFN-α antibody kit. IFN-α results are considered invalid.

Appendix 14

4. REPORT APPROVAL

(b) (6) Date: 01 Nov 2017

(b) (6)

Appendix 14

Table 1
Summary of Cytokine Analysis Values

Appendix 14
Table 1
Summary of Cytokine Analysis Values

IL-1β (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	245.246	32.566	79.866	69.580
	SD	456.250	21.213	70.292	83.561
	N	5	5	5	5
4	Mean	24.878	15.166	18.994	93.112
	SD	22.716	7.750	10.793	169.691
	N	5	5	5	5
	% Diff (G1)	-90	-53	-76	34

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

Appendix 14
Table 1
Summary of Cytokine Analysis Values

IL-6 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	352.000	352.000	352.000	352.000
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	559.208	542.948	445.858	352.000
	SD	283.960	262.041	209.873	0.000
	N	5	5	5	5
	% Diff (G1)	59	54	27	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 Analysis Values

TNF-α (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	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	4.688	6.146 d	5.168	2.930
	SD	2.500	1.905	2.086	0.000
	N	5	5	5	5
	% Diff (G1)	60	110	76	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 Analysis Values

IP-10 (pg/mL)
Males

Group 1 - Reference Item Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	184.084	106.720	106.406	103.616
	SD	120.252	28.986	38.172	22.654
	N	5	5	5	5
4	Mean	773.962 c	678.824 d	868.406 c	107.576
	SD	113.914	100.619	111.287	58.512
	N	5	5	5	5
	% Diff (G1)	320	536	716	4

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 Analysis Values

MIP-1α (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	11.700	11.700	11.700	11.700
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	17.438	14.526	23.128	11.700
	SD	7.860	6.319	15.678	0.000
	N	5	5	5	5
	% Diff (G1)	49	24	98	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 Analysis Values

MCP-1 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	364.498	454.146	306.984	264.334
	SD	175.111	63.423	155.247	168.931
	N	5	5	5	5
4	Mean	824.392 b	707.672 b	700.854 b	333.966
	SD	191.426	135.799	158.192	138.864
	N	5	5	5	5
	% Diff (G1)	126	56	128	26

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 Analysis Values

IL-1β (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	45.322	21.048	33.642	11.700
	SD	75.181	8.676	49.064	0.000
	N	5	5	5	4
4	Mean	103.214	103.306	45.838	164.376
	SD	164.771	188.198	56.918	285.944
	N	5	5	5	5
	% Diff (G1)	128	391	36	1305

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 Analysis Values

IL-6 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	352.000	587.906	598.342	352.000
	SD	0.000	323.963	229.317	0.000
	N	5	5	5	5
4	Mean	352.000	570.652	352.000	352.000
	SD	0.000	307.739	0.000	0.000
	N	5	5	5	5
	% Diff (G1)	0	-3	-41	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 Analysis Values

TNF-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	2.930	7.234	7.136	4.930
	SD	0.000	3.025	2.620	2.801
	N	5	5	5	5
4	Mean	4.792	8.798	6.818	5.278
	SD	2.614	3.842	2.297	3.408
	N	5	5	5	5
	% Diff (G1)	64	22	-4	7

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 Analysis Values

IP-10 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	Day 15 - 6 h Post Dose	Day 29 - 6 h Post Dose	Day 43
1	Mean	98.670	70.428	64.514	59.596
	SD	43.247	9.828	21.510	12.345
	N	5	5	5	5
4	Mean	1099.716 d	991.920 d	956.216 c	122.616
	SD	253.326	174.097	169.799	83.400
	N	5	5	5	5
	% Diff (G1)	1015	1308	1382	106

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 Analysis Values

MIP-1α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	11.700	11.700	11.700	11.700
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	31.488	30.314 d	41.260 e	11.700
	SD	19.778	12.496	17.506	0.000
	N	5	5	5	5
	% Diff (G1)	169	159	253	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 Analysis Values

MCP-1 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	257.378	484.518	446.772	334.606
	SD	109.552	112.945	111.332	143.086
	N	5	5	5	5
4	Mean	938.538 b	1053.934 d	1125.104 a	307.172
	SD	431.494	399.820	532.615	175.305
	N	5	5	5	5
	% Diff (G1)	265	118	152	-8

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

Appendix 14

Appendix 1
Deviations

Appendix 14

DEVIATIONS

All deviations that occurred during this study phase have been acknowledged by the Study Director, assessed for impact, and documented in the study records. All Study Plan deviations related to this phase and those SOP deviations regarded as significant are listed below.

- A rat interferon alpha antibody ELISA kit was used and rat anti-IFN-alpha antibodies were detected instead of the cytokine IFN-alpha. IFN-alpha results are considered invalid. Results will be maintained in the raw data but will not be reported.

Appendix 14

Appendix 2
AP.5002045.Cyt.02

Appendix 14

ANALYTICAL PROCEDURE

charles river | every step of the way.

Title: MULTIPLEX METHOD FOR THE QUANTITATIVE DETECTION OF IL-1β, IL-6, IP-10, MCP-1, MIP-1 AND TNF-α IN RAT PLASMA	AP Number: AP.5002045.Cyt.02	Effective Date: Date of AP signature
	Page 1 of 6 pages	Supersedes: N/A
Approved by: (b) (6)		Date: 28 NOV 2016
Authorized by: (b) (6)		Date: 28 Nov 2016

1. **PURPOSE**
   To describe a multiplex method for the quantitation of IL-1β, IL-6, IP-10, MCP-1, MIP-1 and TNF-α in rat plasma.
2. **SCOPE**
   This analytical procedure applies to all personnel performing activities related to this method.
3. **RESPONSIBILITY**
   All staff performing this assay are responsible for compliance with this analytical procedure.
4. **REQUIRED FORM**
   Appendix #1: Assay information sheet
   Appendix #2: Standards and QCs cytokine preparation sheet
   Appendix #3: Study sample dilution sheet
   Appendix #4: Beads working solution preparation sheet
   Appendix #5: Rat cytokine assay sheet
5. **MATERIALS/EQUIPMENT/REAGENT**

(b) (4)

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(b) (4)

6. PREPARATION OF ASSAY REAGENTS

(b) (4)

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(b) (4)

7. **ASSAY PROCEDURE:**

(b) (4)

8. **THE BIO-PLEX SUSPENSION ARRAY PROTOCOL**

(b) (4)

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(b) (4)

11. ACCEPTANCE CRITERIA

(b) (4)

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(b) (4)

11.3. Run Acceptance Criteria

(b) (4)

11.4. Sample acceptance criteria and reporting

(b) (4)

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[redacted]

12. VERSION HISTORY

Version	Date	Updates
02	Date of AP signature	Clarification on the repeat of samples with low bead error
01	24 Nov 2016	N/A

Appendix 14

Assay information sheet

Study/reference number: 5002045 Assay ID:_____

Verified by/date: _____

1-Kits information

Kit	lot# to be used
Rat cytokine/chemokine magnetic bead panel kit:	

2-Standards and QC information

2.1 Standard lot to be used:

Rat cytokine standard lot #: _____

2.2 Working range:

Working range	Concentration (pg/mL) IL-1β | IL-6 | IP-10 | MCP-1 | MIP-1α | TNF-α
ULOQ	(b) (4)
LLOQ	

2.3 Standard concentration:

Standards ID	Concentration (pg/mL) IL-1β | IL-6 | IP-10 | MCP-1 | MIP-1α | TNF-α
Standard stock	(b) (4)
STD 11	
STD 10	
STD 9	
STD 8	
STD 7	
STD 6	
STD 5	
STD 4	
STD 3	
STD 2	
STD 1	
STD 0	

2.4 Quality control concentration:

QC ID	Concentration (pg/mL) IL-1β | IL-6 | IP-10 | MCP-1 | MIP-1α | TNF-α
HQC B	(b) (4)
HQC A	
MQC B	
MQC A	
LQC B	
LQC A	

3-Threshold value

The threshold value for a replicate to reach a limit of % CV acceptance criteria from LLOQ (pg/mL)*	Concentration (pg/mL) IL-1β | IL-6 | IP-10 | MCP-1 | MIP-1α | TNF-α
Threshold value:	(b) (4)
% CV acceptance criteria:	

*Fold dilution not taken into account.

4-Additional information or N/A ( )

_____

_____

Reviewed by/date:_____

Appendix #1 (AP.5002045.Cyt.02) 1 of 1

Appendix 14

Standards and QCs cytokine preparation sheet

Study/reference number: 5002045

Assay ID:_____

Verified by/date: _____

Reagent ID:	Lot #	Inventory ID:
Rat cytokine/chemokine standard:		
Assay buffer		

Standard ID	Stock ID	# of vial(s) used	Volume of UPW added to each vial (µL)	Left at ambient RT for at least 5 minutes		Pool vials together (if applicable) Performed (√) ( )
				Start:	End:	
STD stock	Rat cytokine /chemokine standard	(b) (4)				

Standard/ QC ID	Stock ID	Stock concentration (pg/mL)			Stock volume	Assay buffer volume	Preparation performed (√)	Total volume (µL)	Final calculated concentration (pg/mL)		
		IL-1β, IP-10, MIP-1α, TNF-α	IL-6	MCP-1					IL-1β, IP-10, MIP-1α, TNF-α	IL-6	MCP-1
STD 11	STD stock	(b) (4)					( )	(b) (4)			
STD 10	STD 11						( )				
STD 9	STD 10						( )				
STD 8	STD 9						( )				
STD 7	STD 8						( )				
STD 6	STD 7						( )				
STD 5	STD 6						( )				
STD 4	STD 5						( )				
STD 3	STD 4						( )				
STD 2	STD 3						( )				
STD 1	STD 2						( )				
STD 0	N/A						( )				
HQC B	STD 10						( )				
HQC A	STD 8						( )				
MQC B	STD 10						( )				
MQC A	STD 8						( )				
LQC B	STD 5						( )				
LQC A	STD 5						( )				

Pipette(s) ID: _____

Timer ID: _____

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

Appendix #2 (AP.5002045.Cyt.02) 1 of 1

Appendix 14

Study sample dilution sheet

Study/reference number: 5002045 Assay ID:________________

Verified by/date: ____

Reagent:	Lot #:	Inventory ID:
Assay buffer		

Sample ID	Fold Dilution	Stock ID	Stock volume (µL)	Assay buffer volume (µL)	Dilution performed (√)	Total volume (µL)
	(b) (4)		(b) (4)		( )	(b) (4)
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
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					( )	
					( )	

Pipette ID(s): ____

Performed by/date: ______________________ Reviewed by/date: ________________

Appendix #3 (AP.5002045.Cyt.02) 1 of 1

Appendix 14

Study/reference number: 5002045 Beads working solution preparation sheet Assay ID: _____

Verified by/date: _____

Bead vials preparation:				Performed (√)
Sonicate antibody-bead bottles and then vortex thoroughly before the solution preparation				( )
Preparation of: **Antibody-immobilized beads working solution**				
Reagent	lot#:	Inventory ID:	Volume (µL)	Performed (√)
(b) (4)			(b) (4)	( )
				( )
				( )
				( )
				( )
				( )
				( )
		Total volume (µL)		Performed (√)
The antibody-immobilized beads working solution was protected from light until use				( )

Pipette ID(s): _____

Sonic bath ID: _____

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

Appendix #4 (AP.5002045.Cyt.02) 1 of 1

Appendix 14

Rat cytokines assay sheet

Study/reference number: 5002045 Assay ID:_____

Verified by/date: _____

Reagents/solutions/instruments/material used on Day 1		
Name	Lot / batch / ID	Entered by/date
(b) (4)		
	Refer to appendix #4	

Reagents/solutions/instruments/material used on Day 2		
Name	Lot / batch / ID	Entered by/date
(b) (4)		

Comment(s): _____

Reviewed by/date:_____

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Appendix 14

Rat cytokines assay sheet

Study/reference number: 5002045

Pre-loading[a] and loading plate sequence assay ID: ____________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
B	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
C	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
D	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
E	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
F	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
G	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B
H	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B

Pre-loading[a] and loading plate sequence assay ID: ____________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
B	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
C	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
D	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
E	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
F	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
G	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B
H	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B

Pre-loading[a] and loading plate sequence assay ID: ____________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
B	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
C	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
D	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
E	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
F	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
G	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B
H	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B

Pre-loading[a] and loading plate sequence assay ID: ____________________

	1	2	3	4	5	6	7	8	9	10	11	12
A	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
B	STD-0	STD-4	STD-8	LQC A	HQC A							MQC A
C	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
D	STD-1	STD-5	STD-9	LQC B	HQC B							MQC B
E	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
F	STD-2	STD-6	STD-10	MQC A							LQC A	HQC A
G	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B
H	STD-3	STD-7	STD-11	MQC B							LQC B	HQC B

a = Only the shaded rows are used for the pre-loading plate sequence (in singlicate).

Reviewed by/date:____________________

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Appendix 14

Rat cytokines assay sheet

Study/reference number: 5002045

Steps	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Assay ID: Time / Performed (√)	Performed by/date
(b) (4)	( )	( )	( )	( )	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	1st: ( ) 2nd: ( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	( ) or N/A ( )	( ) or N/A ( )	( ) or N/A ( )	( ) or N/A ( )	
	( )	( )	( )	( )	

*Includes standards, QCs and diluted study samples.

Reviewed by/date:_____
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Appendix 14

Rat cytokines assay sheet

Study/reference number: 5002045

Data Review						
Assay acceptance criteria Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of STDs in the curve with a % theoretical within ±25% except for LLOQ and ULOQ which should be within ±30%.	/	/	/	/	/	/
Number of LQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/
Assay acceptance criteria Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of STDs in the curve with a % theoretical within ±25% except for LLOQ and ULOQ which should be within ±30%.	/	/	/	/	/	/
Number of LQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/

*with percent theoretical within 25% and within 25% CV between duplicate. Also, at least one replicate has a acquired bead number≥ 30.

Performed by/date: _____

Scientific Review						
Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
Cytokine assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
At least one replicate has a acquired beads number ≥ 30 and the %CV is within 25% (or both replicates are LLOQ)	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
Cytokine assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
At least one replicate has a acquired beads number	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No

Performed by/date: _____

Reviewed by/date: _____

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Appendix 14

Rat cytokines assay sheet

Study/reference number: 5002045

Data Review						
Assay acceptance criteria Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of STDs in the curve with a % theoretical within ±25% except for LLOQ and ULOQ which should be within ±30%.	/	/	/	/	/	/
Number of LQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/
Assay acceptance criteria Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of STDs in the curve with a % theoretical within ±25% except for LLOQ and ULOQ which should be within ±30%.	/	/	/	/	/	/
Number of LQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Number of MQC meet acceptance criteria*	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/

*with percent theoretical within 25% and within 25% CV between duplicate. Also, at least one replicate has a acquired bead number≥ 30.

Performed by/date: _____

Scientific Review						
Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
Cytokine assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
At least one replicate has a acquired beads number ≥ 30 and the %CV is within 25% (or both replicates are LLOQ)	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Assay ID:	IL-1β N/A ( )	IL-6 N/A ( )	IP-10 N/A ( )	MCP-1 N/A ( )	MIP-1α N/A ( )	TNF-α N/A ( )
Cytokine assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
At least one replicate has a acquired beads number	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No

Performed by/date: _____

Reviewed by/date: _____

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Appendix 14

Appendix 3
Individual Cytokine Analysis Values

Appendix 14

Individual Cytokine Analysis Values Explanation Page

Abbreviation	Description
a	Sample was analyzed twice and %CV between replicates was out of acceptance criteria for both analyses. The overall mean of both analyses was reported
b	No result available due to less than 30 beads acquired in 2 different analysis

Note:

For IL-1β and MIP-1α

Lower Limit of Quantitation (LLOQ) = 23.40 pg/mL, <23.40 was assigned as 23.40/2 (11.70 pg/mL) for statistical analysis purposes

For IL-6

Lower Limit of Quantitation (LLOQ) = 704.00 pg/mL, <704.00 was assigned as 704.00/2 (352.00 pg/mL) for statistical analysis purposes

For TNF-α

Lower Limit of Quantitation (LLOQ) = 5.86 pg/mL, <5.86 was assigned as 5.86/2 (2.93 pg/mL) for statistical analysis purposes

For MCP-1

Lower Limit of Quantitation (LLOQ) = 282.00 pg/mL, <282.00 was assigned as 282.00/2 (141.00 pg/mL) for statistical analysis purposes

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)[a]
1	Reference Item	0
2	mRNA-1706	10/13
3	mRNA-1706	50/65
4	mRNA-1706	100/129

[a] Values based on SoA issued on 11 October 2016 / Values based on SoA issued on 03 May 2017.

Appendix 14
Appendix 3
Individual Cytokine Analysis Values

Males

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1α pg/mL	MCP-1 pg/mL
1	1011	1 - 6 h Post Dose	108.92	<704.00	<5.86	176.18	<23.40	286.37
		15 - 6 h Post Dose	41.15	<704.00	<5.86	100.66	<23.40	345.80
		29 - 6 h Post Dose	106.52	<704.00	<5.86	131.95	<23.40	<282.00
		43	211.39	<704.00	<5.86	140.78	<23.40	<282.00
	1012	1 - 6 h Post Dose	<23.40	<704.00	<5.86	134.67	<23.40	309.64
		15 - 6 h Post Dose	<23.40	<704.00	<5.86	60.93	<23.40	480.14
		29 - 6 h Post Dose	<23.40	<704.00	<5.86	56.59	<23.40	366.21
		43	<23.40	<704.00	<5.86	84.06	<23.40	<282.00
	1013	1 - 6 h Post Dose	<23.40	<704.00	<5.86	112.69	<23.40	547.74
		15 - 6 h Post Dose	<23.40	<704.00	<5.86	125.60	<23.40	469.12
		29 - 6 h Post Dose	<23.40	<704.00	<5.86	75.84	<23.40	460.73
		43	<23.40	<704.00	<5.86	98.53	<23.40	455.07
	1014	1 - 6 h Post Dose	35.62	<704.00	<5.86	103.60	<23.40	537.74
		15 - 6 h Post Dose	61.51	<704.00	<5.86	110.41	<23.40	512.14
		29 - 6 h Post Dose	91.43	<704.00	<5.86	122.50	<23.40	425.98
		43	36.80 a	<704.00	<5.86	87.74	<23.40	443.60

Appendix 14
Appendix 3
Individual Cytokine Analysis Values

Males

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1α pg/mL	MCP-1 pg/mL
1	1015	1 - 6 h Post Dose	1058.29	<704.00	<5.86	393.28	<23.40	<282.00
		15 - 6 h Post Dose	36.77 a	<704.00	<5.86	136.00	<23.40	463.53
		29 - 6 h Post Dose	177.98	<704.00	<5.86	145.15	<23.40	<282.00
		43	76.31	<704.00	<5.86	106.97	<23.40	<282.00

Appendix 14
Appendix 3
Individual Cytokine Analysis Values

Males

Group 4 - mRNA-1706 129 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1α pg/mL	MCP-1 pg/mL
4	4011	1 - 6 h Post Dose	64.16	<704.00	<5.86	714.15	<23.40	625.49
		15 - 6 h Post Dose	29.03	<704.00	7.15	633.48	<23.40	716.54
		29 - 6 h Post Dose	35.72	<704.00	5.97	825.44	<23.40	645.86
		43	396.16	<704.00	<5.86	208.77	<23.40	299.70
	4012	1 - 6 h Post Dose	<23.40	<704.00	<5.86	766.71	<23.40	604.57
		15 - 6 h Post Dose	<23.40	<704.00	<5.86	574.81	<23.40	568.34
		29 - 6 h Post Dose	<23.40	<704.00	<5.86	880.54	<23.40	632.34
		43	<23.40	<704.00	<5.86	87.87	<23.40	317.97
	4013	1 - 6 h Post Dose	<23.40	<704.00	<5.86	899.20	26.33	954.21
		15 - 6 h Post Dose	<23.40	853.89	6.96	738.92	<23.40	746.88
		29 - 6 h Post Dose	<23.40	<704.00	<5.86	1052.46	<23.40	502.04
		43	<23.40	<704.00	<5.86	61.17	<23.40	388.92
	4014	1 - 6 h Post Dose	<23.40	886.15	6.37	620.58	<23.40	961.56
		15 - 6 h Post Dose	<23.40	804.85	7.72	623.39	<23.40	909.14
		29 - 6 h Post Dose	24.15	<704.00	7.05	822.87	41.63	883.32
		43	<23.40	<704.00	<5.86	77.85	<23.40	522.24

Appendix 14
Appendix 3
Individual Cytokine Analysis Values

Males

Group 4 - mRNA-1706 129 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1α pg/mL	MCP-1 pg/mL
4	4015	1 - 6 h Post Dose	25.13	853.89	8.28	869.17	25.76	976.13
		15 - 6 h Post Dose	<23.40	<704.00	5.97	823.52	25.83	597.46
		29 - 6 h Post Dose	<23.40	821.29	6.96	760.72	38.91	840.71
		43	34.30	<704.00	<5.86	102.22	<23.40	<282.00

Appendix 14
Appendix 3
Individual Cytokine Analysis Values

Females

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1α pg/mL	MCP-1 pg/mL
1	1511	1 - 6 h Post Dose	<23.40	<704.00	<5.86	52.73	<23.40	321.37
		15 - 6 h Post Dose	25.06	976.55	10.66	58.90	<23.40	565.34
		29 - 6 h Post Dose	<23.40	725.91	9.02	39.97	<23.40	578.83
		43	<23.40	<704.00	<5.86	57.95	<23.40	403.15
	1512	1 - 6 h Post Dose	<23.40	<704.00	<5.86	92.89	<23.40	377.70
		15 - 6 h Post Dose	29.49	906.98	9.54	81.75	<23.40	630.19
		29 - 6 h Post Dose	<23.40	725.91	9.02	55.50	<23.40	546.89
		43	<23.40	<704.00	8.76	46.34	<23.40	522.99
	1513	1 - 6 h Post Dose	179.81	<704.00	<5.86	170.22	<23.40	305.82
		15 - 6 h Post Dose	27.29	<704.00	6.52	66.22	<23.40	415.34
		29 - 6 h Post Dose	121.41	835.89	8.49	92.03	<23.40	421.31
		43	b	<704.00	<5.86	49.26	<23.40	336.26
	1514	1 - 6 h Post Dose	<23.40	<704.00	<5.86	85.48	<23.40	<282.00
		15 - 6 h Post Dose	<23.40	<704.00	<5.86	65.64	<23.40	350.57
		29 - 6 h Post Dose	<23.40	<704.00	6.22	53.54	<23.40	336.26
		43	<23.40	<704.00	<5.86	73.92	<23.40	<282.00

Appendix 14
Appendix 3
Individual Cytokine Analysis Values

Females

Group 1 - Reference Item

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1α pg/mL	MCP-1 pg/mL
1	1515	1 - 6 h Post Dose	<23.40	<704.00	<5.86	92.03	<23.40	<282.00
		15 - 6 h Post Dose	<23.40	<704.00	6.52	79.63	<23.40	461.15
		29 - 6 h Post Dose	<23.40	<704.00	<5.86	81.53	<23.40	350.57
		43	<23.40	<704.00	7.10	70.51	<23.40	269.63

Appendix 14
Appendix 3
Individual Cytokine Analysis Values

Females

Group 4 - mRNA-1706 129 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1α pg/mL	MCP-1 pg/mL
4	4511	1 - 6 h Post Dose	391.79	<704.00	<5.86	1484.16	41.58	656.92
		15 - 6 h Post Dose	439.13	<704.00	<5.86	1219.96	<23.40	504.31
		29 - 6 h Post Dose	142.97	<704.00	7.40	792.94	23.56	813.91
		43	669.28	<704.00	<5.86	248.91	<23.40	<282.00
	4512	1 - 6 h Post Dose	89.18	<704.00	<5.86	934.09	<23.40	709.33
		15 - 6 h Post Dose	<23.40	798.01	13.03	933.54	32.15	1411.55
		29 - 6 h Post Dose	<23.40	<704.00	8.59	845.16	26.95	749.94
		43	<23.40	<704.00	7.20	38.90	<23.40	396.71
	4513	1 - 6 h Post Dose	<23.40	<704.00	8.40	929.03	57.30	1699.71
		15 - 6 h Post Dose	42.30 a	<704.00	7.40	1064.65	45.89	1150.76
		29 - 6 h Post Dose	51.12	<704.00	6.77	1230.72	67.55	2056.30
		43	117.50	<704.00	<5.86	123.27	<23.40	305.68
	4514	1 - 6 h Post Dose	<23.40	<704.00	6.77	915.69	35.16	846.40
		15 - 6 h Post Dose	<23.40	<704.00	10.05	745.90	26.95	788.84
		29 - 6 h Post Dose	<23.40	<704.00	8.40	978.28	44.44	999.20
		43	<23.40	<704.00	10.40	56.68	<23.40	551.47

Appendix 14
Appendix 3
Individual Cytokine Analysis Values

Females

Group 4 - mRNA-1706 129 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	IL-6 pg/mL	TNF-α pg/mL	IP-10 pg/mL	MIP-1α pg/mL	MCP-1 pg/mL
4	4515	1 - 6 h Post Dose	<23.40	<704.00	<5.86	1235.61	<23.40	780.33
		15 - 6 h Post Dose	<23.40	999.25	10.58	995.55	34.88	1414.21
		29 - 6 h Post Dose	<23.40	<704.00	<5.86	933.98	43.80	1006.17
		43	<23.40	<704.00	<5.86	145.32	<23.40	<282.00

Appendix 15

FINAL REPORT

Study Phase: Molecular Biology – Purity Analysis

Test Facility Study No. 5002045

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

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Appendix 15

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Appendix 15

LIST OF TABLES

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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 phase of sister Study 9800399 entitled "ZIKA mRNA: Mammalian Erythrocyte Micronucleus Test in Rat". The analysis was performed under Study No. 5002045 entitled "A 1-Month (3 Doses) Intramuscular Injection Toxicity Study of mRNA-1706 in Sprague-Dawley Rats with a 2-Week Recovery Period".

The 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. 9800399 which is the same bulk test item and lot as in Study No. 5002045.

For the work detailed in this report, the analytical experimental phase start date was 12 Jan 2017 and the end date was 25 Jan 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.

In the absence of left over vials received from the Sponsor on 07 Oct 2016 and used for Study No. 5002045 dosing, the purity assessment under Study No. 5002045 was done with the bulk test item vials transferred from the sister Study no. 9800399. However, the same material, mRNA-1706 lot MTDP16064, was used in both studies.

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

Appendix 15

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.

4.1.2. Bulk Test Item

Identification:	mRNA-1706 (in lipid nanoparticles)
Physical Description:	White to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP16064
Concentration:	1.7/2.2* mg/mL
Retest Date:	6 months after date of manufacture
Storage Conditions:	Kept in a frerefrigeratorezer set to maintain 4°C
Supplier:	Moderna Therapeutics, Inc.

* Concentration based on summary of analysis (SoA) released on 11 Oct 2016 /Concentration based on SoA released on 03 May 2017.

4.1.3. Characterization of Reference Standard and Bulk Test Item Sample

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

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

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

4.2. Methods

4.2.1. Analytical Procedure

(b) (4)

Appendix 15

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
(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

4.4. Deviations

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

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

5. RESULTS AND CONCLUSION

(b) (4)

The end of use bulk test item analysis demonstrate a purity of (b) (4) which is lower than 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)

Upon investigation, all assay reagents and procedure have been used and followed as expected. According to the documentation available, the sample was received undamaged and in good conditions prior to being stored in a refrigerator set maintain 4°C until analysis. Since the root cause for the low purity cannot be linked to any technical issues, the results are considered accurate and valid for reporting.

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6. REPORT APPROVAL

(b) (6)

Date: 01 Nov 2017

(b) (6)

Appendix 15

Table 1 Samples Purity Results

Peak ID	Replicate ID	Replicate ID	Measured Purity Results (%)			Original Purity Results in CofA (%)
			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.5002045.RNA.01	Effective Date: Signature of AP
	Page 1 of 2 pages	Supersedes Date: N/Ap
Prepared by: (b) (6) (b) (6)		Date: 11 Jan 2017
Reviewed by: (b) (6) (b) (6)		Date: 11 Jan 2017
Approved by: (b) (6) (b) (6)		Date: 11 Jan 2017

(b) (4)

3.0 RESPONSIBILITY

(b) (4)

5.0 MATERIALS

(b) (4)

Appendix 15

AP No: AP.5002045.RNA.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 2 of 2 pages

5.3 Reagents

(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: 5002045 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.5002045.RNA.01)

Appendix 15

(b) (4)

Study/Reference No: 5002045 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.5002045.RNA.01)

Appendix 15

(b) (4)

Study/Reference No: 5002045 Assay I.D.: Pro-xx

Page: 3 of 3

Table 4: (b) (4)

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

Comments: _____

All pages reviewed by / Date: _____

Appendix #1 (AP.5002045.RNA.01)

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Appendix 2

(b) (4)

Appendix 15

charles river

ANALYTICAL PROCEDURE

TITLE: (b) (4)	AP No: AP.5002045.RQF.02	Effective Date: Signature of AP
	Page 1 of 5 pages	Supersedes Date: 12-Jan-2017
Prepared by: (b) (6) (b) (6)		Date: 13 Feb 2017
Reviewed by: (b) (6) (b) (6)		Date: 14 Feb 2017
Approved by: (b) (6) (b) (6)		Date: 14 Feb 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)

Appendix 15

AP No: AP.5002045.RQF.02	Effective date: Signature of AP	Supersedes: 12-Jan-2017	Page 2 of 5 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.5002045.RQF.02	Effective date: Signature of AP	Supersedes: 12-Jan-2017	Page 3 of 5 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.5002045.RQF.02	Effective date: Signature of AP	Supersedes: 12-Jan-2017	Page 4 of 5 pages

8.2 (b) (4)

8.3

8.4 (b) (4)

Appendix 15

AP No: AP.5002045.RQF.02	Effective date: Signature of AP	Supersedes: 12-Jan-2017	Page 5 of 5 pages

9.0 REVISION HISTORY

Version	Date	Reason for revision
02	Signature of AP	Section 6.4.1: Updated to clarify that the aliquots will be prepared if required. Section 7.0: New note added to clarify the purpose of Standard Sensitivity RNA Ladder requirements. Section 8.4: To clarify that the reference standard control is loaded in duplicate and to clarify that purity is calculated based on percentage area represented by 3 peak areas (pre, main and post peak). Section 8.4.1 and 8.4.3: To clarify that the acceptance criteria applies to the main peak percentage areas as described in the MVS. None of the above mentioned clarifications affected the assays performed under study 5001952, since the assays were conducted as described in the additional comments.
01	12-Jan-2017	New AP

Appendix 15

(b) (4)

Study/Reference No: 5002045 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.5002045.RQF.02)

Appendix 15

(b) (4)

Study/Reference No: 5002045 Assay I.D.: Pro-xx

Page: 2 of 6

Preparation of: (b) (4)

Batch / Lot #

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

Performed by / Date:

Preparation of: (b) (4)

Batch / Lot #

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

Performed by / Date:

Preparation of: (b) (4)

Batch / Lot #

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

Performed by / Date:

Comments: _____

Appendix #1 (AP.5002045.RQF.02)

Appendix 15

(b) (4)

Study/Reference No: 5002045 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.5002045.RQF.02)

Appendix 15

(b) (4)

Study/Reference No: 5002045 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.5002045.RQF.02)

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(b) (4)

Study/Reference No: 5002045 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.5002045.RQF.02)

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(b) (4)

Study/Reference No: 5002045 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.5002045.RQF.02)

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 #2: (AP.5002045.RQF.02) Page 01 of 01

Appendix 15

Appendix 3
Certificates of Analysis

Appendix 15

Eurofins Advantar Laboratories, Inc.
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Summary of Analysis ***DATE: 11 October 2016***

Part 1 Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0001.00 (CPR12213)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button

ASSAY (TEST METHOD)	TARGET RANGE	TEST DATE	RESULTS
RNA Content (mg/mL) (MRA-C0000-GTM0011.00)	(b) (4)	10/07/2016	(b) (4)
Bacterial Endotoxins (USP<85>)		08/30/2016	
Bioburden (USP<61>)		09/06/2016	

The data generated at Eurofins Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Eurofins Advantar has archived the raw data.

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

Oct. 11, 2016
Date

Appendix 15

Eurofins Advantar Laboratories, Inc.
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San Diego, CA 92121
Phone: (858) 228-7788

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Summary of Analysis ***DATE: 30 November 2016***

Part 2, Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0002.00 (CPR12558)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion	
Time point: Time Zero **Storage Condition:** 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button	
ASSAY (TEST METHOD)	**TARGET RANGE**	**TEST DATE**	**RESULTS**
Appearance (MRA-C0000-GTM0016.00)	White to off-white dispersion, no visible particulates	09/23/2016	Conforms (CPR12206 Page 7)
Identification (MRA-C0000-GTM0019.00)	Matches migration rate of standard	09/19/2016	Conforms (CPR12207 Page 12)
Purity (MRA-C0000-GTM0019.00)	(b) (4)	09/19/2016	(b) (4)
Related Impurities (MRA-C0000-GTM0019.00)	Report % Pre-main peak and % Post main peak areas	09/19/2016	
Encapsulated %RNA (MRA-C0000-GTM0014.00)	(b) (4)	10/06/2016	
Mean Particle Size (nm) (MRA-C0000-GTM0015.01)	Report result	09/28/2016	
Polydispersity (MRA-C0000-GTM0015.01)	(b) (4)	09/28/2016	
Lipid Identification (b) (4)		10/14/2016	
Cholesterol	Matches retention time of standard		Matches retention time of standard
DSPC	Matches retention time of standard		Matches retention time of standard
PEG2000-DMG	Matches retention time of standard		Matches retention time of standard
(UHPLC-CAD)	Matches retention time of standard		Matches retention time of standard
			(CPR12206 ADR B1)
Lipid Content (mg/mL) (b) (4)	Lipid (mg/mL) (b) (4)	10/14/2016	(b) (4)
Cholesterol			
DSPC			
PEG2000-DMG			
(UHPLC-CAD)			

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Summary of Analysis ***DATE: 30 November 2016***

Part 2, Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0002.00 (CPR12558)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button

ASSAY (TEST METHOD)	TARGET RANGE	TEST DATE	RESULTS
Lipid Process and Degradation Impurities	Report total % Area and RRT	10/14/2016	(b) (4)
pH (MRA-C0000-GTM0017.00)	Report result	09/23/2016	
Osmolality (mOsm/kg) (USP <785>)	Report result	09/23/2016	
Particulate matter (USP<788> Method 2)	(b) (4)	08/29/2016	
Residual solvents from formulation: Ethanol (MRA-C0000-GTM0018.01) (USP <467>)		09/16/2016	

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Summary of Analysis ***DATE: 30 November 2016***

Part 2, Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.00 **Document Number:** MRA-C0019-RTR0002.00 (CPR12558)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion	
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button	
ASSAY (TEST METHOD)	**TARGET RANGE**	**TEST DATE**	**RESULTS**
Elemental Impurities (ICP-OES)	Report Results	09/16/2016	(b) (4)

[1] Lyso-PEG-01 & RRT 0.390/0.395 co-elute, peak skimming/splitting was used to integrate.

The data generated at Eurofins Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Eurofins Advantar has archived the raw data.

(b) (6) _____

Nov. 30, 2016
Date

Appendix 15

Eurofins Advantar Laboratories, Inc.
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San Diego, CA 92121
Phone: (858) 228-7788

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[1]Revised Summary of Analysis *DATE: 3 May 2017*

Part 1 Release Testing of mRNA-1706 LNP Lot MTDP16064

Protocol Number: MRA-C0019-RTP0001.01 **Document Number:** MRA-C0019-RTR0001.01 (CPR15236)	**Date Received at Eurofins Advantar:** August 29, 2016	**Product Description:** 0.5 mL of 2 mg/mL mRNA-1706 in a white to off-white lipid nanoparticle dispersion
Time point: Time Zero **Storage Condition**: 5°C	**Product Lot #:** MTDP16064	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-SZ-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Red Button

ASSAY (TEST METHOD)	TARGET RANGE	TEST DATE	RESULTS
RNA Content (mg/mL) (MRA-C0000-GTM0011.00)	(b) (4)	10/07/2016	(b) (4)
Bacterial Endotoxins (USP<85>)		08/30/2016	
Bioburden (USP<61>)		09/06/2016	

(b) (4)

The data generated at Eurofins Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Eurofins Advantar has archived the raw data.

(b) (6)

03MAY2017
Date

Appendix 15

moderna
messenger therapeutics

200 Technology Square • Cambridge, MA 02139
Phone 617.714.6500 • Fax 617.583.1998

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

Si (b) (6)
Generated by: (b) (6)
29 APR 2016
Date:
(b) (6)
Reviewed by: (b) (6)
29 APR 2016
Date:

Appendix 15

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messenger therapeutics

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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
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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moderna
messenger therapeutics

200 Technology Square • Cambridge, MA 02139
Phone 617.714.6500 • Fax 617.583.1998

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	(b) (4)	CPR10319 p15 CPR10318 p16 CPR10319 p27 CPR10320 p11
Cap content	LCMS (MRA-C0000-GTM0002.01)	(b) (4)	(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) — Date: 25 Apr 17

(b) (6)
Reviewed by: (b) (6) — Date: 25 APR 2017

Appendix 16

Study Phase: Serology ELISA to detect Anti-Therapeutic Antibody (ATA)

Test Site Reference No. BS-3037
Test Facility Study No. 5002045

A 1-Month Study (3 doses) of mRNA-1706 by Intramuscular Injection in 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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1. RESPONSIBLE PERSONNEL

Principal Investigator (b) (6)

2. INTRODUCTION

This report describes the detection of anti-ZIKV antibodies in vaccinated Sprague-Dawley rat sera from Charles River Study No. 5002045, entitled "A 1-Month Study (3 doses) of mRNA-1706 by Intramuscular Injection in 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 220 serum samples (100 samples from Day 1, 78 samples from Day 30, and 20 samples from Day 43; 20 separate pre-bleed samples labeled as "SP", and Day 30 samples for reference animals 1104 and 4105) were received at Integrated BioTherapeutics, Inc. (IBT) from Charles River Laboratories on December 13, 2016.

This study phase was not within the scope of regulations governing the conduct of nonclinical laboratory studies and was not intended to comply with such regulations. However, this non GLP study phase was conducted in accordance with the Standard Operating Procedures of Integrated Biotherapeutics, Inc.

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3. EXPERIMENTAL DESIGN

Table 1: Study Design

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

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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:	01AUG2017
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:	7,190 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 5002045)
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:	01AUG2017
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)

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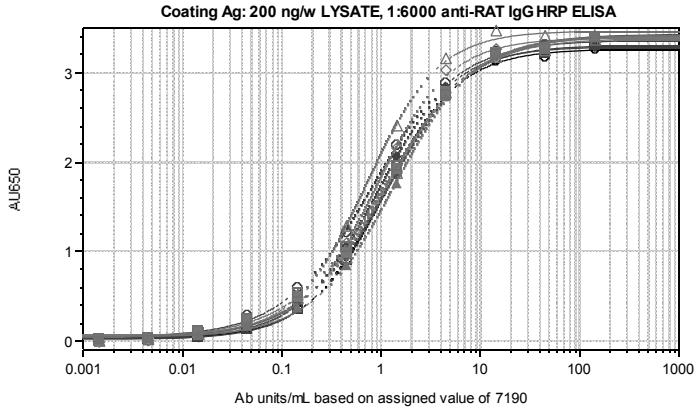
5. RESULTS AND DISCUSSIONS

5.1. Standard

The standard is a well-characterized anti-ZIKV pooled rat serum whose titer (Antibody Units/mL) and has been assigned 7,190 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)	0.0412	0.988	0.789	3.36	0.999
Plot#11 (ZIKA Std 11: Concentration vs MeanVal...	0.0389	1.19	0.707	3.47	0.999
Plot#12 (ZIKA Std 12: Concentration vs MeanVal...	0.014	1.15	0.86	3.39	1
Plot#9 (ZIKA Std 9: Concentration vs MeanValue)	0.0285	1.13	1.07	3.26	1
Plot#10 (ZIKA Std 10: Concentration vs MeanVal...	0.0172	1.12	1.07	3.31	1
Plot#8 (ZIKA Std 8: Concentration vs MeanValue)	0.0265	1.11	0.909	3.29	1
Plot#3 (ZIKA Std 3: Concentration vs MeanValue)	0.0432	1.02	1.14	3.38	0.999
Plot#4 (ZIKA Std 4: Concentration vs MeanValue)	0.0434	0.987	1.14	3.42	0.999
Plot#5 (ZIKA Std 5: Concentration vs MeanValue)	0.0388	0.98	1.19	3.43	0.999
Plot#6 (ZIKA Std 6: Concentration vs MeanValue)	0.0457	1	1.11	3.41	0.999
Plot#7 (ZIKA Std 7: Concentration vs MeanValue)	0.0433	1.07	1.34	3.42	0.999
Plot#2 (ZIKA Std 2: Concentration vs MeanValue)	0.0373	0.939	1.06	3.42	0.999

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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

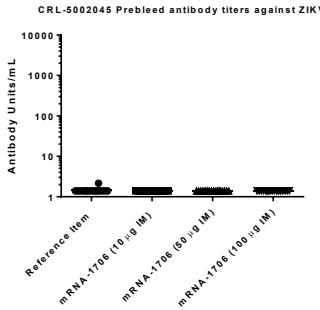
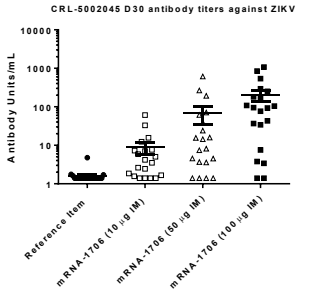
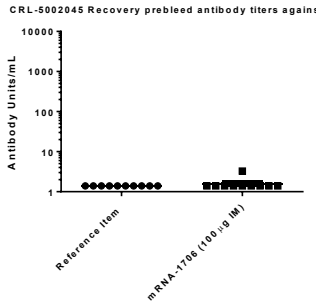
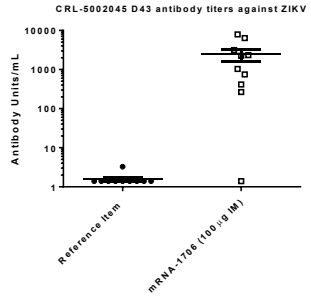
Main Study		Recovery Study	
Day 1	Day 30	Day 1	Day 43
			

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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	Mean Values Day 1	Day 30	Mean Values Day 30	Animal ID	Day 1	Mean Values Day 1	Day 30	Mean Values Day 30	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43
1	Reference Item	0	200	0	1001	1.4	1.476	1.4	1.758	1501	1.4	1.400	1.4	1.466	1011	1.4	1.400	1.4	1.400	1511	1.4	1.400	1.4	1.400
					1002	1.4		1.4		1502	1.4		1.4		1012	1.4		1.4		1512	1.4		1.4	
					1003	2.16		4.76		1503	1.4		1.4		1013	1.4		1.4		1513	1.4		1.4	
					1104	1.4		1.4		1504	1.4		1.4		1014	1.4		1.4		1514	1.4		1.4	
					1005	1.4		1.4		1505	1.4		1.4		1015	1.4		1.4		1515	1.4		1.4	
					1006	1.4		1.4		1506	1.4		1.7											
					1007	1.4		1.62		1507	1.4		1.4											
					1008	1.4		1.4		1508	1.4		1.76											
					1009	1.4		1.4		1509	1.4		1.4											
					1010	1.4		1.4		1510	1.4		1.4											

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animal ID	Day 1	Mean Values Day 1	Day 30	Mean Values Day 30	Animal ID	Day 1	Mean Values Day 1	Day 30	Mean Values Day 30
2	mRNA-1706	10	200	0.05	2001	1.4	1.400	1.4	3.938	2501	1.4	1.400	1.4	13.88
					2002	1.4		2.62		2502	1.4		15.7	
					2003	1.4		1.86		2503	1.4		32.99	
					2004	1.4		1.57		2504	1.4		7.04	
					2005	1.4		4.17		2505	1.4		3.51	
					2006	1.4		5.02		2506	1.4		7.25	
					2007	1.4		1.4		2507	1.4		5.85	
					2008	1.4		1.4		2508	1.4		2.44	
					2009	1.4		7.63		2509	1.4		60.92	
					2010	1.4		12.31		2510	1.4		1.66	

Note: Values below the level of quantitation were assigned a value of 1.4 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	Mean Values Day 1	Day 30	Mean Values Day 30	Animal ID	Day 1	Mean Values Day 1	Day 30	Mean Values Day 30
3	mRNA-1706	50	200	0.25	3001	1.4	1.400	3.58	10.55	3501	1.4	1.400	15.52	124.9
					3002	1.4		4.54		3502	1.4		266.57	
					3003	1.4		15.96		3503	1.4		8.19	
					3004	1.4		4.51		3504	1.4		70.95	
					3005	1.4		61.55		3505	1.4		616.26	
					3006	1.4		7.46		3506	1.4		1.4	
					3007	1.4		1.4		3507	1.4		192.31	
					3008	1.4		1.4		3508	1.4		14.35	
					3009	1.4		3.67		3509	1.4		24.01	
					3010	1.4		1.4		3510	1.4		39.01	

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animal ID	Day 1	Mean Values Day 1	Day 30	Mean Values Day 30	Animal ID	Day 1	Mean Values Day 1	Day 30	Mean Values Day 30	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43	Animal ID	Day 1	Mean Values Day 1	Day 43	Mean Values Day 43
4	mRNA-1706	100	200	0.5	4001	1.4	1.400	104.2	80.476	4501	1.4	1.400	251.91	316.8	4011	1.4	1.400	3158	1330	4511	1.4	1.774	1034.1	3574
					4002	1.4		76.57		4502	1.4		1.4		4012	1.4		2327		4512	1.4		6388.7	
					4003	1.4		7.57		4503	1.4		34.12		4013	1.4		1.4		4513	1.4		7938.8	
					4004	1.4		93.01		4504	1.4		537.95		4014	1.4		750		4514	1.4		265.19	
					4105	1.4		3.4		4505	1.4		108.53		4015	1.4		414.5		4515	3.27		2245.5	
					4006	1.4		1.4		4506	1.4		846.46											
					4007	1.4		177.2		4507	1.4		95.34											
					4008	1.4		43.13		4508	1.4		1073.3											
					4009	1.4		3.79		4509	1.4		36.78											
					4010	1.4		294.5		4510	1.4		181.92											

Note: Values below the level of quantitation were assigned a value of 1.4 AU/mL for plotting purposes

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Table 8: Antibody Titers (Antibody Units/mL) against ZIKV lysate for SP

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animal ID	Day 1	Mean Values Day 1		Animal ID	Day 1	Mean Values Day 1
SP					103	1.4	1.400		57	1.4	1.400
					107	1.4			62	1.4	
					108	1.4			72	1.4	
					18	1.4			84	1.4	
					38	1.4			87	1.4	
					41	1.4			88	1.4	
					45	1.4			93	1.4	
					47	1.4			96	1.4	
					52	1.4			1004	1.4	
					55	1.4			4005	1.4	

Note: Values below the level of quantitation were assigned a value of 1.4 AU/mL for plotting purposes

Appendix 16

6. CONCLUSION

A total of 220 rat serum samples was successfully tested to detect anti-ZIKV antibodies against ZIKV virus lysate.

7. REPORT APPROVAL

(b) (6) Date: June 26, 2017

Integrated BioTherapeutics, Inc.

8. REFERENCES:

N/A

Appendix 17

Pathology Report

Clarification

Following issuance of a new certificate of analysis, the dose levels/dose concentrations used during the study were updated as per table below.

Group No.	Test Material	Dose Level[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)
1	Reference Item	0	200	0
2	mRNA-1706	10 /13	200	0.05 / 0.07
3	mRNA-1706	50 / 65	200	0.25 / 0.33
4	mRNA-1706	100 / 129	200	0.5 / 0.65

[a] Values based on summary of analysis (SoA) issued on 11 Oct 2016 / Values based on SoA issued on 03 May 2017.

Doses were not updated in the pathology report and in the related tables and appendices.

Appendix 17

FINAL REPORT

Study Phase: Pathology

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 doses) Intramuscular Injection Toxicity Study of mRNA-1706 in Sprague-Dawley Rats with a 2-Week Recovery Period

TEST SITE:
Charles River Laboratories, Inc.
15 Worman's Mill Court, Suite I
Frederick, MD 21701
United States

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

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QUALITY ASSURANCE STATEMENT

Study Number: 5002045

This phase has been audited by Quality Assurance in accordance with the applicable Good Laboratory Practice regulations. Reports were submitted in accordance with standard operating procedures as follows:

QA INSPECTION DATES

		Dates Findings Submitted to:			
Date(s) of Audit	Phase(s) Audited	Principal Investigator	Principal Investigator Management	Study Director	Study Director Management
20-Jan-2017 23-Jan-2017	Draft Phase Report - Pathology	23-Jan-2017	23-Jan-2017	23-Jan-2017	23-Jan-2017

Process-based inspections relevant to this study were conducted according to a predetermined schedule. The outcome of each inspection was reported to Management and, where relevant for processes seen as part of a study, the Study Director.

Facilities relevant to this study are included in Charles River's annual facility inspection programme. The outcome of each inspection is reported to Management.

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

(b) (6)

(b) (6)

09 Mar 2017

Date

Appendix 17

COMPLIANCE STATEMENT AND REPORT APPROVAL

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

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

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

(b) (6)

(b) (6) Date: 09 MAR 2017

Appendix 17

1. SUMMARY

Intramuscular administration of mRNA-1706 to Sprague-Dawley rats did not result in any early deaths or organ weight changes and was well tolerated systemically. Test article-related changes were restricted to the injection site and regional lymph nodes, the spleen, and the liver and these changes were reversed by the end of the recovery period.

At the end of the administration period (Day 30), test article-related swelling and a firm consistency were noted grossly at the injection site, and regional (inguinal, popliteal and iliac) lymph nodes showed test article-related enlargement. Microscopically this correlated with minimal to moderate inflammation at the injection site in all animals administered the test article, and with minimal to mild mixed cell infiltration in and around the popliteal and inguinal lymph nodes, at ≥ 10 µg/dose. Minimal to mild depletion of lymphocytes in the periarteriolar sheath was also present in spleen of both male and female rats administered mRNA-1706; this change showed a dose-related trend, and was present at all doses. In the liver of male animals, the incidence of minimal hepatocytic vacuolation showed a dose-related trend, but females administered mRNA-1706 were no more likely to show this change than their contemporary controls.

At the end of the recovery period (Day 43), the changes in the liver and spleen, and the inflammatory changes associated with the injection site and regional lymph nodes were resolved. Although enlarged regional lymph nodes were recorded grossly in occasional males that had previously been administered mRNA-1706, no microscopic correlate was found.

2. RESPONSIBLE PERSONNEL

Principal Investigator, Pathology	(b) (6) Charles River Laboratories, Inc. Frederick, Maryland
Test Site Management	(b) (6) Charles River Laboratories, Inc. Frederick, Maryland

3. INTRODUCTION

This report presents the pathology findings in Sprague-Dawley rats assigned to Study No. 5002045. The objective of this study was 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, MA. (b) (6), served as the Study Director.

4. MATERIALS AND METHODS

Experimental procedures applicable to pathology investigations are summarized in Text Table 1. Deviations to the pathology procedures performed by the Test Site are listed in Appendix 1.

Appendix 17

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

All animals were submitted for necropsy on Day 30 (Terminal Euthanasia) or Day 43 (Recovery Euthanasia). Necropsies were performed and organ weights were collected by Charles River Laboratories Montreal ULC personnel. Statistical analysis of organ weight data was performed by the Test Facility. Tissues required for microscopic evaluation were trimmed, processed routinely, embedded in paraffin, and stained with hematoxylin and eosin by Charles River Laboratories Montreal ULC. Microscopic evaluation was conducted by the Principal Investigator, a board-certified veterinary pathologist on all protocol-specified tissues from all Terminal Euthanasia animals in Groups 1 and 4 and all gross lesions from all animals. Additionally, target tissues identified by the pathologist [site, injection; lymph node, inguinal; lymph node, popliteal; liver; spleen] were evaluated in all Group 2 and 3 terminal euthanasia animals and full tissue from all recovery euthanasia animals in Groups 1 and 4. Tissues were evaluated by light microscopy.

4.1. Computerized Systems

Critical computerized systems used in the study by the Test Site are listed in Text Table 2.

Text Table 2
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	8	Histopathology

4.2. Disposition of Study Materials

All study-specific raw data, pathology materials, documentation and Final Report generated from this study phase are to be sent to the Test Facility for archiving. Study materials will be retained for a period of 1 year following issue of the audited Draft Report. Electronic Provantis data generated by the Test Site will be archived, and the software and hardware required to produce it in a readable form will be maintained and available. The electronic data will be archived in Charles River Laboratories, Inc., Wilmington, MA.

Appendix 17

5. RESULTS AND DISCUSSIONS

5.1. Mortality

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

5.2. Gross Pathology

5.2.1. Terminal Euthanasia Animals (Day 30)

(Table 1 and Appendix 8)

Test article-related gross pathology findings were restricted to the injection site [firm consistency, swelling] and to the inguinal, popliteal, and iliac lymph nodes [enlargement], and are summarized in Text Table 3.

Text Table 3
Summary of Gross Pathology Findings – Terminal 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, injection (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency, firm	0	10	10	10	0	10	10	10
Swelling	0	4	7	7	0	6	8	9
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	2	5	6	0	1	1	4
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	8	7	0	4	5	4
Lymph node[a] (No. Examined)	0	1	7	4	0	2	4	6
Enlargement	0	1	7	4	0	2	4	6

[a]The tissue, Lymph node, included iliac and mediastinal lymph nodes at collection. Here, only iliac lymph nodes are presented.

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

5.2.2. Recovery Euthanasia Animals (Day 43)

(Table 2 and Appendix 8)

Test article-related enlargement of the regional lymph nodes noted at the terminal euthanasia was still observed, but at a lower incidence, in males at the end of the recovery period (Day 43) and is

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summarized in Text Table 4, however no microscopic correlate was noted at this time point. Injection sites were grossly unremarkable at the end of the recovery period.

Text Table 4
Summary of Gross Pathology Findings – Recovery Euthanasia (Day 43)

	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	**5**	**-**	**-**	**5**	**5**	**-**	**-**	**5**
Lymph node, inguinal (No. Examined)	5	-	-	5	5	-	-	5
Enlargement	0	-	-	2	0	-	-	0
Lymph node, popliteal (No. Examined)	5	-	-	5	5	-	-	5
Enlargement	0	-	-	2	0	-	-	0

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

5.3. Organ Weights

5.3.1. Terminal Euthanasia Animals (Day 30)

(Table 3, Table 4, Table 5, Appendix 2, Appendix 3, and Appendix 4)

No test article-related organ weight changes were noted. There were isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, the organ weight differences observed were considered incidental and/or related to difference of sexual maturity and unrelated to administration of mRNA-1706.

5.3.2. Recovery Euthanasia Animals (Day 43)

(Table 6, Table 7, Table 8, Appendix 5, Appendix 6, and Appendix 7)

No test article-related organ weight changes were noted. There were isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, the organ weight differences observed were considered incidental and/or related to difference of sexual maturity and unrelated to administration of mRNA-1706.

5.4. Histopathology

5.4.1. Terminal Euthanasia (Day 30)

(Table 9 and Appendix 8)

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Test article-related microscopic findings were noted in the liver of male animals, and in both sexes in the spleen, the injection site, and in tissues surrounding lymph nodes regional to the injection site, and are summarized in Text Table 5.

Text Table 5
Summary of Microscopic Findings – Terminal 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
Liver (No. Examined)	10	10	10	10	10	10	10	10
Vacuolation	(1)[a]	(3)	(4)	(5)	(7)	(8)	(8)	(5)
Minimal	1	3	4	5	7	8	8	5
Spleen (No. Examined)	10	10	10	10	10	10	10	10
Decreased cellularity; lymphoid, periarteriolar lymphoid sheath	(0)	(4)	(7)	(10)	(0)	(5)	(9)	(10)
Minimal	0	4	7	7	0	5	9	5
Mild	0	0	0	3	0	0	0	5
Site, injection (No. Examined)	10	10	10	10	10	10	10	10
Inflammation	(0)	(10)	(10)	(10)	(0)	(10)	(10)	(10)
Minimal	0	0	0	0	0	1	0	0
Mild	0	0	0	0	0	6	2	4
Moderate	0	10	10	10	0	3	8	6
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Infiltration, mixed cell	(0)	(0)	(0)	(2)	(0)	(0)	(1)	(3)
Minimal	0	0	0	1	0	0	0	0
Mild	0	0	0	1	0	0	1	3
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Infiltration, mixed cell	(0)	(6)	(7)	(8)	(0)	(9)	(10)	(9)
Minimal	0	0	2	6	0	7	4	2
Mild	0	6	5	2	0	2	6	7

[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 Sprague-Dawley rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

5.4.2. Recovery Euthanasia (Day 43)

(Table 10 and Appendix 8)

Findings noted at the terminal euthanasia were not observed at the end of the recovery period (Day 43). Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of Sprague-Dawley rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered unrelated to administration of mRNA-1706.

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6. CONCLUSIONS

Intramuscular administration of mRNA-1706 to Sprague-Dawley rats did not result in any early deaths or organ weight changes and was well tolerated systemically. Test article-related changes were restricted to the injection site and regional lymph nodes, the spleen, and the liver and these changes were reversed by the end of the recovery period.

At the end of the administration period (Day 30), test article-related swelling and a firm consistency were noted grossly at the injection site, and regional (inguinal, popliteal and iliac) lymph nodes showed test article-related enlargement. Microscopically this correlated with minimal to moderate inflammation at the injection site in all animals administered the test article, and with minimal to mild mixed cell infiltration in and around the popliteal and inguinal lymph nodes, at ≥ 10 μg/dose. Minimal to mild depletion of lymphocytes in the periarteriolar sheath was also present in spleen of both male and female rats administered mRNA-1706; this change showed a dose-related trend, and was present at all doses. In the liver of male animals, the incidence of minimal hepatocytic vacuolation showed a dose-related trend, but females administered mRNA-1706 were no more likely to show this change than their contemporary controls.

At the end of the recovery period (Day 43), the changes in the liver and spleen, and the inflammatory changes associated with the injection site and regional lymph nodes were resolved. Although enlarged regional lymph nodes were recorded grossly in occasional males that had previously been administered mRNA-1706, no microscopic correlate was found.

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Table 1
Summary of Gross Pathology Findings (Day 30)

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5002045 - Intergroup Comparison of Gross Pathology Findings

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 MARROW SMEAR								
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	10	10	.	.	.	.
ESOPHAGUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	9	10	10	10	10
Nodule	0	0	0	1	0	0	0	0
EYE								
Submitted	10	10	10	10	10	10	10	10

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5002045 - Intergroup Comparison of Gross Pathology Findings

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
EYE (Continued...)								
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
GLAND, ADRENAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, HARDERIAN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, MAMMARY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PARATHYROID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PITUITARY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PROSTATE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	9	.	.	.	.
Small	0	0	0	1	.	.	.	.
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	9	10	10	9	9	10	10	9

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5002045 - Intergroup Comparison of Gross Pathology Findings

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, THYROID (Continued...)								
Small	1	0	0	1	1	0	0	0
Focus; dark	0	0	0	0	0	0	0	1
HEART								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
KIDNEY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	10	10	9	10	10	9	9
Dilatation; pelvis	1	0	0	1	0	0	0	0
Discoloration; pale	0	0	0	0	0	0	1	1
LARGE INTESTINE, CECUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, COLON								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, RECTUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	8	10	10	10	10
Parasite	0	0	0	2	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	8	7	7	6	8	5	8	5
Focus; pale	1	3	3	4	2	5	2	5
Focus; raised	1	0	0	0	0	0	0	0
Small	1	0	0	0	0	0	0	0
Mass	0	0	0	0	0	1	0	0
LUNG								
Submitted	10	10	10	10	10	10	10	10

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5002045 - Intergroup Comparison of Gross Pathology Findings

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
LUNG (Continued...)								
No Visible Lesions	7	9	8	6	9	10	9	10
Focus; dark	3	1	2	4	1	0	1	0
LYMPH NODE								
Submitted	0	1	7	4	0	3	4	7
Enlargement	.	1	7	4	.	2	4	7
Focus; dark	.	0	0	1	.	1	0	0
LYMPH NODE, INGUINAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	7	5	4	10	9	9	6
Enlargement	0	2	5	6	0	1	1	4
Focus; dark	0	1	0	0	0	0	0	0
LYMPH NODE, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	10	10	10	10	10	10	9
Focus; dark	1	0	0	0	0	0	0	1
LYMPH NODE, MESENTERIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LYMPH NODE, POPLITEAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	7	2	3	10	6	5	6
Enlargement	0	3	8	7	0	4	5	4
MUSCLE, QUADRICEPS								
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

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5002045 - Intergroup Comparison of Gross Pathology Findings

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
OVARY								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	9	8	10
Cyst; pale	.	.	.	.	0	1	2	0
PANCREAS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SITE, INJECTION								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	0	0	0	10	0	0	0
Abnormal consistency; firm	0	10	10	10	0	10	10	10
Swelling	0	4	7	7	0	6	8	9
Focus; dark	0	0	0	1	0	0	0	0
Thick	0	0	0	1	0	0	0	1
SKIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	10	9	10	10	10	10
Scab; dark	0	1	0	1	0	0	0	0
SMALL INTESTINE, DUODENUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, ILEUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, JEJUNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, CERVICAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, LUMBAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

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5002045 - Intergroup Comparison of Gross Pathology Findings

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
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	9	10	10	10
Constriction	0	0	0	0	1	0	0	0
STOMACH								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	9	10	10	8	7	6	10
Focus; dark	1	0	0	0	1	2	3	0
Focus; depressed	0	1	0	0	1	1	0	0
Focus; pale	0	0	0	0	0	0	1	0
TESTIS								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
THYMUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	10	10	8	8	8	8
Focus; dark	0	1	0	0	2	2	2	1
Small	0	0	0	0	0	0	0	1
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
URETER								
Submitted	0	0	0	1	0	0	0	0
Dilatation	.	.	.	1	.	.	.	.
Thick	.	.	.	1	.	.	.	.
Focus; dark	.	.	.	1	.	.	.	.

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5002045 - Intergroup Comparison of Gross Pathology Findings

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								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	9	10	10	10	10
Dilatation	0	0	0	1	0	0	0	0
Thick	0	0	0	1	0	0	0	0
Focus; dark	0	0	0	1	0	0	0	0
Calculus	0	0	0	1	0	0	0	0
UTERUS								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
VAGINA								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10

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Table 2
Summary of Gross Pathology Findings (Day 43)

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5002045 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
ADIPOSE TISSUE				
Submitted	1	0	0	0
Mass	1	.	.	.
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 MARROW SMEAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, FEMUR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, STERNUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BRAIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
CERVIX				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
EPIDIDYMIS				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
ESOPHAGUS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

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5002045 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	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
GLAND, ADRENAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
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

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5002045 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
HEART				
Submitted	5	5	5	5
No Visible Lesions	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	4	4	5	5
Parasite	1	1	0	0
LARYNX				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LIVER				
Submitted	5	5	5	5
No Visible Lesions	3	3	3	4
Focus; pale	2	2	2	1
LUNG				
Submitted	5	5	5	5
No Visible Lesions	5	4	5	5
Focus; dark	0	1	0	0
LYMPH NODE				
Submitted	1	0	1	0
Focus; dark	1	.	0	.
Discoloration; dark	0	.	1	.
LYMPH NODE, INGUINAL				
Submitted	5	5	5	5

Appendix 17

5002045 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, INGUINAL (Continued...)				
No Visible Lesions	5	3	5	5
Enlargement	0	2	0	0
LYMPH NODE, MANDIBULAR				
Submitted	5	5	5	5
No Visible Lesions	2	4	5	5
Focus; dark	3	1	0	0
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	3	5	5
Enlargement	0	2	0	0
MUSCLE, QUADRICEPS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, OPTIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, SCIATIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
OVARY				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
PANCREAS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SITE, INJECTION				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 17

5002045 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
SKIN				
Submitted	5	5	5	5
No Visible Lesions	4	5	5	5
Scab; dark	1	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	5	5	5
SPINAL CORD, CERVICAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, LUMBAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, THORACIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPLEEN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
STOMACH				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
TESTIS				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
THYMUS				
Submitted	5	5	5	5

Appendix 17

5002045 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
THYMUS (Continued...)				
No Visible Lesions	3	5	3	5
Focus; dark	2	0	2	0
TONGUE				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
TRACHEA				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
URINARY BLADDER				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
UTERUS				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
VAGINA				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5

Appendix 17

Table 3
Summary of Organ Weight Values - Absolute (Day 30)

Appendix 17

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	479.2	2.1798	1.0508	0.06078	0.01217	0.9874	0.02049
	SD	39.1	0.0682	0.1036	0.01094	0.00140	0.1626	0.00401
	N	10	10	10	10	10	10	10
2M	Mean	460.8	2.1775	1.0854	0.05895	0.01257	0.9714	0.01946
	SD	22.0	0.1080	0.0560	0.00754	0.00129	0.1624	0.00261
	N	10	10	10	10	10	10	10
	%Diff G1	-3.8	-0.1055	3.2927	-3.01086	3.28677	-1.6204	-5.02684
3M	Mean	450.2	2.1504	1.0397	0.06090	0.01193	0.9342	0.01812
	SD	17.9	0.0492	0.0597	0.00671	0.00119	0.1145	0.00273
	N	10	10	10	10	10	10	10
	%Diff G1	-6.1	-1.3487	-1.0563	0.19743	-1.97206	-5.3879	-11.56662
4M	Mean	436.6b	2.1671	1.0115	0.06094	0.01177	0.8096a	0.02086
	SD	25.7	0.0962	0.0668	0.00674	0.00176	0.1294	0.00517
	N	10	10	10	10	10	10	10
	%Diff G1	-8.9	-0.5826	-3.7400	0.26324	-3.28677	-18.0069	1.80576

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

Appendix 17

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	1.6336	3.0078	14.3384	1.6228	--	0.9897	3.7350
	SD	0.1501	0.3033	2.1034	0.1334	--	0.1806	0.2441
	N	10	10	10	10	--	10	10
2M	Mean	1.6517	2.8877	13.5639	1.7262	--	1.0511	3.8732
	SD	0.1062	0.2190	1.1649	0.1629	--	0.1225	0.2061
	N	10	10	10	10	--	10	10
	%Diff G1	1.1080	-3.9930	-5.4016	6.3717	--	6.2039	3.7001
3M	Mean	1.7145	2.8657	13.7670	1.7387	--	1.0551	3.8709
	SD	0.1912	0.1525	1.1473	0.1305	--	0.1153	0.3383
	N	10	10	10	10	--	10	10
	%Diff G1	4.9523	-4.7244	-3.9851	7.1420	--	6.6081	3.6386
4M	Mean	1.6238	3.0253	13.6621	1.6582	--	1.1240	3.5951
	SD	0.1327	0.1919	1.3978	0.1084	--	0.1871	0.2463
	N	10	10	10	10	--	10	10
	%Diff G1	-0.5999	0.5818	-4.7167	2.1814	--	13.5698	-3.7456

Appendix 17

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	0.5085	--
	SD	0.0931	--
	N	10	--
2M	Mean	0.4938	--
	SD	0.0942	--
	N	10	--
	%Diff G1	-2.8909	--
3M	Mean	0.5466	--
	SD	0.0906	--
	N	10	--
	%Diff G1	7.4926	--
4M	Mean	0.5221	--
	SD	0.0846	--
	N	10	--
	%Diff G1	2.6745	--

Appendix 17

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	282.3	2.0167	--	0.06836	0.01682	--	0.01518
	SD	20.7	0.0832	--	0.01386	0.00210	--	0.00252
	N	10	10	--	10	10	--	10
2F	Mean	292.0	2.0147	--	0.07144	0.01530	--	0.01891b
	SD	20.4	0.0668	--	0.00977	0.00118	--	0.00284
	N	10	10	--	10	10	--	10
	%Diff G1	3.4	-0.0992	--	4.50556	-9.03686	--	24.57181
3F	Mean	287.3	2.0329	--	0.08118	0.01466b	--	0.01566
	SD	25.4	0.0680	--	0.01054	0.00083	--	0.00262
	N	10	10	--	10	10	--	10
	%Diff G1	1.8	0.8033	--	18.75366	-12.84185	--	3.16206
4F	Mean	286.8	2.0212	--	0.07868	0.01441b	--	0.01657
	SD	24.6	0.0676	--	0.01398	0.00164	--	0.00264
	N	10	10	--	10	10	--	10
	%Diff G1	1.6	0.2231	--	15.09655	-14.32818	--	9.15679

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

Appendix 17

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	1.1424	1.7772	7.8836	1.2560	0.1063	0.6504	--
	SD	0.1294	0.1220	1.0299	0.0712	0.0122	0.0735	--
	N	10	10	10	10	10	10	--
2F	Mean	1.1695	1.9620a	8.5442	1.3337	0.1292	0.7212	--
	SD	0.0856	0.1627	0.4395	0.0698	0.0604	0.1331	--
	N	10	10	10	10	10	10	--
	%Diff G1	2.3722	10.3984	8.3794	6.1863	21.5428	10.8856	--
3F	Mean	1.1753	2.0074b	8.7051a	1.3379a	0.1584	0.7537	--
	SD	0.1202	0.1989	0.6488	0.0820	0.1117	0.0600	--
	N	10	10	10	10	10	10	--
	%Diff G1	2.8799	12.9530	10.4204	6.5207	49.0122	15.8825	--
4F	Mean	1.1584	1.9884a	8.7186a	1.3690b	0.1166	0.7205	--
	SD	0.1054	0.1561	0.7003	0.0642	0.0228	0.0802	--
	N	10	10	10	10	10	10	--
	%Diff G1	1.4006	11.8839	10.5916	8.9968	9.6896	10.7780	--

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

Appendix 17

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	0.4678	0.5573
	SD	0.0670	0.1442
	N	10	10
2F	Mean	0.4938	0.5310
	SD	0.0815	0.0811
	N	10	10
	%Diff G1	5.5579	-4.7192
3F	Mean	0.5022	0.6308
	SD	0.0912	0.2213
	N	10	10
	%Diff G1	7.3536	13.1886
4F	Mean	0.4708	0.7571
	SD	0.1472	0.2595
	N	10	10
	%Diff G1	0.6413	35.8514

Appendix 17

Table 4
Summary of Organ Weight Values - Relative to Body Weight (Day 30)

Appendix 17

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	0.45787	0.22138	0.0127	0.0025	0.20632	0.0043	0.34120
	SD	0.04336	0.03408	0.0024	0.0003	0.02903	0.0010	0.02214
	N	10	10	10	10	10	10	10
2M	Mean	0.47302	0.23593	0.0128	0.0027	0.21190	0.0042	0.35883
	SD	0.02317	0.01532	0.0019	0.0003	0.04106	0.0005	0.02338
	N	10	10	10	10	10	10	10
	%Diff G1	3.30966	6.57378	0.8170	7.3566	2.70584	-2.1968	5.16614
3M	Mean	0.47835	0.23140	0.0136	0.0027	0.20780	0.0040	0.38071b
	SD	0.02242	0.01803	0.0018	0.0003	0.02704	0.0006	0.03775
	N	10	10	10	10	10	10	10
	%Diff G1	4.47354	4.52643	6.6056	4.2121	0.71779	-6.6413	11.57885
4M	Mean	0.49812	0.23244	0.0140	0.0027	0.18652	0.0048	0.37221a
	SD	0.03942	0.02049	0.0014	0.0003	0.03438	0.0011	0.02701
	N	10	10	10	10	10	10	10
	%Diff G1	8.79136	4.99828	9.6886	5.5947	-9.59602	10.5891	9.08695

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

Appendix 17

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	0.62734	2.98161	0.33951	--	0.20611	0.78406	0.10590
	SD	0.03229	0.24742	0.02680	--	0.03105	0.08166	0.01500
	N	10	10	10	--	10	10	10
2M	Mean	0.62729	2.94027	0.37412b	--	0.22769	0.84365	0.10700
	SD	0.04711	0.14993	0.02203	--	0.01953	0.07937	0.01827
	N	10	10	10	--	10	10	10
	%Diff G1	-0.00748	-1.38642	10.19534	--	10.46640	7.60104	1.03975
3M	Mean	0.63729	3.05461	0.38642c	--	0.23484	0.86191	0.12175
	SD	0.03984	0.16258	0.02875	--	0.02890	0.09173	0.02175
	N	10	10	10	--	10	10	10
	%Diff G1	1.58682	2.44837	13.81965	--	13.93853	9.92957	14.96606
4M	Mean	0.69409b	3.12670	0.37997b	--	0.25634c	0.82534	0.12034
	SD	0.04487	0.21657	0.01547	--	0.03104	0.06528	0.02334
	N	10	10	10	--	10	10	10
	%Diff G1	10.64024	4.86607	11.91768	--	24.36654	5.26580	13.63675

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

Appendix 17

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

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	0.71755	--	0.0242	0.0060	--	0.0054	0.40468
	SD	0.05607	--	0.0048	0.0010	--	0.0009	0.03624
	N	10	--	10	10	--	10	10
2F	Mean	0.69302	--	0.0247	0.0053	--	0.0065a	0.40261
	SD	0.05374	--	0.0046	0.0007	--	0.0008	0.04431
	N	10	--	10	10	--	10	10
	%Diff G1	-3.41909	--	1.9660	-11.9847	--	20.3484	-0.51150
3F	Mean	0.71240	--	0.0286	0.0051a	--	0.0055	0.40963
	SD	0.06545	--	0.0051	0.0004	--	0.0011	0.02911
	N	10	--	10	10	--	10	10
	%Diff G1	-0.71881	--	17.8550	-14.5501	--	2.0497	1.22295
4F	Mean	0.70955	--	0.0274	0.0050a	--	0.0058	0.40616
	SD	0.06571	--	0.0044	0.0006	--	0.0006	0.04811
	N	10	--	10	10	--	10	10
	%Diff G1	-1.11615	--	13.1757	-15.8752	--	6.8972	0.36486

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

Appendix 17

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	0.63047	2.78949	0.44609	0.03774	0.23047	--	0.16694
	SD	0.03273	0.26236	0.02687	0.00440	0.02041	--	0.03047
	N	10	10	10	10	10	--	10
2F	Mean	0.67398	2.93301	0.45827	0.04429	0.24735	--	0.16923
	SD	0.06079	0.15573	0.03289	0.01969	0.04591	--	0.02582
	N	10	10	10	10	10	--	10
	%Diff G1	6.90009	5.14481	2.73011	17.37176	7.32556	--	1.37064
3F	Mean	0.70142	3.03672a	0.46817	0.05431	0.26379	--	0.17406
	SD	0.07048	0.15712	0.04149	0.03563	0.02692	--	0.02337
	N	10	10	10	10	10	--	10
	%Diff G1	11.25286	8.86254	4.94920	43.92356	14.45822	--	4.26153
4F	Mean	0.69695	3.04489a	0.47962	0.04083	0.25241	--	0.16311
	SD	0.07322	0.15995	0.03540	0.00817	0.03108	--	0.04974
	N	10	10	10	10	10	--	10
	%Diff G1	10.54350	9.15566	7.51496	8.19415	9.52007	--	-2.29336

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

Appendix 17

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	0.19767
	SD	0.04882
	N	10
2F	Mean	0.18181
	SD	0.02434
	N	10
	%Diff G1	-8.02026
3F	Mean	0.22245
	SD	0.08536
	N	10
	%Diff G1	12.53879
4F	Mean	0.26740
	SD	0.09671
	N	10
	%Diff G1	35.27974

Appendix 17

Table 5
Summary of Organ Weight Values - Relative to Brain Weight (Day 30)

Appendix 17

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	48.18608	2.7888	0.5591	45.44748	0.9406	75.06766	138.22696
	SD	4.29802	0.5008	0.0709	8.36857	0.1866	7.85258	15.71199
	N	10	10	10	10	10	10	10
2M	Mean	49.92066	2.7145	0.5777	44.67510	0.8946	76.10248	132.59863
	SD	2.97706	0.3808	0.0544	7.87671	0.1225	7.14300	6.99597
	N	10	10	10	10	10	10	10
	%Diff G1	3.59977	-2.6664	3.3212	-1.69950	-4.8989	1.37851	-4.07180
3M	Mean	48.38718	2.8334	0.5542	43.40972	0.8414	79.68734	133.27867
	SD	3.31669	0.3191	0.0480	4.89943	0.1156	8.19313	6.74125
	N	10	10	10	10	10	10	10
	%Diff G1	0.41734	1.5978	-0.8757	-4.48377	-10.5510	6.15401	-3.57984
4M	Mean	46.72017	2.8148	0.5442	37.47920	0.9612	74.99001	139.87362
	SD	3.18513	0.3062	0.0857	6.56972	0.2287	6.13855	11.11681
	N	10	10	10	10	10	10	10
	%Diff G1	-3.04218	0.9294	-2.6582	-17.53295	2.1870	-0.10344	1.19127

Appendix 17

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	659.63012	74.48752	--	45.56806	171.38320	23.39115	--
	SD	105.90281	6.23712	--	9.11381	10.62636	4.65312	--
	N	10	10	--	10	10	10	--
2M	Mean	623.42127	79.27262	--	48.30690	178.55790	22.64700	--
	SD	50.99011	6.15173	--	5.47035	16.77169	3.98060	--
	N	10	10	--	10	10	10	--
	%Diff G1	-5.48926	6.42403	--	6.01042	4.18635	-3.18132	--
3M	Mean	640.33700	80.83473	--	49.00658	180.24282	25.41907	--
	SD	52.78714	5.42429	--	4.62036	18.23377	4.20216	--
	N	10	10	--	10	10	10	--
	%Diff G1	-2.92484	8.52117	--	7.54590	5.16948	8.66961	--
4M	Mean	631.32770	76.66285	--	52.00356	166.06422	24.15553	--
	SD	68.61652	6.24546	--	9.39287	11.67436	4.18303	--
	N	10	10	--	10	10	10	--
	%Diff G1	-4.29065	2.92039	--	14.12283	-3.10356	3.26782	--

Appendix 17

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	--	3.3971	0.8350	--	0.7520	56.78950	88.26792
	SD	--	0.7285	0.1064	--	0.1142	7.37278	7.18102
	N	--	10	10	--	10	10	10
2F	Mean	--	3.5475	0.7594	--	0.9397b	58.05924	97.47623
	SD	--	0.4811	0.0516	--	0.1464	3.91935	8.76486
	N	--	10	10	--	10	10	10
	%Diff G1	--	4.4268	-9.0596	--	24.9585	2.23587	10.43222
3F	Mean	--	4.0040	0.7222b	--	0.7715	57.87384	98.89731a
	SD	--	0.5926	0.0531	--	0.1315	6.30977	10.84342
	N	--	10	10	--	10	10	10
	%Diff G1	--	17.8654	-13.5062	--	2.5866	1.90940	12.04219
4F	Mean	--	3.8968	0.7132b	--	0.8192	57.37896	98.40124a
	SD	--	0.7244	0.0786	--	0.1251	5.67185	7.35621
	N	--	10	10	--	10	10	10
	%Diff G1	--	14.7088	-14.5833	--	8.9308	1.03797	11.48019

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

Appendix 17

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	391.66401	62.32081	5.28931	32.21311	--	23.16868	27.62350
	SD	56.26228	3.35161	0.74392	2.94529	--	2.95659	6.88888
	N	10	10	10	10	--	10	10
2F	Mean	424.35290	66.23906d	6.39301	35.81292	--	24.55153	26.40460
	SD	22.76446	3.71313	2.86700	6.59731	--	4.25263	4.20142
	N	10	10	10	10	--	10	10
	%Diff G1	8.34616	6.28722	20.86674	11.17497	--	5.96862	-4.41256
3F	Mean	428.48798	65.82854	7.77627	37.11460a	--	24.69921	31.04597
	SD	33.10853	3.72292	5.45520	3.21529	--	4.44272	10.90877
	N	10	10	10	10	--	10	10
	%Diff G1	9.40193	5.62850	47.01876	15.21582	--	6.60603	12.38968
4F	Mean	431.63860	67.75029e	5.77491	35.63947	--	23.34409	37.43121
	SD	36.29871	2.81246	1.13621	3.65945	--	7.36874	12.62907
	N	10	10	10	10	--	10	10
	%Diff G1	10.20635	8.71214	9.18092	10.63652	--	0.75711	35.50491

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

Appendix 17

Table 6
Summary of Organ Weight Values - Absolute (Day 43)

Appendix 17

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	510.6	2.2338	1.1706	0.05546	0.01372	1.1448	0.01850
	SD	37.4	0.0983	0.1110	0.01008	0.00200	0.1584	0.00169
	N	5	5	5	5	5	5	5
4M	Mean	522.8	2.2654	1.2458	0.05692	0.01386	1.1204	0.01576
	SD	55.2	0.0491	0.1136	0.01532	0.00127	0.1548	0.00516
	N	5	5	5	5	5	5	5
	%Diff G1	2.4	1.4146	6.4241	2.63253	1.02041	-2.1314	-14.81081

Appendix 17

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	1.7126	2.9384	14.4494	1.6282	--	0.9126	3.4970
	SD	0.1016	0.2140	1.9056	0.0902	--	0.1454	0.2225
	N	5	5	5	5	--	5	5
4M	Mean	1.8242	3.1336	14.4862	1.7342	--	0.9902	3.8160
	SD	0.2364	0.3101	1.8350	0.1456	--	0.1129	0.4497
	N	5	5	5	5	--	5	5
	%Diff G1	6.5164	6.6431	0.2547	6.5103	--	8.5032	9.1221

Appendix 17

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	0.4592	--
	SD	0.1070	--
	N	5	--
4M	Mean	0.4952	--
	SD	0.0738	--
	N	5	--
	%Diff G1	7.8397	--

Appendix 17

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	323.2	2.0106	--	0.06728	0.01572	--	0.01584
	SD	25.9	0.0901	--	0.00509	0.00047	--	0.00211
	N	5	5	--	5	5	--	5
4F	Mean	306.8	1.9846	--	0.06532	0.01600	--	0.01544
	SD	10.3	0.0825	--	0.00546	0.00122	--	0.00509
	N	5	5	--	5	5	--	5
	%Diff G1	-5.1	-1.2931	--	-2.91320	1.78117	--	-2.52525

Appendix 17

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	1.2912	2.1790	9.4702	1.3234	0.0892	0.7126	--
	SD	0.0913	0.1369	1.1052	0.0663	0.0054	0.1174	--
	N	5	5	5	5	5	5	--
4F	Mean	1.1252a	1.9500a	8.5482	1.3614	0.0958	0.6680	--
	SD	0.0696	0.1019	0.5258	0.0678	0.0219	0.0429	--
	N	5	5	5	5	5	5	--
	%Diff G1	-12.8563	-10.5094	-9.7358	2.8714	7.3991	-6.2588	--

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

Appendix 17

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	0.4326	0.5750
	SD	0.0891	0.2410
	N	5	5
4F	Mean	0.4974	0.6802
	SD	0.0838	0.2552
	N	5	5
	%Diff G1	14.9792	18.2957

Appendix 17

Table 7
Summary of Organ Weight Values - Relative to Body Weight (Day 43)

Appendix 17

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	0.43835	0.23074	0.0109	0.0027	0.22431	0.0037	0.33626
	SD	0.01783	0.03178	0.0021	0.0003	0.02779	0.0005	0.02293
	N	5	5	5	5	5	5	5
4M	Mean	0.43695	0.23891	0.0108	0.0027	0.21661	0.0030	0.34888
	SD	0.04399	0.01485	0.0021	0.0003	0.04206	0.0007	0.02172
	N	5	5	5	5	5	5	5
	%Diff G1	-0.31944	3.54303	-1.4038	-0.5889	-3.43538	-18.7888	3.75158

Appendix 17

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	0.57599	2.82125	0.31948	--	0.17793	0.68893	0.08993
	SD	0.02846	0.18623	0.01643	--	0.01476	0.07665	0.01994
	N	5	5	5	--	5	5	5
4M	Mean	0.60052	2.77070	0.33327	--	0.18945	0.73010	0.09622
	SD	0.03567	0.20733	0.02955	--	0.01045	0.04234	0.02163
	N	5	5	5	--	5	5	5
	%Diff G1	4.25722	-1.79182	4.31510	--	6.47791	5.97579	7.00005

Appendix 17

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

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	0.62634	--	0.0209	0.0049	--	0.0049	0.39996
	SD	0.06975	--	0.0018	0.0004	--	0.0003	0.01578
	N	5	--	5	5	--	5	5
4F	Mean	0.64683	--	0.0213	0.0052	--	0.0050	0.36709a
	SD	0.01340	--	0.0024	0.0004	--	0.0017	0.02589
	N	5	--	5	5	--	5	5
	%Diff G1	3.27116	--	2.2016	6.8113	--	3.1618	-8.21888

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

Appendix 17

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	0.67550	2.92425	0.41197	0.02774	0.21958	--	0.13444
	SD	0.03391	0.13625	0.04215	0.00288	0.02559	--	0.02962
	N	5	5	5	5	5	--	5
4F	Mean	0.63570	2.78555	0.44415	0.03125	0.21757	--	0.16169
	SD	0.02843	0.12144	0.02648	0.00704	0.00765	--	0.02340
	N	5	5	5	5	5	--	5
	%Diff G1	-5.89183	-4.74294	7.81201	12.63067	-0.91206	--	20.27641

Appendix 17

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	0.17804
	SD	0.07229
	N	5
4F	Mean	0.22249
	SD	0.08672
	N	5
	%Diff G1	24.96716

Appendix 17

Table 8
Summary of Organ Weight Values - Relative to Brain Weight (Day 43)

Appendix 17

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	52.50764	2.4895	0.6128	51.23538	0.8312	76.70243	131.52983
	SD	5.71948	0.4852	0.0745	6.49971	0.1018	4.02779	7.47546
	N	5	5	5	5	5	5	5
4M	Mean	54.97295	2.5091	0.6114	49.43290	0.6943	80.57065	138.25474
	SD	4.62306	0.6585	0.0489	6.53476	0.2239	10.74270	12.47424
	N	5	5	5	5	5	5	5
	%Diff G1	4.69514	0.7873	-0.2358	-3.51804	-16.4656	5.04315	5.11284

Appendix 17

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	645.16626	72.90989	--	40.75188	156.87896	20.48766	--
	SD	60.21530	3.18987	--	5.13786	13.16558	4.23795	--
	N	5	5	--	5	5	5	--
4M	Mean	639.73929	76.49228	--	43.67299	168.34055	21.84316	--
	SD	82.32632	5.22848	--	4.48731	18.58206	3.09463	--
	N	5	5	--	5	5	5	--
	%Diff G1	-0.84117	4.91345	--	7.16803	7.30601	6.61616	--

Appendix 17

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	--	3.3481	0.7834	--	0.7910	64.43566	108.73146
	SD	--	0.2323	0.0497	--	0.1297	6.91801	10.97047
	N	--	5	5	--	5	5	5
4F	Mean	--	3.3039	0.8078	--	0.7839	56.81224	98.37640
	SD	--	0.4020	0.0741	--	0.2749	4.85440	6.33455
	N	--	5	5	--	5	5	5
	%Diff G1	--	-1.3199	3.1070	--	-0.8943	-11.83106	-9.52352

Appendix 17

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	473.42512	65.87539	4.44672	35.63071	--	21.52481	28.55713
	SD	74.50807	3.38937	0.38269	6.92272	--	4.51429	11.55174
	N	5	5	5	5	--	5	5
4F	Mean	430.56101	68.72510	4.83744	33.64447	--	25.02038	34.34218
	SD	13.28588	5.05268	1.10703	1.24719	--	3.72493	13.23231
	N	5	5	5	5	--	5	5
	%Diff G1	-9.05404	4.32590	8.78672	-5.57451	--	16.23970	20.25784

Appendix 17

Table 9
Summary of Histopathology Findings (Day 30)

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

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	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE, FEMUR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE, STERNUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BRAIN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
CERVIX								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
EPIDIDYMIS								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
ESOPHAGUS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	9	10	.	.	10
Hemorrhage	0	.	.	1	0	.	.	0
.... mild	0	.	.	1	0	.	.	0
EYE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	9	.	.	9
Rosette; retina	1	.	.	0	1	.	.	1
.... mild	1	.	.	0	1	.	.	1
GALT								
Examined	10	0	0	10	9	0	0	10
No Visible Lesions	10	.	.	10	9	.	.	10
Not Examined: Not Present In Section.	0	0	0	0	1	0	0	0

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

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	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, HARDERIAN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, MAMMARY								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, PARATHYROID								
Examined	7	0	0	9	8	0	0	10
No Visible Lesions	7	.	.	9	8	.	.	10
Not Examined: Not Present In Section.	3	0	0	1	2	0	0	0
GLAND, PITUITARY								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Cyst	1	.	.	0	0	.	.	0
GLAND, PROSTATE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	8	.	.	.	.
Infiltration, lymphocytic	0	.	.	2	.	.	.	.
.... mild	0	.	.	2	.	.	.	.
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	.	.	9	10	.	.	9
Cyst	0	.	.	1	0	.	.	0
Hemorrhage	0	.	.	0	0	.	.	1
.... mild	0	.	.	0	0	.	.	1

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

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								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	9	10	.	.	10
Infiltration, mixed cell	0	.	.	1	0	.	.	0
.... mild	0	.	.	1	0	.	.	0
KIDNEY								
Examined	10	0	0	10	10	0	1	10
No Visible Lesions	8	.	.	7	7	.	1	5
Infiltration, mononuclear cell	1	.	.	0	1	.	0	2
.... minimal	1	.	.	0	0	.	0	2
.... mild	0	.	.	0	1	.	0	0
Dilatation	1	.	.	1	0	.	0	0
.... mild	1	.	.	0	0	.	0	0
.... marked	0	.	.	1	0	.	0	0
Basophilia; tubular	0	.	.	1	0	.	0	1
.... minimal	0	.	.	1	0	.	0	1
Chronic progressive nephropathy	0	.	.	1	2	.	0	2
.... minimal	0	.	.	1	2	.	0	2
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
No Visible Lesions	10	.	.	10	10	.	.	10
LARGE INTESTINE, RECTUM								
Examined	10	0	0	10	9	0	0	10
No Visible Lesions	10	.	.	10	9	.	.	10
Not Examined: Not Present In Section.	0	0	0	0	1	0	0	0
LIVER								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	8	4	5	3	2	1	1	4
Fatty change	0	3	1	3	0	2	1	1
.... minimal	0	3	1	3	0	2	1	1
Vacuolation	1	3	4	5	7	8	8	5
.... minimal	1	3	4	5	7	8	8	5

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

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...)								
Necrosis	0	0	2	1	1	2	0	1
.... minimal	0	0	1	0	1	2	0	0
.... mild	0	0	1	1	0	0	0	1
Infiltration, lymphocytic	0	0	0	0	2	0	0	0
.... minimal	0	0	0	0	2	0	0	0
Inflammation, granulomatous	1	0	0	0	0	0	0	0
.... minimal	1	0	0	0	0	0	0	0
LUNG								
Examined	10	1	2	10	10	0	1	10
No Visible Lesions	10	0	0	8	10	.	1	10
Congestion	0	1	2	2	0	.	0	0
.... mild	0	1	2	2	0	.	0	0
LYMPH NODE								
Examined	0	1	7	4	0	3	4	7
No Visible Lesions	.	1	5	3	.	2	4	6
Hemorrhage	.	0	0	0	.	1	0	0
.... minimal	.	0	0	0	.	1	0	0
Hyperplasia; lymphoid	.	0	2	1	.	0	0	1
.... moderate	.	0	2	1	.	0	0	1
Infiltration, mixed cell	.	0	0	0	.	0	0	1
.... mild	.	0	0	0	.	0	0	1
LYMPH NODE, INGUINAL								
Examined	10	10	9	10	10	10	10	10
No Visible Lesions	10	9	6	7	9	8	8	5
Not Examined: Not Present In Wet Tissues.	0	0	1	0	0	0	0	0
Infiltration, mixed cell	0	0	0	2	0	0	1	3
.... minimal	0	0	0	1	0	0	0	0
.... mild	0	0	0	1	0	0	1	3
Hyperplasia; lymphoid	0	1	3	1	1	0	1	2
.... mild	0	1	3	1	1	0	1	2
Hemorrhage	0	0	0	0	0	2	0	0
.... minimal	0	0	0	0	0	2	0	0

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

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								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	9
Hemorrhage	1	.	.	0	0	.	.	1
.... minimal	1	.	.	0	0	.	.	1
LYMPH NODE, MESENTERIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	9	.	.	10
Hemorrhage	0	.	.	0	1	.	.	0
.... mild	0	.	.	0	1	.	.	0
LYMPH NODE, POPLITEAL								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	3	3	2	10	1	0	1
Infiltration, mixed cell	0	6	7	8	0	9	10	9
.... minimal	0	0	2	6	0	7	4	2
.... mild	0	6	5	2	0	2	6	7
Hyperplasia; lymphoid	0	1	0	0	0	0	0	0
.... mild	0	1	0	0	0	0	0	0
MUSCLE, QUADRICEPS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
NERVE, OPTIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
NERVE, SCIATIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	9	10	.	.	10
Infiltration, mixed cell; perineurial	0	.	.	1	0	.	.	0
.... moderate	0	.	.	1	0	.	.	0
OVARY								
Examined	.	.	.	.	10	1	2	10
No Visible Lesions	.	.	.	.	10	0	0	10
Cyst; bursal	.	.	.	.	0	1	2	0
PANCREAS								
Examined	10	0	0	10	10	0	0	10

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

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
PANCREAS (Continued...)								
No Visible Lesions	10	.	.	10	9	.	.	9
Atrophy; acinar	0	.	.	0	1	.	.	1
.... minimal	0	.	.	0	0	.	.	1
.... mild	0	.	.	0	1	.	.	0
SITE, INJECTION								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	0	0	0	10	0	0	0
Hemorrhage	0	1	0	1	0	0	0	0
.... moderate	0	1	0	1	0	0	0	0
Inflammation	0	10	10	10	0	10	10	10
.... minimal	0	0	0	0	0	1	0	0
.... mild	0	0	0	0	0	6	2	4
.... moderate	0	10	10	10	0	3	8	6
SKIN								
Examined	10	1	0	10	10	0	0	10
No Visible Lesions	10	0	.	9	10	.	.	10
Acanthosis	0	1	.	1	0	.	.	0
.... mild	0	0	.	1	0	.	.	0
.... moderate	0	1	.	0	0	.	.	0
Exudate	0	1	.	1	0	.	.	0
.... mild	0	1	.	1	0	.	.	0
SMALL INTESTINE, DUODENUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, ILEUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, JEJUNUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPINAL CORD, CERVICAL								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

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
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
SPLEEN								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	6	3	0	10	5	1	0
Decreased cellularity; lymphoid, periarteriolar lymphoid sheath	0	4	7	10	0	5	9	10
.... minimal	0	4	7	7	0	5	9	5
.... mild	0	0	0	3	0	0	0	5
STOMACH								
Examined	10	1	0	10	10	3	4	10
No Visible Lesions	10	1	.	10	10	2	4	10
Necrosis; mucosal	0	0	.	0	0	1	0	0
.... mild	0	0	.	0	0	1	0	0
TESTIS								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	9	.	.	.	.
Multinucleated giant cells	0	.	.	1	.	.	.	.
.... minimal	0	.	.	1	.	.	.	.
THYMUS								
Examined	10	1	0	10	10	2	2	10
No Visible Lesions	9	0	.	10	10	2	1	8
Hemorrhage	1	1	.	0	0	0	1	2
.... minimal	1	0	.	0	0	0	0	2
.... mild	0	1	.	0	0	0	1	0
TONGUE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
TRACHEA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

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
URETER								
Examined	0	0	0	1	0	0	0	0
Infiltration, mixed cell	.	.	.	1	.	.	.	.
.... mild	.	.	.	1	.	.	.	.
URINARY BLADDER								
Examined	10	0	0	10	9	0	0	10
No Visible Lesions	10	.	.	9	9	.	.	10
Not Examined: Not Present In Section.	0	0	0	0	1	0	0	0
Hemorrhage	0	.	.	1	0	.	.	0
.... mild	0	.	.	1	0	.	.	0
Metaplasia, squamous	0	.	.	1	0	.	.	0
.... marked	0	.	.	1	0	.	.	0
Dilatation	0	.	.	1	0	.	.	0
.... mild	0	.	.	1	0	.	.	0
UTERUS								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
VAGINA								
Examined	.	.	.	.	9	0	0	10
No Visible Lesions	.	.	.	.	9	.	.	10
Not Examined: Not Present In Section.	.	.	.	.	1	0	0	0

Appendix 17

Table 10
Summary of Histopathology Findings (Day 43)

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
ADIPOSE TISSUE				
Examined	1	0	0	0
Necrosis	1	.	.	.
.... mild	1	.	.	.
ARTERY, AORTA				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BONE MARROW				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, FEMUR				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, STERNUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BRAIN				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
CERVIX				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
EPIDIDYMIS				
Examined	5	5	.	.
No Visible Lesions	5	5	.	.
ESOPHAGUS				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
EYE				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
GALT				
Examined	5	4	5	4
No Visible Lesions	5	4	5	4
Not Examined: Not Present In Section.	0	1	0	1

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, ADRENAL				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, HARDERIAN				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, MAMMARY				
Examined	5	5	5	4
No Visible Lesions	5	5	5	4
Not Examined: Not Present In Section.	0	0	0	1
GLAND, PARATHYROID				
Examined	5	5	4	5
No Visible Lesions	5	5	4	5
Not Examined: Not Present In Section.	0	0	1	0
GLAND, PITUITARY				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PROSTATE				
Examined	5	5	.	.
No Visible Lesions	4	3	.	.
Infiltration, lymphocytic	1	2	.	.
.... minimal	1	1	.	.
.... mild	0	1	.	.
GLAND, SALIVARY, MANDIBULAR				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, SEMINAL VESICLE				
Examined	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, THYROID				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
HEART				
Examined	5	5	5	5
No Visible Lesions	5	5	5	4

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
HEART (Continued...)				
Infiltration, mononuclear cell	0	0	0	1
.... minimal	0	0	0	1
KIDNEY				
Examined	5	5	5	5
No Visible Lesions	3	4	5	4
Infiltration, mononuclear cell	1	0	0	1
.... minimal	1	0	0	1
Basophilia; tubular	0	1	0	0
.... minimal	0	1	0	0
Chronic progressive nephropathy	1	0	0	0
.... minimal	1	0	0	0
LARGE INTESTINE, CECUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, COLON				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, RECTUM				
Examined	5	5	5	5
No Visible Lesions	3	5	5	5
Parasitism	2	0	0	0
LIVER				
Examined	5	5	5	5
No Visible Lesions	3	3	4	4
Fatty change; midzonal	1	0	0	0
.... mild	1	0	0	0
Necrosis	1	0	0	0
.... minimal	1	0	0	0
Infiltration, lymphocytic	1	2	1	1
.... minimal	1	2	1	1
LUNG				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE				
Examined	1	0	1	0
Hemorrhage	1	.	1	.
.... minimal	1	.	0	.
.... mild	0	.	1	.
LYMPH NODE, INGUINAL				
Examined	5	5	5	5
No Visible Lesions	5	4	5	5
Hemorrhage	0	1	0	0
.... mild	0	1	0	0
LYMPH NODE, MANDIBULAR				
Examined	5	5	5	5
No Visible Lesions	2	4	5	5
Hemorrhage	3	1	0	0
.... minimal	3	1	0	0
LYMPH NODE, MESENTERIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
LYMPH NODE, POPLITEAL				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
MUSCLE, QUADRICEPS				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, OPTIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, SCIATIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
OVARY				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
PANCREAS				
Examined	5	5	5	5

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
PANCREAS (Continued...)				
No Visible Lesions	5	5	5	5
SITE, INJECTION				
Examined	5	5	5	5
No Visible Lesions	5	5	5	4
Infiltration, mononuclear cell	0	0	0	1
.... minimal	0	0	0	1
SKIN				
Examined	5	5	5	4
No Visible Lesions	4	5	5	4
Not Examined: Not Present In Section.	0	0	0	1
Acanthosis	1	0	0	0
.... moderate	1	0	0	0
Exudate	1	0	0	0
.... mild	1	0	0	0
SMALL INTESTINE, DUODENUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, ILEUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, JEJUNUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, CERVICAL				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, LUMBAR				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, THORACIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPLEEN				
Examined	5	5	5	5

Appendix 17 5002045 - Intergroup Comparison of Histopathology Findings

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	100 ug/dose Group 4	0 ug/dose Group 1	100 ug/dose Group 4
Number of Animals:	5	5	5	5
SPLEEN (Continued...)				
No Visible Lesions	5	5	5	5
STOMACH				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
TESTIS				
Examined	5	5	.	.
No Visible Lesions	5	5	.	.
THYMUS				
Examined	5	5	5	5
No Visible Lesions	3	5	4	5
Hemorrhage	2	0	1	0
.... minimal	2	0	1	0
TONGUE				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
TRACHEA				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
URINARY BLADDER				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
UTERUS				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
VAGINA				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5

Appendix 17

Appendix 1
Deviations

Appendix 17

DEVIATIONS

All deviations (if any) that occurred during this study phase have been acknowledged by the Study Director, assessed for impact, and documented in the study records. All protocol deviations and those SOP deviations regarded as significant are listed below. None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

- Tissues that were supposed to be microscopically evaluated per protocol but were not available on the slide (and therefore not evaluated) are listed in the Individual Animal Data of the Pathology report as not present.

Appendix 17

Appendix 2
Individual Organ Weight Values -Absolute (Day 30)

Appendix 17

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	456	2.322	1.123	0.0604	0.0122	0.862	0.0183
	1002	442	2.178	1.197	0.0740	0.0113	0.919	0.0195
	1003	488	2.179	1.177	0.0712	0.0122	1.077	0.0215
	1104	485	2.132	1.012	0.0459	0.0130	0.990	0.0160MPI
	1005	419	2.238	1.091	0.0492	0.0116	0.864	0.0224
	1006	443	2.086	0.974	0.0484	0.0117	0.972	0.0223
	1007	511	2.144	0.859	0.0692	0.0102	0.918	0.0226
	1008	540	2.224	0.995	0.0571	0.0126	0.836	0.0189
	1009	483	2.178	1.090	0.0746	0.0114	1.045	0.0288
	1010	525	2.117	0.990	0.0578	0.0155	1.391	0.0146
2M	2001	504	2.288	1.132	0.0557	0.0106	0.974	0.0192
	2002	457	2.255	1.045	0.0501	0.0132	1.023	0.0195
	2003	480	2.069	1.050	0.0607	0.0127	0.694	0.0234
	2004	467	2.347	1.088	0.0598	0.0152	1.114	0.0197
	2005	432	2.172	1.167	0.0714	0.0119	0.999	0.0199
	2006	428	2.004	0.981	0.0499	0.0119	1.215	0.0162
	2007	470	2.252	1.050	0.0503	0.0132	0.904	0.0213
	2008	454	2.157	1.078	0.0622	0.0131	0.782	0.0155
	2009	461	2.081	1.131	0.0608	0.0128	0.873	0.0172
	2010	455	2.150	1.132	0.0686	0.0111	1.136	0.0227

Appendix 17

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	1.549	2.705	11.321	1.709	--	0.775	3.670
	1002	1.670	2.958	13.474	1.708	--	0.980	3.992
	1003	1.532	3.262	14.520	1.577	--	1.034	4.181
	1104	1.677	3.066	14.358	1.620	--	1.293	3.599
	1005	1.329	2.523	11.386	1.383	--	0.740	3.765
	1006	1.516	2.608	13.814MPI	1.401	--	0.858	3.331
	1007	1.733	3.373	14.865	1.691	--	0.930	3.479
	1008	1.728	3.183	17.550	1.647	--	0.974	3.789
	1009	1.820	3.072	14.547	1.768	--	1.072	3.853
	1010	1.782	3.328	17.549	1.724	--	1.241	3.691
2M	2001	1.741	3.114	15.667	2.060	--	1.253	3.599
	2002	1.535	2.878	13.708	1.620	--	1.023	3.594
	2003	1.733	2.770	14.510	1.743	--	1.151	3.954
	2004	1.556	3.339	13.133	1.927	--	1.039	3.771
	2005	1.552	2.969	12.049	1.527	--	0.875	4.216
	2006	1.599	2.741	12.124	1.558	--	0.907	4.094
	2007	1.524	2.831	14.030	1.654	--	1.003	3.701
	2008	1.745	2.542	14.616	1.690	--	1.204	3.928
	2009	1.755	2.781	13.142	1.724	--	0.979	3.888
	2010	1.777	2.912	12.660	1.759	--	1.077	3.987

Appendix 17

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	0.498	--
	1002	0.417	--
	1003	0.486	--
	1104	0.588	--
	1005	0.419	--
	1006	0.438	--
	1007	0.534	--
	1008	0.449	--
	1009	0.536	--
	1010	0.720	--
2M	2001	0.652	--
	2002	0.403	--
	2003	0.348	--
	2004	0.538	--
	2005	0.411	--
	2006	0.454	--
	2007	0.532	--
	2008	0.471	--
	2009	0.526	--
	2010	0.603	--

Appendix 17

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	457	2.139	1.041	0.0495	0.0119	0.941	0.0155
	3002	442	2.174	1.007	0.0702	0.0141	1.120	0.0169
	3003	430	2.139	1.003	0.0602	0.0120	0.791	0.0205
	3004	439	2.191	1.106	0.0574	0.0121	1.069	0.0195
	3005	444	2.192	1.065	0.0638	0.0115	1.003	0.0170
	3006	469	2.087	0.956	0.0633	0.0114	0.860	0.0172
	3007	456	2.144	1.065	0.0540	0.0121	1.020	0.0159
	3008	440	2.053	1.156	0.0661	0.0093	0.806	0.0146
	3009	489	2.177	1.008	0.0558	0.0122	0.892	0.0214
	3010	436	2.208	0.990	0.0687	0.0127	0.840	0.0227
4M	4001	430	2.129	0.963	0.0571	0.0112	0.866	0.0258
	4002	408	2.289	0.974	0.0489	0.0096	0.872	0.0200
	4003	401	2.074	1.028	0.0523	0.0092	0.919	0.0151
	4004	479	2.093	0.908	0.0628	0.0113	0.862	0.0269
	4105	450	2.202	1.064	0.0685	0.0145	0.509MPI	0.0210
	4006	458	2.163	0.978	0.0599	0.0140	0.656	0.0124MPI
	4007	440	2.362	1.124	0.0696	0.0116	0.848	0.0282
	4008	460	2.052	1.095	0.0628	0.0134	0.923	0.0186
	4009	432	2.148	0.968	0.0607	0.0120	0.808	0.0230
	4010	408	2.159	1.013	0.0668	0.0109	0.833	0.0176

Appendix 17

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	1.747	2.680	14.231	1.650	--	1.069	3.894
	3002	1.619	2.986	14.476	1.712	--	1.204	3.797
	3003	1.611	2.868	12.442	1.603	--	1.081	3.611
	3004	1.959	2.928	13.325	2.011	--	0.986	4.355
	3005	1.578	3.107	14.143	1.652	--	1.243	3.776
	3006	1.694	2.998	14.479	1.746	--	0.953	3.737
	3007	1.480	2.661	13.506	1.823	--	0.979	3.990
	3008	1.556	2.711	12.605	1.587	--	0.864	4.517
	3009	2.088	2.945	16.059	1.859	--	1.056	3.440
	3010	1.813	2.773	12.404	1.744	--	1.116	3.592
4M	4001	1.429	2.964	13.506	1.530	--	1.077	3.404
	4002	1.535	2.830	12.100	1.551	--	0.960	3.269
	4003	1.406	2.986	12.143	1.565	--	0.843	3.380
	4004	1.680	3.217	16.537	1.857	--	1.443	3.339
	4105	1.702	3.423	14.257	1.600	--	1.310	3.711
	4006	1.703	2.862	12.735	1.795	--	1.194	3.657
	4007	1.774	3.054	15.336	1.722	--	1.116	3.993
	4008	1.720	3.092	13.655	1.674	--	1.264	3.844
	4009	1.552	2.779	13.350	1.681	--	0.909	3.535
	4010	1.737	3.046	13.002	1.607	--	1.124	3.819

Appendix 17

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	0.494	--
	3002	0.677	--
	3003	0.620	--
	3004	0.606	--
	3005	0.488	--
	3006	0.653	--
	3007	0.406	--
	3008	0.460	--
	3009	0.494	--
	3010	0.568	--
4M	4001	0.605	--
	4002	0.627	--
	4003	0.623	--
	4004	0.588	--
	4105	0.374	--
	4006	0.469	--
	4007	0.489	--
	4008	0.475	--
	4009	0.511	--
	4010	0.460	--

Appendix 17

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	283	2.150	--	0.0682	0.0170	--	0.0182
	1502	314	2.050	--	0.0711	0.0178	--	0.0168
	1503	269	2.063	--	0.0469	0.0151	--	0.0114MPI
	1504	291	2.054	--	0.0639	0.0160	--	0.0145
	1505	304	1.892	--	0.0914	0.0159	--	0.0143
	1506	275	1.910	--	0.0596	0.0165	--	0.0143
	1507	306	2.090	--	0.0765	0.0158	--	0.0179
	1508	266	1.935	--	0.0519	0.0174	--	0.0157
	1509	254	2.033	--	0.0856	0.0221	--	0.0175
	1510	261	1.990	--	0.0685	0.0146	--	0.0112
2F	2501	312	1.965	--	0.0709	0.0142	--	0.0231
	2502	253	1.905	--	0.0762	0.0161	--	0.0177
	2503	275	2.081	--	0.0821	0.0169	--	0.0176
	2504	305	1.975	--	0.0565	0.0145	--	0.0163
	2505	312	2.072	--	0.0563	0.0149	--	0.0230
	2506	267	2.106	--	0.0782	0.0170	--	0.0169
	2507	294	1.950	--	0.0732	0.0149	--	0.0217
	2508	292	2.014	--	0.0821	0.0145	--	0.0179
	2509	306	2.076	--	0.0765	0.0163	--	0.0198
	2510	304	2.003	--	0.0624	0.0137	--	0.0151

Appendix 17

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	1.060	1.782	8.088	1.308	0.097	0.728	--
	1502	1.310	1.977	9.201	1.305	0.116	0.788	--
	1503	0.964	1.554	7.211	1.150	0.098	0.576	--
	1504	1.184	1.730	7.044	1.274	0.101	0.692	--
	1505	1.274	1.911	9.775	1.206	0.126	0.623	--
	1506	1.067	1.744	7.663	1.287	0.113	0.569	--
	1507	1.220	1.888	8.356	1.391	0.104	0.687	--
	1508	1.280	1.709	6.824	1.183	0.106	0.572	--
	1509	1.104	1.777	8.059	1.214	0.118	0.657	--
	1510	0.961	1.700	6.615	1.242	0.084	0.612	--
2F	2501	1.114	2.349	9.198	1.306	0.121	0.887	--
	2502	1.130	1.826	8.160	1.188	0.127	0.578	--
	2503	1.104	1.866	8.551	1.370	0.132	0.556	--
	2504	1.136	1.860	8.584	1.400	0.112	0.769	--
	2505	1.241	1.864	9.134	1.352	0.105	0.755	--
	2506	1.287	2.035	8.086	1.353	0.114	0.916	--
	2507	1.125	1.957	8.072	1.440	0.109	0.835	--
	2508	1.337	2.017	8.201MPI	1.342	0.087	0.637	--
	2509	1.113	2.044	9.041	1.274	0.296MPI	0.708	--
	2510	1.108	1.802	8.415	1.312	0.089	0.571	--

Appendix 17

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	0.497	0.628
	1502	0.428	0.523
	1503	0.589	0.442
	1504	0.462	0.940
	1505	0.413	0.501
	1506	0.475	0.564
	1507	0.479	0.482
	1508	0.376	0.528
	1509	0.555	0.495
	1510	0.404	0.470
2F	2501	0.556	0.632
	2502	0.479	0.535
	2503	0.399	0.493
	2504	0.408	0.457
	2505	0.581	0.664
	2506	0.474	0.388
	2507	0.614	0.522
	2508	0.373	0.584
	2509	0.531	0.535
	2510	0.523	0.500

Appendix 17

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	311	2.077	--	0.0700	0.0146	--	0.0202
	3502	296	1.983	--	0.0941	0.0159	--	0.0172
	3503	267	2.022	--	0.0777	0.0135	--	0.0133
	3504	269	2.086	--	0.0669	0.0149	--	0.0172
	3505	287	1.990	--	0.0922	0.0149	--	0.0123
	3506	297	1.988	--	0.0842	0.0142	--	0.0152
	3507	310	2.165	--	0.0817	0.0139	--	0.0116
	3508	327	2.007	--	0.0663	0.0161	--	0.0159
	3509	261	1.932	--	0.0912	0.0144	--	0.0167
	3510	248	2.079	--	0.0875	0.0142	--	0.0170
4F	4501	294	2.105	--	0.0701	0.0162	--	0.0191
	4502	306	2.049	--	0.0791	0.0145	--	0.0202
	4503	288	2.013	--	0.0836	0.0146	--	0.0158
	4504	251	1.946	--	0.0530	0.0132	--	0.0110
	4505	289	2.099	--	0.0863	0.0113	--	0.0162
	4506	263	1.984	--	0.0651	0.0145	--	0.0153
	4507	298	2.039	--	0.0961	0.0141	--	0.0172
	4508	249	2.052	--	0.0851	0.0147	--	0.0146
	4509	318	1.885	--	0.0975	0.0136	--	0.0177
	4510	312	2.040	--	0.0709	0.0174	--	0.0186

Appendix 17

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	1.201	2.197	9.282	1.486	0.395MPI	0.855	--
	3502	1.151	2.184	8.380	1.329	0.331MPI	0.686	--
	3503	1.034	1.788	7.714	1.279	0.124	0.804	--
	3504	1.107	1.929	8.421	1.279	0.068	0.716	--
	3505	1.092	1.841	9.242	1.235	0.115	0.797	--
	3506	1.322	1.899	9.038	1.439	0.107	0.765	--
	3507	1.185	1.802	8.969	1.376	0.153	0.767	--
	3508	1.434	2.396	9.755	1.316	0.089	0.707	--
	3509	1.090	1.989	7.979	1.256	0.077	0.779	--
	3510	1.137	2.049	8.271	1.384	0.125	0.661	--
4F	4501	1.072	1.975	8.807	1.462	0.104	0.714	--
	4502	1.269	2.178	9.416	1.369	0.091	0.681	--
	4503	0.981	2.107	8.287	1.336	0.109	0.660	--
	4504	1.029	1.680	7.298	1.260	0.097	0.636	--
	4505	1.095	1.813	8.980	1.385	0.156	0.865	--
	4506	1.190	1.983	8.706	1.272	0.143	0.684	--
	4507	1.241	1.983	8.510	1.435	0.098	0.637	--
	4508	1.272	2.144	8.167	1.390	0.102	0.755	--
	4509	1.230	1.916	9.342	1.385	0.127	0.730	--
	4510	1.205	2.105	9.673	1.396	0.139	0.843	--

Appendix 17

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	0.559	0.409
	3502	0.590	0.590
	3503	0.484	1.092
	3504	0.564	0.829
	3505	0.476	0.430
	3506	0.486	0.447
	3507	0.517	0.538
	3508	0.631	0.843
	3509	0.348	0.538
	3510	0.367	0.592
4F	4501	0.566	0.468
	4502	0.399	0.573
	4503	0.427	0.608
	4504	0.437	0.699
	4505	0.643	0.620
	4506	0.563	0.867
	4507	0.457	1.041
	4508	0.121MPI	1.030
	4509	0.599	0.468
	4510	0.496	1.197

Appendix 17

Appendix 3
Individual Organ Weight Values - Relative to Body Weight (Day 30)

Appendix 17

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	0.5092	0.2463	0.01325	0.00268	0.1890	0.00401	0.3397
	1002	0.4928	0.2708	0.01674	0.00256	0.2079	0.00441	0.3778
	1003	0.4465	0.2412	0.01459	0.00250	0.2207	0.00441	0.3139
	1104	0.4396	0.2087	0.00946	0.00268	0.2041	0.00330MPI	0.3458
	1005	0.5341	0.2604	0.01174	0.00277	0.2062	0.00535	0.3172
	1006	0.4709	0.2199	0.01093	0.00264	0.2194	0.00503	0.3422
	1007	0.4196	0.1681	0.01354	0.00200	0.1796	0.00442	0.3391
	1008	0.4119	0.1843	0.01057	0.00233	0.1548	0.00350	0.3200
	1009	0.4509	0.2257	0.01545	0.00236	0.2164	0.00596	0.3768
	1010	0.4032	0.1886	0.01101	0.00295	0.2650	0.00278	0.3394
2M	2001	0.4540	0.2246	0.01105	0.00210	0.1933	0.00381	0.3454
	2002	0.4934	0.2287	0.01096	0.00289	0.2239	0.00427	0.3359
	2003	0.4310	0.2188	0.01265	0.00265	0.1446	0.00488	0.3610
	2004	0.5026	0.2330	0.01281	0.00325	0.2385	0.00422	0.3332
	2005	0.5028	0.2701	0.01653	0.00275	0.2313	0.00461	0.3593
	2006	0.4682	0.2292	0.01166	0.00278	0.2839	0.00379	0.3736
	2007	0.4791	0.2234	0.01070	0.00281	0.1923	0.00453	0.3243
	2008	0.4751	0.2374	0.01370	0.00289	0.1722	0.00341	0.3844
	2009	0.4514	0.2453	0.01319	0.00278	0.1894	0.00373	0.3807
	2010	0.4725	0.2488	0.01508	0.00244	0.2497	0.00499	0.3905

Appendix 17

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	0.5932	2.4827	0.3748	--	0.1700	0.8048	0.1092
	1002	0.6692	3.0484	0.3864	--	0.2217	0.9032	0.0943
	1003	0.6684	2.9754	0.3232	--	0.2119	0.8568	0.0996
	1104	0.6322	2.9604	0.3340	--	0.2666	0.7421	0.1212
	1005	0.6021	2.7174	0.3301	--	0.1766	0.8986	0.1000
	1006	0.5887	3.1183MPI	0.3163	--	0.1937	0.7519	0.0989
	1007	0.6601	2.9090	0.3309	--	0.1820	0.6808	0.1045
	1008	0.5894	3.2500	0.3050	--	0.1804	0.7017	0.0831
	1009	0.6360	3.0118	0.3660	--	0.2219	0.7977	0.1110
	1010	0.6339	3.3427	0.3284	--	0.2364	0.7030	0.1371
2M	2001	0.6179	3.1085	0.4087	--	0.2486	0.7141	0.1294
	2002	0.6298	2.9996	0.3545	--	0.2239	0.7864	0.0882
	2003	0.5771	3.0229	0.3631	--	0.2398	0.8238	0.0725
	2004	0.7150	2.8122	0.4126	--	0.2225	0.8075	0.1152
	2005	0.6873	2.7891	0.3535	--	0.2025	0.9759	0.0951
	2006	0.6404	2.8327	0.3640	--	0.2119	0.9565	0.1061
	2007	0.6023	2.9851	0.3519	--	0.2134	0.7874	0.1132
	2008	0.5599	3.2194	0.3722	--	0.2652	0.8652	0.1037
	2009	0.6033	2.8508	0.3740	--	0.2124	0.8434	0.1141
	2010	0.6400	2.7824	0.3866	--	0.2367	0.8763	0.1325

Appendix 17

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	--
	1104	--
	1005	--
	1006	--
	1007	--
	1008	--
	1009	--
	1010	--
2M	2001	--
	2002	--
	2003	--
	2004	--
	2005	--
	2006	--
	2007	--
	2008	--
	2009	--
	2010	--

Appendix 17

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	0.4681	0.2278	0.01083	0.00260	0.2059	0.00339	0.3823
	3002	0.4919	0.2278	0.01588	0.00319	0.2534	0.00382	0.3663
	3003	0.4974	0.2333	0.01400	0.00279	0.1840	0.00477	0.3747
	3004	0.4991	0.2519	0.01308	0.00276	0.2435	0.00444	0.4462
	3005	0.4937	0.2399	0.01437	0.00259	0.2259	0.00383	0.3554
	3006	0.4450	0.2038	0.01350	0.00243	0.1834	0.00367	0.3612
	3007	0.4702	0.2336	0.01184	0.00265	0.2237	0.00349	0.3246
	3008	0.4666	0.2627	0.01502	0.00211	0.1832	0.00332	0.3536
	3009	0.4452	0.2061	0.01141	0.00249	0.1824	0.00438	0.4270
	3010	0.5064	0.2271	0.01576	0.00291	0.1927	0.00521	0.4158
4M	4001	0.4951	0.2240	0.01328	0.00260	0.2014	0.00600	0.3323
	4002	0.5610	0.2387	0.01199	0.00235	0.2137	0.00490	0.3762
	4003	0.5172	0.2564	0.01304	0.00229	0.2292	0.00377	0.3506
	4004	0.4370	0.1896	0.01311	0.00236	0.1800	0.00562	0.3507
	4105	0.4893	0.2364	0.01522	0.00322	0.1131MPI	0.00467	0.3782
	4006	0.4723	0.2135	0.01308	0.00306	0.1432	0.00271MPI	0.3718
	4007	0.5368	0.2555	0.01582	0.00264	0.1927	0.00641	0.4032
	4008	0.4461	0.2380	0.01365	0.00291	0.2007	0.00404	0.3739
	4009	0.4972	0.2241	0.01405	0.00278	0.1870	0.00532	0.3593
	4010	0.5292	0.2483	0.01637	0.00267	0.2042	0.00431	0.4257

Appendix 17

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	0.5864	3.1140	0.3611	--	0.2339	0.8521	0.1081
	3002	0.6756	3.2751	0.3873	--	0.2724	0.8590	0.1532
	3003	0.6670	2.8935	0.3728	--	0.2514	0.8398	0.1442
	3004	0.6670	3.0353	0.4581	--	0.2246	0.9920	0.1380
	3005	0.6998	3.1854	0.3721	--	0.2800	0.8505	0.1099
	3006	0.6392	3.0872	0.3723	--	0.2032	0.7968	0.1392
	3007	0.5836	2.9618	0.3998	--	0.2147	0.8750	0.0890
	3008	0.6161	2.8648	0.3607	--	0.1964	1.0266	0.1045
	3009	0.6022	3.2840	0.3802	--	0.2160	0.7035	0.1010
	3010	0.6360	2.8450	0.4000	--	0.2560	0.8239	0.1303
4M	4001	0.6893	3.1409	0.3558	--	0.2505	0.7916	0.1407
	4002	0.6936	2.9657	0.3801	--	0.2353	0.8012	0.1537
	4003	0.7446	3.0282	0.3903	--	0.2102	0.8429	0.1554
	4004	0.6716	3.4524	0.3877	--	0.3013	0.6971	0.1228
	4105	0.7607	3.1682	0.3556	--	0.2911	0.8247	0.0831
	4006	0.6249	2.7806	0.3919	--	0.2607	0.7985	0.1024
	4007	0.6941	3.4855	0.3914	--	0.2536	0.9075	0.1111
	4008	0.6722	2.9685	0.3639	--	0.2748	0.8357	0.1033
	4009	0.6433	3.0903	0.3891	--	0.2104	0.8183	0.1183
	4010	0.7466	3.1868	0.3939	--	0.2755	0.9360	0.1127

Appendix 17

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	--
	4105	--
	4006	--
	4007	--
	4008	--
	4009	--
	4010	--

Appendix 17

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	0.7597	--	0.02410	0.00601	--	0.00643	0.3746
	1502	0.6529	--	0.02264	0.00567	--	0.00535	0.4172
	1503	0.7669	--	0.01743	0.00561	--	0.00424MPI	0.3584
	1504	0.7058	--	0.02196	0.00550	--	0.00498	0.4069
	1505	0.6224	--	0.03007	0.00523	--	0.00470	0.4191
	1506	0.6945	--	0.02167	0.00600	--	0.00520	0.3880
	1507	0.6830	--	0.02500	0.00516	--	0.00585	0.3987
	1508	0.7274	--	0.01951	0.00654	--	0.00590	0.4812
	1509	0.8004	--	0.03370	0.00870	--	0.00689	0.4346
	1510	0.7625	--	0.02625	0.00559	--	0.00429	0.3682
2F	2501	0.6298	--	0.02272	0.00455	--	0.00740	0.3571
	2502	0.7530	--	0.03012	0.00636	--	0.00700	0.4466
	2503	0.7567	--	0.02985	0.00615	--	0.00640	0.4015
	2504	0.6475	--	0.01852	0.00475	--	0.00534	0.3725
	2505	0.6641	--	0.01804	0.00478	--	0.00737	0.3978
	2506	0.7888	--	0.02929	0.00637	--	0.00633	0.4820
	2507	0.6633	--	0.02490	0.00507	--	0.00738	0.3827
	2508	0.6897	--	0.02812	0.00497	--	0.00613	0.4579
	2509	0.6784	--	0.02500	0.00533	--	0.00647	0.3637
	2510	0.6589	--	0.02053	0.00451	--	0.00497	0.3645

Appendix 17

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	0.6297	2.8580	0.4622	0.0343	0.2572	--	0.1756
	1502	0.6296	2.9303	0.4156	0.0369	0.2510	--	0.1363
	1503	0.5777	2.6807	0.4275	0.0364	0.2141	--	0.2190
	1504	0.5945	2.4206	0.4378	0.0347	0.2378	--	0.1588
	1505	0.6286	3.2155	0.3967	0.0414	0.2049	--	0.1359
	1506	0.6342	2.7865	0.4680	0.0411	0.2069	--	0.1727
	1507	0.6170	2.7307	0.4546	0.0340	0.2245	--	0.1565
	1508	0.6425	2.5654	0.4447	0.0398	0.2150	--	0.1414
	1509	0.6996	3.1728	0.4780	0.0465	0.2587	--	0.2185
	1510	0.6513	2.5345	0.4759	0.0322	0.2345	--	0.1548
2F	2501	0.7529	2.9481	0.4186	0.0388	0.2843	--	0.1782
	2502	0.7217	3.2253	0.4696	0.0502	0.2285	--	0.1893
	2503	0.6785	3.1095	0.4982	0.0480	0.2022	--	0.1451
	2504	0.6098	2.8144	0.4590	0.0367	0.2521	--	0.1338
	2505	0.5974	2.9276	0.4333	0.0337	0.2420	--	0.1862
	2506	0.7622	3.0285	0.5067	0.0427	0.3431	--	0.1775
	2507	0.6656	2.7456	0.4898	0.0371	0.2840	--	0.2088
	2508	0.6908	2.8086MPI	0.4596	0.0298	0.2182	--	0.1277
	2509	0.6680	2.9546	0.4163	0.0967MPI	0.2314	--	0.1735
	2510	0.5928	2.7681	0.4316	0.0293	0.1878	--	0.1720

Appendix 17

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	0.2219
	1502	0.1666
	1503	0.1643
	1504	0.3230
	1505	0.1648
	1506	0.2051
	1507	0.1575
	1508	0.1985
	1509	0.1949
	1510	0.1801
2F	2501	0.2026
	2502	0.2115
	2503	0.1793
	2504	0.1498
	2505	0.2128
	2506	0.1453
	2507	0.1776
	2508	0.2000
	2509	0.1748
	2510	0.1645

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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	0.6678	--	0.02251	0.00469	--	0.00650	0.3862
	3502	0.6699	--	0.03179	0.00537	--	0.00581	0.3889
	3503	0.7573	--	0.02910	0.00506	--	0.00498	0.3873
	3504	0.7755	--	0.02487	0.00554	--	0.00639	0.4115
	3505	0.6934	--	0.03213	0.00519	--	0.00429	0.3805
	3506	0.6694	--	0.02835	0.00478	--	0.00512	0.4451
	3507	0.6984	--	0.02635	0.00448	--	0.00374	0.3823
	3508	0.6138	--	0.02028	0.00492	--	0.00486	0.4385
	3509	0.7402	--	0.03494	0.00552	--	0.00640	0.4176
	3510	0.8383	--	0.03528	0.00573	--	0.00685	0.4585
4F	4501	0.7160	--	0.02384	0.00551	--	0.00650	0.3646
	4502	0.6696	--	0.02585	0.00474	--	0.00660	0.4147
	4503	0.6990	--	0.02903	0.00507	--	0.00549	0.3406
	4504	0.7753	--	0.02112	0.00526	--	0.00438	0.4100
	4505	0.7263	--	0.02986	0.00391	--	0.00561	0.3789
	4506	0.7544	--	0.02475	0.00551	--	0.00582	0.4525
	4507	0.6842	--	0.03225	0.00473	--	0.00577	0.4164
	4508	0.8241	--	0.03418	0.00590	--	0.00586	0.5108
	4509	0.5928	--	0.03066	0.00428	--	0.00557	0.3868
	4510	0.6538	--	0.02272	0.00558	--	0.00596	0.3862

Appendix 17

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	0.7064	2.9846	0.4778	0.1270MPI	0.2749	--	0.1797
	3502	0.7378	2.8311	0.4490	0.1118MPI	0.2318	--	0.1993
	3503	0.6697	2.8891	0.4790	0.0464	0.3011	--	0.1813
	3504	0.7171	3.1305	0.4755	0.0253	0.2662	--	0.2097
	3505	0.6415	3.2202	0.4303	0.0401	0.2777	--	0.1659
	3506	0.6394	3.0431	0.4845	0.0360	0.2576	--	0.1636
	3507	0.5813	2.8932	0.4439	0.0494	0.2474	--	0.1668
	3508	0.7327	2.9832	0.4024	0.0272	0.2162	--	0.1930
	3509	0.7621	3.0571	0.4812	0.0295	0.2985	--	0.1333
	3510	0.8262	3.3351	0.5581	0.0504	0.2665	--	0.1480
4F	4501	0.6718	2.9956	0.4973	0.0354	0.2429	--	0.1925
	4502	0.7118	3.0771	0.4474	0.0297	0.2225	--	0.1304
	4503	0.7316	2.8774	0.4639	0.0378	0.2292	--	0.1483
	4504	0.6693	2.9076	0.5020	0.0386	0.2534	--	0.1741
	4505	0.6273	3.1073	0.4792	0.0540	0.2993	--	0.2225
	4506	0.7540	3.3103	0.4837	0.0544	0.2601	--	0.2141
	4507	0.6654	2.8557	0.4815	0.0329	0.2138	--	0.1534
	4508	0.8610	3.2799	0.5582	0.0410	0.3032	--	0.0486MPI
	4509	0.6025	2.9377	0.4355	0.0399	0.2296	--	0.1884
	4510	0.6747	3.1003	0.4474	0.0446	0.2702	--	0.1590

Appendix 17

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	0.1315
	3502	0.1993
	3503	0.4090
	3504	0.3082
	3505	0.1498
	3506	0.1505
	3507	0.1735
	3508	0.2578
	3509	0.2061
	3510	0.2387
4F	4501	0.1592
	4502	0.1873
	4503	0.2111
	4504	0.2785
	4505	0.2145
	4506	0.3297
	4507	0.3493
	4508	0.4137
	4509	0.1472
	4510	0.3837

Appendix 17

Appendix 4
Individual Organ Weight Values - Relative to Brain Weight (Day 30)

Appendix 17

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	48.3635	2.60121	0.52541	37.1232	0.78811	66.7097	116.4944
	1002	54.9587	3.39761	0.51882	42.1947	0.89532	76.6758	135.8127
	1003	54.0156	3.26755	0.55989	49.4263	0.98669	70.3075	149.7017
	1104	47.4672	2.15291	0.60976	46.4353	0.75047MPI	78.6585	143.8086
	1005	48.7489	2.19839	0.51832	38.6059	1.00089	59.3834	112.7346
	1006	46.6922	2.32023	0.56088	46.5964	1.06903	72.6750	125.0240
	1007	40.0653	3.22761	0.47575	42.8172	1.05410	80.8302	157.3228
	1008	44.7392	2.56745	0.56655	37.5899	0.84982	77.6978	143.1205
	1009	50.0459	3.42516	0.52342	47.9798	1.32231	83.5629	141.0468
	1010	46.7643	2.73028	0.73217	65.7062	0.68966	84.1757	157.2036
2M	2001	49.4755	2.43444	0.46329	42.5699	0.83916	76.0927	136.1014
	2002	46.3415	2.22173	0.58537	45.3659	0.86475	68.0710	127.6275
	2003	50.7492	2.93378	0.61382	33.5428	1.13098	83.7603	133.8811
	2004	46.3571	2.54793	0.64764	47.4648	0.83937	66.2974	142.2667
	2005	53.7293	3.28729	0.54788	45.9945	0.91621	71.4549	136.6943
	2006	48.9521	2.49002	0.59381	60.6287	0.80838	79.7904	136.7764
	2007	46.6252	2.23357	0.58615	40.1421	0.94583	67.6732	125.7105
	2008	49.9768	2.88363	0.60732	36.2541	0.71859	80.8994	117.8489
	2009	54.3489	2.92167	0.61509	41.9510	0.82653	84.3345	133.6377
	2010	52.6512	3.19070	0.51628	52.8372	1.05581	82.6512	135.4419

Appendix 17

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 %
1M	1001	487.5538	73.6003	--	33.3764	158.0534	21.4470	--
	1002	618.6410	78.4206	--	44.9954	183.2874	19.1460	--
	1003	666.3607	72.3726	--	47.4530	191.8770	22.3038	--
	1104	673.4522	75.9850	--	60.6473	168.8086	27.5797	--
	1005	508.7578	61.7962	--	33.0652	168.2306	18.7221	--
	1006	662.2244MPI	67.1620	--	41.1314	159.6836	20.9971	--
	1007	693.3302	78.8713	--	43.3769	162.2668	24.9067	--
	1008	789.1187	74.0558	--	43.7950	170.3687	20.1888	--
	1009	667.9063	81.1754	--	49.2195	176.9054	24.6097	--
	1010	828.9561	81.4360	--	58.6207	174.3505	34.0104	--
2M	2001	684.7465	90.0350	--	54.7640	157.2990	28.4965	--
	2002	607.8936	71.8404	--	45.3659	159.3792	17.8714	--
	2003	701.3050	84.2436	--	55.6307	191.1068	16.8197	--
	2004	559.5654	82.1048	--	44.2693	160.6732	22.9229	--
	2005	554.7422	70.3039	--	40.2855	194.1068	18.9227	--
	2006	604.9900	77.7445	--	45.2595	204.2914	22.6547	--
	2007	623.0018	73.4458	--	44.5382	164.3428	23.6234	--
	2008	677.6078	78.3496	--	55.8183	182.1048	21.8359	--
	2009	631.5233	82.8448	--	47.0447	186.8333	25.2763	--
	2010	588.8372	81.8140	--	50.0930	185.4419	28.0465	--

Appendix 17

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 %
3M	3001	48.6676	2.31417	0.55633	43.9925	0.72464	81.6737	125.2922
	3002	46.3201	3.22907	0.64857	51.5179	0.77737	74.4710	137.3505
	3003	46.8911	2.81440	0.56101	36.9799	0.95839	75.3156	134.0813
	3004	50.4792	2.61981	0.55226	48.7905	0.89000	89.4112	133.6376
	3005	48.5858	2.91058	0.52464	45.7573	0.77555	71.9891	141.7427
	3006	45.8074	3.03306	0.54624	41.2075	0.82415	81.1691	143.6512
	3007	49.6735	2.51866	0.56437	47.5746	0.74160	69.0299	124.1138
	3008	56.3078	3.21968	0.45300	39.2596	0.71115	75.7915	132.0507
	3009	46.3023	2.56316	0.56040	40.9738	0.98300	95.9118	135.2779
	3010	44.8370	3.11141	0.57518	38.0435	1.02808	82.1105	125.5888
4M	4001	45.2325	2.68201	0.52607	40.6764	1.21184	67.1207	139.2203
	4002	42.5513	2.13630	0.41940	38.0952	0.87374	67.0599	123.6348
	4003	49.5661	2.52170	0.44359	44.3105	0.72806	67.7917	143.9730
	4004	43.3827	3.00048	0.53989	41.1849	1.28524	80.2676	153.7028
	4105	48.3197	3.11081	0.65849	23.1153MPI	0.95368	77.2934	155.4496
	4006	45.2150	2.76930	0.64725	30.3282	0.57328MPI	78.7332	132.3162
	4007	47.5868	2.94666	0.49111	35.9018	1.19390	75.1058	129.2972
	4008	53.3626	3.06043	0.65302	44.9805	0.90643	83.8207	150.6823
	4009	45.0652	2.82588	0.55866	37.6164	1.07076	72.2533	129.3762
	4010	46.9199	3.09403	0.50486	38.5827	0.81519	80.4539	141.0838

Appendix 17

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	665.3109	77.1388	--	49.9766	182.0477	23.0949	--
	3002	665.8694	78.7489	--	55.3818	174.6550	31.1408	--
	3003	581.6737	74.9416	--	50.5376	168.8172	28.9855	--
	3004	608.1698	91.7846	--	45.0023	198.7677	27.6586	--
	3005	645.2099	75.3650	--	56.7062	172.2628	22.2628	--
	3006	693.7710	83.6608	--	45.6636	179.0609	31.2889	--
	3007	629.9440	85.0280	--	45.6623	186.1007	18.9366	--
	3008	613.9795	77.3015	--	42.0848	220.0195	22.4062	--
	3009	737.6665	85.3927	--	48.5071	158.0156	22.6918	--
	3010	561.7754	78.9855	--	50.5435	162.6812	25.7246	--
4M	4001	634.3823	71.8647	--	50.5871	159.8873	28.4171	--
	4002	528.6151	67.7588	--	41.9397	142.8135	27.3919	--
	4003	585.4870	75.4581	--	40.6461	162.9701	30.0386	--
	4004	790.1099	88.7243	--	68.9441	159.5318	28.0936	--
	4105	647.4569	72.6612	--	59.4914	168.5286	16.9846	--
	4006	588.7656	82.9866	--	55.2011	169.0707	21.6828	--
	4007	649.2803	72.9043	--	47.2481	169.0517	20.7028	--
	4008	665.4483	81.5789	--	61.5984	187.3294	23.1481	--
	4009	621.5084	78.2588	--	42.3184	164.5717	23.7896	--
	4010	602.2233	74.4326	--	52.0611	176.8874	21.3062	--

Appendix 17

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 %
1F	1501	--	3.17209	0.79070	--	0.84651	49.3023	82.8837
	1502	--	3.46829	0.86829	--	0.81951	63.9024	96.4390
	1503	--	2.27339	0.73194	--	0.55259MPI	46.7281	75.3272
	1504	--	3.11100	0.77897	--	0.70594	57.6436	84.2259
	1505	--	4.83087	0.84038	--	0.75581	67.3362	101.0042
	1506	--	3.12042	0.86387	--	0.74869	55.8639	91.3089
	1507	--	3.66029	0.75598	--	0.85646	58.3732	90.3349
	1508	--	2.68217	0.89922	--	0.81137	66.1499	88.3204
	1509	--	4.21053	1.08706	--	0.86080	54.3040	87.4078
	1510	--	3.44221	0.73367	--	0.56281	48.2915	85.4271
2F	2501	--	3.60814	0.72265	--	1.17557	56.6921	119.5420
	2502	--	4.00000	0.84514	--	0.92913	59.3176	95.8530
	2503	--	3.94522	0.81211	--	0.84575	53.0514	89.6684
	2504	--	2.86076	0.73418	--	0.82532	57.5190	94.1772
	2505	--	2.71718	0.71911	--	1.11004	59.8938	89.9614
	2506	--	3.71320	0.80722	--	0.80247	61.1111	96.6287
	2507	--	3.75385	0.76410	--	1.11282	57.6923	100.3590
	2508	--	4.07646	0.71996	--	0.88878	66.3853	100.1490
	2509	--	3.68497	0.78516	--	0.95376	53.6127	98.4586
	2510	--	3.11533	0.68397	--	0.75387	55.3170	89.9651

Appendix 17

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 %
1F	1501	376.1860	60.8372	4.5116	33.8605	--	23.1163	29.2093
	1502	448.8293	63.6585	5.6585	38.4390	--	20.8780	25.5122
	1503	349.5395	55.7441	4.7504	27.9205	--	28.5507	21.4251
	1504	342.9406	62.0253	4.9172	33.6904	--	22.4927	45.7644
	1505	516.6490	63.7421	6.6596	32.9281	--	21.8288	26.4799
	1506	401.2042	67.3822	5.9162	29.7906	--	24.8691	29.5288
	1507	399.8086	66.5550	4.9761	32.8708	--	22.9187	23.0622
	1508	352.6615	61.1370	5.4780	29.5607	--	19.4315	27.2868
	1509	396.4092	59.7147	5.8042	32.3168	--	27.2996	24.3483
	1510	332.4121	62.4121	4.2211	30.7538	--	20.3015	23.6181
2F	2501	468.0916	66.4631	6.1578	45.1399	--	28.2952	32.1628
	2502	428.3465	62.3622	6.6667	30.3412	--	25.1444	28.0840
	2503	410.9082	65.8337	6.3431	26.7179	--	19.1735	23.6905
	2504	434.6329	70.8861	5.6709	38.9367	--	20.6582	23.1392
	2505	440.8301	65.2510	5.0676	36.4382	--	28.0405	32.0463
	2506	383.9506	64.2450	5.4131	43.4948	--	22.5071	18.4236
	2507	413.9487	73.8462	5.5897	42.8205	--	31.4872	26.7692
	2508	407.1996MPI	66.6336	4.3198	31.6286	--	18.5204	28.9970
	2509	435.5010	61.3680	14.2582MPI	34.1040	--	25.5780	25.7707
	2510	420.1198	65.5017	4.4433	28.5072	--	26.1108	24.9626

Appendix 17

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 %
3F	3501	--	3.37025	0.70294	--	0.97256	57.8238	105.7776
	3502	--	4.74534	0.80182	--	0.86737	58.0434	110.1362
	3503	--	3.84273	0.66766	--	0.65776	51.1375	88.4273
	3504	--	3.20709	0.71429	--	0.82454	53.0681	92.4736
	3505	--	4.63317	0.74874	--	0.61809	54.8744	92.5126
	3506	--	4.23541	0.71429	--	0.76459	66.4990	95.5231
	3507	--	3.77367	0.64203	--	0.53580	54.7344	83.2333
	3508	--	3.30344	0.80219	--	0.79223	71.4499	119.3822
	3509	--	4.72050	0.74534	--	0.86439	56.4182	102.9503
	3510	--	4.20875	0.68302	--	0.81770	54.6898	98.5570
4F	4501	--	3.33017	0.76960	--	0.90736	50.9264	93.8242
	4502	--	3.86042	0.70766	--	0.98585	61.9327	106.2958
	4503	--	4.15301	0.72529	--	0.78490	48.7332	104.6696
	4504	--	2.72354	0.67831	--	0.56526	52.8777	86.3309
	4505	--	4.11148	0.53835	--	0.77180	52.1677	86.3745
	4506	--	3.28125	0.73085	--	0.77117	59.9798	99.9496
	4507	--	4.71309	0.69152	--	0.84355	60.8632	97.2536
	4508	--	4.14717	0.71637	--	0.71150	61.9883	104.4834
	4509	--	5.17241	0.72149	--	0.93899	65.2520	101.6446
	4510	--	3.47549	0.85294	--	0.91176	59.0686	103.1863

Appendix 17

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	446.8946	71.5455	19.0178MPI	41.1651	--	26.9138	19.6919
	3502	422.5920	67.0197	16.6919MPI	34.5940	--	29.7529	29.7529
	3503	381.5035	63.2542	6.1325	39.7626	--	23.9367	54.0059
	3504	403.6913	61.3135	3.2598	34.3241	--	27.0374	39.7411
	3505	464.4221	62.0603	5.7789	40.0503	--	23.9196	21.6080
	3506	454.6278	72.3843	5.3823	38.4809	--	24.4467	22.4849
	3507	414.2725	63.5566	7.0670	35.4273	--	23.8799	24.8499
	3508	486.0488	65.5705	4.4345	35.2267	--	31.4400	42.0030
	3509	412.9917	65.0104	3.9855	40.3209	--	18.0124	27.8468
	3510	397.8355	66.5705	6.0125	31.7941	--	17.6527	28.4752
4F	4501	418.3848	69.4537	4.9406	33.9192	--	26.8884	22.2328
	4502	459.5412	66.8131	4.4412	33.2357	--	19.4729	27.9649
	4503	411.6741	66.3686	5.4148	32.7869	--	21.2121	30.2037
	4504	375.0257	64.7482	4.9846	32.6824	--	22.4563	35.9198
	4505	427.8228	65.9838	7.4321	41.2101	--	30.6336	29.5379
	4506	438.8105	64.1129	7.2077	34.4758	--	28.3770	43.6996
	4507	417.3615	70.3776	4.8063	31.2408	--	22.4129	51.0544
	4508	398.0019	67.7388	4.9708	36.7934	--	5.8967MPI	50.1949
	4509	495.5968	73.4748	6.7374	38.7268	--	31.7772	24.8276
	4510	474.1667	68.4314	6.8137	41.3235	--	24.3137	58.6765

Appendix 17

Appendix 5
Individual Organ Weight Values -Absolute (Day 43)

Appendix 17

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	512	2.316	1.197	0.0494	0.0145	1.001	0.0176
	1012	483	2.114	1.058	0.0528	0.0108	1.008	0.0186
	1013	572	2.352	1.050	0.0520	0.0150	1.348	0.0163
	1014	508	2.206	1.276	0.0733	0.0157	1.092	0.0208
	1015	478	2.181	1.272	0.0498	0.0126	1.275	0.0192
4M	4011	493	2.191	1.112	0.0493	0.0119	0.965	0.0108
	4012	456	2.263	1.179	0.0339	0.0144	1.290	0.0109
	4013	538	2.294	1.350	0.0673	0.0133	0.947	0.0195
	4014	604	2.257	1.377	0.0714	0.0150	1.190	0.0224
	4015	523	2.322	1.211	0.0627	0.0147	1.210	0.0152

Appendix 17

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	1.843	2.944	15.385	1.618	--	0.866	3.630
	1012	1.718	2.733	12.997	1.506	--	0.831	3.395
	1013	1.737	3.133	17.097	1.706	--	1.165	3.175
	1014	1.706	3.168	14.447	1.726	--	0.897	3.752
	1015	1.559	2.714	12.321	1.585	--	0.804	3.533
4M	4011	1.724	2.814	14.552	1.555	--	0.880	3.262
	4012	1.684	2.851	11.902	1.654	--	0.861	3.550
	4013	1.778	3.487	16.333	1.705	--	1.028	3.974
	4014	2.242	3.411	16.077	1.835	--	1.105	4.453
	4015	1.693	3.105	13.567	1.922	--	1.077	3.841

Appendix 17

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	0.621	--
	1012	0.443	--
	1013	0.493	--
	1014	0.337	--
	1015	0.402	--
4M	4011	0.433	--
	4012	0.583	--
	4013	0.560	--
	4014	0.419	--
	4015	0.481	--

Appendix 17

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	318	2.099	--	0.0700	0.0157	--	0.0161
	1512	329	2.058	--	0.0747	0.0157	--	0.0156
	1513	361	1.905	--	0.0652	0.0154	--	0.0192
	1514	289	2.069	--	0.0618	0.0153	--	0.0136
	1515	319	1.922	--	0.0647	0.0165	--	0.0147
4F	4511	316	2.040	--	0.0581	0.0176	--	0.0170
	4512	317	2.093	--	0.0622	0.0142	--	0.0091
	4513	300	1.972	--	0.0652	0.0164	--	0.0128
	4514	293	1.889	--	0.0717	0.0160	--	0.0155
	4515	308	1.929	--	0.0694	0.0158	--	0.0228

Appendix 17

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	1.320	2.192	8.933	1.378	0.088	0.712	--
	1512	1.246	2.149	9.491	1.359	0.082	0.751	--
	1513	1.406	2.288	11.054	1.225	0.095	0.802	--
	1514	1.163	1.963	8.065	1.285	0.094	0.512	--
	1515	1.321	2.303	9.808	1.370	0.087	0.786	--
4F	4511	1.062	1.997	8.494	1.282	0.122	0.681	--
	4512	1.150	1.914	9.461	1.373	0.066	0.722	--
	4513	1.049	1.912	8.365	1.349	0.109	0.651	--
	4514	1.148	1.829	8.147	1.336	0.083	0.606	--
	4515	1.217	2.098	8.274	1.467	0.099	0.680	--

Appendix 17

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	0.465	0.447
	1512	0.372	0.998
	1513	0.520	0.444
	1514	0.497	0.436
	1515	0.309	0.550
4F	4511	0.548	0.529
	4512	0.583	0.904
	4513	0.370	0.478
	4514	0.462	1.008
	4515	0.524	0.482

Appendix 17

Appendix 6
Individual Organ Weight Values - Relative to Body Weight (Day 43)

Appendix 17

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	0.4523	0.2338	0.00965	0.00283	0.1955	0.00344	0.3600
	1012	0.4377	0.2190	0.01093	0.00224	0.2087	0.00385	0.3557
	1013	0.4112	0.1836	0.00909	0.00262	0.2357	0.00285	0.3037
	1014	0.4343	0.2512	0.01443	0.00309	0.2150	0.00409	0.3358
	1015	0.4563	0.2661	0.01042	0.00264	0.2667	0.00402	0.3262
4M	4011	0.4444	0.2256	0.01000	0.00241	0.1957	0.00219	0.3497
	4012	0.4963	0.2586	0.00743	0.00316	0.2829	0.00239	0.3693
	4013	0.4264	0.2509	0.01251	0.00247	0.1760	0.00362	0.3305
	4014	0.3737	0.2280	0.01182	0.00248	0.1970	0.00371	0.3712
	4015	0.4440	0.2315	0.01199	0.00281	0.2314	0.00291	0.3237

Appendix 17

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	0.5750	3.0049	0.3160	--	0.1691	0.7090	0.1213
	1012	0.5658	2.6909	0.3118	--	0.1720	0.7029	0.0917
	1013	0.5477	2.9890	0.2983	--	0.2037	0.5551	0.0862
	1014	0.6236	2.8439	0.3398	--	0.1766	0.7386	0.0663
	1015	0.5678	2.5776	0.3316	--	0.1682	0.7391	0.0841
4M	4011	0.5708	2.9517	0.3154	--	0.1785	0.6617	0.0878
	4012	0.6252	2.6101	0.3627	--	0.1888	0.7785	0.1279
	4013	0.6481	3.0359	0.3169	--	0.1911	0.7387	0.1041
	4014	0.5647	2.6618	0.3038	--	0.1829	0.7373	0.0694
	4015	0.5937	2.5941	0.3675	--	0.2059	0.7344	0.0920

Appendix 17

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	--

Appendix 17

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	0.6601	--	0.02201	0.00494	--	0.00506	0.4151
	1512	0.6255	--	0.02271	0.00477	--	0.00474	0.3787
	1513	0.5277	--	0.01806	0.00427	--	0.00532	0.3895
	1514	0.7159	--	0.02138	0.00529	--	0.00471	0.4024
	1515	0.6025	--	0.02028	0.00517	--	0.00461	0.4141
4F	4511	0.6456	--	0.01839	0.00557	--	0.00538	0.3361
	4512	0.6603	--	0.01962	0.00448	--	0.00287	0.3628
	4513	0.6573	--	0.02173	0.00547	--	0.00427	0.3497
	4514	0.6447	--	0.02447	0.00546	--	0.00529	0.3918
	4515	0.6263	--	0.02253	0.00513	--	0.00740	0.3951

Appendix 17

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	0.6893	2.8091	0.4333	0.0277	0.2239	--	0.1462
	1512	0.6532	2.8848	0.4131	0.0249	0.2283	--	0.1131
	1513	0.6338	3.0620	0.3393	0.0263	0.2222	--	0.1440
	1514	0.6792	2.7907	0.4446	0.0325	0.1772	--	0.1720
	1515	0.7219	3.0746	0.4295	0.0273	0.2464	--	0.0969
4F	4511	0.6320	2.6880	0.4057	0.0386	0.2155	--	0.1734
	4512	0.6038	2.9845	0.4331	0.0208	0.2278	--	0.1839
	4513	0.6373	2.7883	0.4497	0.0363	0.2170	--	0.1233
	4514	0.6242	2.7805	0.4560	0.0283	0.2068	--	0.1577
	4515	0.6812	2.6864	0.4763	0.0321	0.2208	--	0.1701

Appendix 17

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	0.1406
	1512	0.3033
	1513	0.1230
	1514	0.1509
	1515	0.1724
4F	4511	0.1674
	4512	0.2852
	4513	0.1593
	4514	0.3440
	4515	0.1565

Appendix 17

Appendix 7
Individual Organ Weight Values - Relative to Brain Weight (Day 43)

Appendix 17

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	51.6839	2.13299	0.62608	43.2211	0.75993	79.5769	127.1157
	1012	50.0473	2.49763	0.51088	47.6821	0.87985	81.2677	129.2810
	1013	44.6429	2.21088	0.63776	57.3129	0.69303	73.8520	133.2058
	1014	57.8422	3.32276	0.71170	49.5014	0.94288	77.3345	143.6083
	1015	58.3219	2.28336	0.57772	58.4594	0.88033	71.4810	124.4383
4M	4011	50.7531	2.25011	0.54313	44.0438	0.49293	78.6855	128.4345
	4012	52.0990	1.49801	0.63632	57.0040	0.48166	74.4145	125.9832
	4013	58.8492	2.93374	0.57977	41.2816	0.85004	77.5065	152.0052
	4014	61.0102	3.16349	0.66460	52.7249	0.99247	99.3354	151.1298
	4015	52.1533	2.70026	0.63307	52.1102	0.65461	72.9113	133.7209

Appendix 17

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	664.2919	69.8618	--	37.3921	156.7358	26.8135	--
	1012	614.8061	71.2394	--	39.3094	160.5960	20.9555	--
	1013	726.9133	72.5340	--	49.5323	134.9915	20.9609	--
	1014	654.8957	78.2412	--	40.6618	170.0816	15.2765	--
	1015	564.9243	72.6731	--	36.8638	161.9899	18.4319	--
4M	4011	664.1716	70.9722	--	40.1643	148.8818	19.7627	--
	4012	525.9390	73.0888	--	38.0468	156.8714	25.7623	--
	4013	711.9878	74.3243	--	44.8126	173.2345	24.4115	--
	4014	712.3172	81.3026	--	48.9588	197.2973	18.5645	--
	4015	584.2808	82.7735	--	46.3824	165.4177	20.7149	--

Appendix 17

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	--	3.33492	0.74798	--	0.76703	62.8871	104.4307
	1512	--	3.62974	0.76288	--	0.75802	60.5442	104.4218
	1513	--	3.42257	0.80840	--	1.00787	73.8058	120.1050
	1514	--	2.98695	0.73949	--	0.65732	56.2107	94.8768
	1515	--	3.36629	0.85848	--	0.76483	68.7305	119.8231
4F	4511	--	2.84804	0.86275	--	0.83333	52.0588	97.8922
	4512	--	2.97181	0.67845	--	0.43478	54.9451	91.4477
	4513	--	3.30629	0.83164	--	0.64909	53.1947	96.9574
	4514	--	3.79566	0.84701	--	0.82054	60.7729	96.8237
	4515	--	3.59772	0.81908	--	1.18196	63.0897	108.7610

Appendix 17

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	425.5836	65.6503	4.1925	33.9209	--	22.1534	21.2959
	1512	461.1759	66.0350	3.9845	36.4917	--	18.0758	48.4937
	1513	580.2625	64.3045	4.9869	42.0997	--	27.2966	23.3071
	1514	389.8018	62.1073	4.5433	24.7463	--	24.0213	21.0730
	1515	510.3018	71.2799	4.5265	40.8949	--	16.0770	28.6160
4F	4511	416.3725	62.8431	5.9804	33.3824	--	26.8627	25.9314
	4512	452.0306	65.5996	3.1534	34.4959	--	27.8548	43.1916
	4513	424.1886	68.4077	5.5274	33.0122	--	18.7627	24.2394
	4514	431.2864	70.7253	4.3939	32.0805	--	24.4574	53.3616
	4515	428.9269	76.0498	5.1322	35.2514	--	27.1643	24.9870

Appendix 17

Appendix 8
Individual Animal Data Gross and Histopathology Findings

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1001	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PITUITARY : Cyst

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, 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1002	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1003	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1, right caudal (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1, right caudal (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1104	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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : epididymis right submitted in 2 pieces
GLAND, THYROID : Small : bilateral (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
STOMACH : Focus; dark : 1, mucosa, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
NO CORRELATE : No correlating lesion [STOMACH : Focus; dark : 1, mucosa, glandular (G) | GLAND, THYROID : Small : bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, 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, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1005	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

No observations found

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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1006	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; raised : 1, pale, firm, fissure, left medial (TGL)
LIVER : Small : left medial (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Inflammation, granulomatous; multifocal, minimal [LIVER : Focus; raised : 1, pale, firm, fissure, left medial (G)]
NO CORRELATE : No correlating lesion [LIVER : Small : left medial (G)]
THYMUS : Hemorrhage; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1007	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation; 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1008	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Dilatation; pelvis : right (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Dilatation; mild [KIDNEY : Dilatation; pelvis : 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1009	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : GL adrenal left accidentally cut.
LUNG : Focus; dark : 1 to 3, right caudal, left lobe (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1 to 3, right caudal, 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; 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1010	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : epididymis right accidentally cut
LIVER : Focus; pale : >10 (TGL)
LUNG : Focus; dark : 1, right caudal (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EYE : Rosette; mild, retina
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : >10 (G) | LUNG : Focus; dark : 1, right caudal (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1011	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 43 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, lymphocytic; minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1012	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 43 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lymph node lesion submitted cass D; Adipose tissue lesion submitted cass C.
ADIPOSE TISSUE : Mass; [a] : 10x5x3 mm, dark, firm, pedunculated, abdominal, adjacent to epididymis left. (TGL)

LIVER : Focus; pale : 1, fissure, medial lobe. (TGL)
LYMPH NODE : Focus; dark : >10, mediastinal. (TGL)
THYMUS : Focus; dark : >10, left lobe. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

ADIPOSE TISSUE : Necrosis; focal, mild [ADIPOSE TISSUE : Mass; [a] : 10x5x3 mm, dark, firm, pedunculated, abdominal, adjacent to epididymis left. (G)]
LARGE INTESTINE, RECTUM : Nematode evident within lumen
LARGE INTESTINE, RECTUM : Parasitism
LYMPH NODE : Hemorrhage; minimal [LYMPH NODE : Focus; dark : >10, mediastinal. (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, medial lobe. (G)]
THYMUS : Hemorrhage; 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; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; 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

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1013	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 43 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : >10. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, right. (TGL)
THYMUS : Focus; dark : >10. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Fatty change; midzonal, mild [LIVER : Focus; pale : >10. (G)]
LIVER : Necrosis; focal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, right. (G)]
NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : >10. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1014	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 43 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Skin lesion submitted cass C.
LARGE INTESTINE, RECTUM : Parasite : >10.
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)
SKIN : Scab; dark : 2, cranium, right. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LARGE INTESTINE, RECTUM : Nematode present in lumen
LARGE INTESTINE, RECTUM : Parasitism
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (G)]
SKIN : Acanthosis; moderate
SKIN : Exudate; mild [SKIN : Scab; dark : 2, cranium, right. (G)]
THYMUS : Hemorrhage; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1015	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 43 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PROSTATE : Infiltration, lymphocytic; minimal
KIDNEY : Chronic progressive nephropathy; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal: 1501	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death: 30 (5)		

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

STOMACH : Focus; depressed : 1, dark, mucosa, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [STOMACH : Focus; depressed : 1, dark, mucosa, glandular (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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1502	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

STOMACH : Focus; dark : >10, mucosa, glandular (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Infiltration, lymphocytic; minimal
NO CORRELATE : No correlating lesion [STOMACH : Focus; dark : >10, mucosa, glandular (G) | THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; 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:

GALT - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1503	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, THYROID : Small : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Vacuolation; minimal
LYMPH NODE, MESENTERIC : Hemorrhage; mild
NO CORRELATE : No correlating lesion [GLAND, THYROID : Small : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1504	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Tongue accidentally cut

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
PANCREAS : Atrophy; acinar, mild

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; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1505	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
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; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1506	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Infiltration, mononuclear cell; mild
LIVER : Vacuolation; minimal
LIVER : Infiltration, lymphocytic; 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; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; 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; UTERUS

Histo Pathology - The following Tissues were Not Examined:

LARGE INTESTINE, RECTUM - Not Present In Section.
URINARY BLADDER - Not Present In Section.
VAGINA - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1507	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1, left lobe (TGL)
SPLEEN : Constriction : 1 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EYE : Rosette; mild, retina
LIVER : Vacuolation; minimal
NO CORRELATE : No correlating lesion [SPLEEN : Constriction : 1 (G) | LUNG : Focus; dark : 1, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1508	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lung left lobe accidentally cut

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

No observations found

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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1509	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; 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, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; 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:

GLAND, PARATHYROID - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1510	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death: 30 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Ovary right submitted in 2 pieces
LIVER : Focus; pale : 1, fissure, right medial (TGL)
THYMUS : Focus; dark : 2, left lobe (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LIVER : Necrosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : 2, 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, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; 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:

GLAND, PARATHYROID - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal: 1511	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death: 43 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1512	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 43 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lymph node lesion submitted cass G
LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE : Discoloration; dark : Mediastinal (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE : Hemorrhage; mild [LYMPH NODE : Discoloration; dark : Mediastinal (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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1513	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 43 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, lymphocytic; 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; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal: 1514	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death: 43 (7)		

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

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, 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, QUADRICEPS; 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:

GLAND, PARATHYROID - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	1515	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death: 43 (7)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Brain accidentally cut
THYMUS : Focus; dark : >10, left lobe (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

THYMUS : Hemorrhage; 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; MUSCLE, QUADRICEPS; 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

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Epididymis left submitted in two pieces; Liver lesion submitted cass A.
LIVER : Focus; pale : 1, near hilus, right lateral. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral. (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : left (G)]
SITE, INJECTION : Hemorrhage; moderate
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : Left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
STOMACH : Focus; depressed : 2, dark, mucosa, glandular, adjacent to limiting ridge (TGL)
THYMUS : Focus; dark : 5, right lobe (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : left (G)]
NO CORRELATE : No correlating lesion [STOMACH : Focus; depressed : 2, dark, mucosa, glandular, adjacent to limiting ridge (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
THYMUS : Hemorrhage; mild [THYMUS : Focus; dark : 5, right lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SPLEEN; STOMACH

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 2, right caudal (TGL)
LYMPH NODE, INGUINAL : Focus; dark : >10, left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LUNG : Congestion; mild [LUNG : Focus; dark : 2, right caudal (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Focus; dark : >10, left (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:

LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Skin lesion submitted bag 1.
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SKIN : Scab; dark : 3, tail, base. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SKIN : Acanthosis; moderate
SKIN : Exudate; mild [SKIN : Scab; dark : 3, tail, base. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

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:

LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lymph node lesion submitted cass G
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 protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : iliac left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : GI adrenal right accidentally cut.
LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : Left (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:

LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Kidney right accidentally cut
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, POPLITEAL : Hyperplasia; lymphoid, mild [LYMPH NODE, POPLITEAL : Enlargement : bilateral (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left. (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left. (G) | SITE, INJECTION : Swelling : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
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:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LYMPH NODE : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
THYMUS : Focus; dark : >10, left lobe (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Necrosis; focal, minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : iliac left (G) | THYMUS : Focus; dark : >10, left lobe (G)]
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE; LYMPH NODE, INGUINAL; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
STOMACH : Focus; depressed : 2, dark, mucosa, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

SITE, INJECTION : Inflammation; minimal [SITE, INJECTION : Abnormal consistency; firm : left (G)]
STOMACH : Necrosis; mucosal, focal, mild [STOMACH : Focus; depressed : 2, dark, mucosa, glandular (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
STOMACH : Focus; dark : 4, mucosa, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Vacuolation; minimal
LYMPH NODE, INGUINAL : Hemorrhage; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
NO CORRELATE : No correlating lesion [STOMACH : Focus; dark : 4, mucosa, glandular (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

SPLEEN; STOMACH

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
STOMACH : Focus; dark : 3, mucosa, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

NO CORRELATE : No correlating lesion [STOMACH : Focus; dark : 3, mucosa, glandular (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

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; STOMACH

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE : Focus; dark : >10, mediastinal. (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE : Hemorrhage; minimal [LYMPH NODE : Focus; dark : >10, mediastinal. (G)]
LYMPH NODE, INGUINAL : Hemorrhage; minimal [LYMPH NODE, INGUINAL : Enlargement : left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Brain accidentally cut
LIVER : Focus; pale : 2, fissure, right medial (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
THYMUS : Focus; dark : >10,left lobe (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 2, fissure, right medial (G)]
LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : >10,left lobe (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

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 2, fissure, right medial (TGL)
LIVER : Mass; [a] : 8x6x4mm, dark,firm, medial lobe (TGL)
LYMPH NODE, POPLITEAL : Enlargement : bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LIVER : Necrosis; focal, minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : bilateral (G)]
NO CORRELATE : No correlating lesion [LIVER : Mass; [a] : 8x6x4mm, dark,firm, medial lobe (G) | LIVER : Focus; pale : 2, fissure, right medial (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

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
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 protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : iliac left (G)]
OVARY : Cyst; bursal [OVARY : Cyst; pale : 1, left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [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

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G; Kidney right accidentally cut.
LYMPH NODE : Enlargement : Iliac, left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : Iliac, 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

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : ID chip damaged ; Lymph node lesion submitted cass G
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : bilateral (G) | LYMPH NODE : Enlargement : iliac left (G)]

SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : Left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (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

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Brain accidentally cut
LIVER : Focus; pale : 2, near hilus, medial lobe (TGL)
LUNG : Focus; dark : 1 to 2, right lobes (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LIVER : Necrosis; focal, mild [LIVER : Focus; pale : 2, near hilus, medial lobe (G)]
LUNG : Congestion; mild [LUNG : Focus; dark : 1 to 2, right lobes (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
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:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Left (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:

None

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, INGUINAL - Not Present In Wet Tissues.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : lymph node lesion submitted cass G ; Gland adrenal left accidentally cut; Brain accidentally cut

LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE : Hyperplasia; lymphoid, moderate [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LYMPH NODE : Enlargement : Iliac, left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : Iliac, left (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:

LIVER; LYMPH NODE

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lymph node lesion submitted cass G
LUNG : Focus; dark : 1, edge, left (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LUNG : Congestion; mild [LUNG : Focus; dark : 1, edge, left (G)]
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : iliac left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LYMPH NODE : Enlargement : Iliac, left (TGL)
LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE : Hyperplasia; lymphoid, moderate [LYMPH NODE : Enlargement : Iliac, left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Left (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:

LIVER; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lymph node lesion submitted cass G
LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Necrosis; focal, minimal
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : left (G) | LYMPH NODE, POPLITEAL : Enlargement : bilateral (G) | LYMPH NODE : Enlargement : iliac 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

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
OVARY : Cyst; pale : 1, bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
THYMUS : Focus; dark : 3, right lobe (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : left (G) | LYMPH NODE : Enlargement : iliac left (G)]
OVARY : Cyst; bursal [OVARY : Cyst; pale : 1, bilateral (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; mild [THYMUS : Focus; dark : 3, right lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Discoloration; pale : cortex, bilateral (TGL)
LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
OVARY : Cyst; pale : 1, left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : left (G)]
NO CORRELATE : No correlating lesion [KIDNEY : Discoloration; pale : cortex, bilateral (G)]
OVARY : Cyst; bursal [OVARY : Cyst; pale : 1, 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

Histo Pathology - The following Tissues were Within Normal Limits:

KIDNEY; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G ; Liver lesion submitted cass A.
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)
STOMACH : Focus; dark : 7, mucosa, glandular (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G) | LYMPH NODE : Enlargement : iliac left (G) | STOMACH : Focus; dark : 7, mucosa, glandular (G) | THYMUS : Focus; dark : >10 (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

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE; LYMPH NODE, INGUINAL; STOMACH; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : urinary bladder submitted cass A
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
STOMACH : Focus; dark : 6, mucosa, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

NO CORRELATE : No correlating lesion [STOMACH : Focus; dark : 6, mucosa, glandular (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

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; STOMACH

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [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

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LYMPH NODE : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
STOMACH : Focus; pale : >10, mucosa, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : iliac left (G) | STOMACH : Focus; pale : >10, mucosa, glandular (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:

LYMPH NODE; LYMPH NODE, INGUINAL; STOMACH

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Kidney right accidentally cut longitudinally, therefore left cut transversally
LUNG : Focus; dark : 1, edge, right caudal (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
STOMACH : Focus; dark : 4, mucosa, glandular (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [STOMACH : Focus; dark : 4, mucosa, glandular (G) | LUNG : Focus; dark : 1, edge, right caudal (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

Histo Pathology - The following Tissues were Within Normal Limits:

LUNG; STOMACH

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : iliac 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

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, INGUINAL : Infiltration, mixed cell; mild
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [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

Histo Pathology - The following Tissues were Within Normal Limits:

None

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LARGE INTESTINE, RECTUM : Parasite : >10
LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Basophilia; tubular, minimal
LYMPH NODE, INGUINAL : Infiltration, mixed cell; minimal [LYMPH NODE, INGUINAL : Enlargement : Left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]

NO CORRELATE : No correlating lesion
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath
TESTIS : Multinucleated giant cells; 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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

Histo Pathology - The following Tissues were Not Examined:

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lymph node lesion submitted cass G ; Gland pituitary submitted in 2 pieces
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE : Focus; dark : >10, iliac left (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left. (TGL)
SITE, INJECTION : Swelling : left. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : left (G) | LYMPH NODE : Enlargement : iliac left (G) | LYMPH NODE : Focus; dark : >10, iliac 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

Histo Pathology - The following Tissues were Within Normal Limits:

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5002045 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G; Larynx accidentally cut.
LYMPH NODE : Enlargement : Iliac, left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Right (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)
SITE, INJECTION : Focus; dark : 1, left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Right (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : Iliac, left (G)]
SITE, INJECTION : Hemorrhage; moderate [SITE, INJECTION : Focus; dark : 1, left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, 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; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Skin lesion cranium submitted cass A, inguinal left submitted with injection site left

ESOPHAGUS : Nodule; [a] : 1, dark, firm, middle, wall, cut surface: material dark thick (TGL)
LARGE INTESTINE, RECTUM : Parasite : >10
LUNG : Focus; dark : 2, right caudal (TGL)
LYMPH NODE, INGUINAL : Enlargement : bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
SKIN : Scab; dark : 1 to 3, cranium right, inguinal left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

ESOPHAGUS : Hemorrhage; mild [ESOPHAGUS : Nodule; [a] : 1, dark, firm, middle, wall, cut surface: material dark thick (G)]
KIDNEY : Chronic progressive nephropathy; minimal
LUNG : Congestion; mild [LUNG : Focus; dark : 2, right caudal (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : bilateral (G) | LYMPH NODE, POPLITEAL : Enlargement : bilateral (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SKIN : Acanthosis; mild
SKIN : Exudate; mild [SKIN : Scab; dark : 1 to 3, cranium right, inguinal left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

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5002045 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; 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; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; 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; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Animal:	4105	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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Ureter lesion right submitted on cardboard cass E, left cass F; LN lesion iliac right submitted cass G, left cass H; Urinary bladder lesion calculus submitted vial 1 bag 1.

GLAND, PROSTATE : Small : Ventral (TGL)
KIDNEY : Dilatation; pelvis : Bilateral (TGL)
LUNG : Focus; dark : 1, right accessory (TGL)
LYMPH NODE : Enlargement : Iliac, bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
URETER : Dilatation : Bilateral (TGL)
URETER : Thick : Wall, bilateral (TGL)
URETER : Focus; dark : >10, wall, bilateral (TGL)
URINARY BLADDER : Dilatation (TGL)
URINARY BLADDER : Thick : Wall (TGL)
URINARY BLADDER : Focus; dark : >10, mucosa (TGL)
URINARY BLADDER : Calculus : >10, from 1mm to 7 mm in diameter, pale.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PROSTATE : Infiltration, lymphocytic; mild
KIDNEY : Dilatation; marked [KIDNEY : Dilatation; pelvis : Bilateral (G)]
LIVER : Necrosis; focal, mild
LYMPH NODE : Hyperplasia; lymphoid, moderate [LYMPH NODE : Enlargement : Iliac, bilateral (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [URETER : Dilatation : Bilateral (G) | URETER : Focus; dark : >10, wall, bilateral (G) | LUNG : Focus; dark : 1, right accessory (G) | GLAND, PROSTATE : Small : Ventral (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath
URETER : Infiltration, mixed cell; mild [URETER : Thick : Wall, bilateral (G)]

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology Observations [Correlation] (Continued):

URINARY BLADDER : Hemorrhage; mild [URINARY BLADDER : Focus; dark : >10, mucosa (G)]
URINARY BLADDER : Metaplasia, squamous; marked [URINARY BLADDER : Thick : Wall (G)]
URINARY BLADDER : Dilatation; mild [URINARY BLADDER : Dilatation (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Epididymis left accidentally cut
GLAND, THYROID : Small : left (TGL)
LIVER : Focus; pale : 4, dorsal, left lateral (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

NERVE, SCIATIC : Infiltration, mixed cell; perineurial, moderate
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 4, dorsal, left lateral (G) | GLAND, THYROID : Small : left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LUNG : Focus; dark : 4, right caudal (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

HEART : Infiltration, mixed cell; mild
LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 4, right caudal (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:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lymph node lesion submitted cass G; Brain accidentally cut.
LIVER : Focus; pale : 1, fissure, medial lobe (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, THYROID : Cyst
LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, fissure, medial lobe (G)]
LYMPH NODE, INGUINAL : Infiltration, mixed cell; mild [LYMPH NODE, INGUINAL : Enlargement : left (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : left (G) | LYMPH NODE : Enlargement : iliac 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

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1, right caudal, right accessory, left lobe (TGL)
LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)
SITE, INJECTION : Thick : Left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LUNG : Congestion; mild [LUNG : Focus; dark : 1, right caudal, right accessory, left lobe (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G) | SITE, INJECTION : Thick : Left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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:

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, POPLITEAL : Enlargement : bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PROSTATE : Infiltration, lymphocytic; mild
LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Vacuolation; minimal
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : bilateral (G)]
NO CORRELATE : No correlating lesion
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:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LARGE INTESTINE, RECTUM : Parasite : >10.

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Basophilia; tubular, minimal
LIVER : Infiltration, lymphocytic; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; 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:

GALT - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PITUITARY : Pars distalis examined
GLAND, PROSTATE : Infiltration, lymphocytic; mild
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral. (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; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, INGUINAL : Enlargement : Bilateral. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Bilateral. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PROSTATE : Infiltration, lymphocytic; minimal
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Bilateral. (G) | LYMPH NODE, POPLITEAL : Enlargement : Bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1, right cranial. (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Enlargement : Left. (G) | LUNG : Focus; dark : 1, right cranial. (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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LYMPH NODE, INGUINAL : Enlargement : Right. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, lymphocytic; minimal
LYMPH NODE, INGUINAL : Hemorrhage; mild
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : Right. (G) | 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; 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, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, right (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Vacuolation; minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, right (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G) | LYMPH NODE : Enlargement : iliac left (G)]
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; 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:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lymph node lesion submitted cass G
KIDNEY : Discoloration; pale : bilateral (TGL)
LIVER : Focus; pale : >10 (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EYE : Rosette; mild, retina
KIDNEY : Basophilia; tubular, minimal
LIVER : Vacuolation; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : >10 (G) | KIDNEY : Discoloration; pale : bilateral (G) | LYMPH NODE : Enlargement : iliac 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

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
GLAND, THYROID : Focus; dark : 1, left (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, THYROID : Hemorrhage; mild [GLAND, THYROID : Focus; dark : 1, left (G)]
KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Necrosis; focal, mild
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : left (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : iliac left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath

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; MUSCLE, QUADRICEPS; 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:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Chronic progressive nephropathy; minimal
LYMPH NODE, INGUINAL : Infiltration, mixed cell; mild
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : iliac left (G)]
SITE, INJECTION : Inflammation; moderate [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity; lymphoid, mild, periarteriolar lymphoid sheath

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; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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:

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Lymph node lesion submitted cass G
LYMPH NODE : Enlargement : mediastinal (TGL)
LYMPH NODE, POPLITEAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : left (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE : Enlargement : mediastinal (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
THYMUS : Hemorrhage; 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; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : Horn right of uterus accidentally cut
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Chronic progressive nephropathy; minimal
LIVER : Vacuolation; minimal
LYMPH NODE, INGUINAL : Infiltration, mixed cell; mild [LYMPH NODE, INGUINAL : Enlargement : left (G)]
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; minimal
SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : lymph node lesion submitted cass G
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)
THYMUS : Small (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Fatty change; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LIVER : Vacuolation; minimal
LYMPH NODE : Hyperplasia; lymphoid, moderate [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE : Infiltration, mixed cell; mild [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, INGUINAL : Infiltration, mixed cell; mild
LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [THYMUS : Small (G)]
PANCREAS : Atrophy; acinar, 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

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GENERAL OBSERVATIONS : LN lesion submitted cass G.
LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
LYMPH NODE, INGUINAL : Enlargement : bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
THYMUS : Focus; dark : 1, right lobe (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Infiltration, mononuclear cell; minimal
LIVER : Vacuolation; minimal
LYMPH NODE, INGUINAL : Hyperplasia; lymphoid, mild [LYMPH NODE, INGUINAL : Enlargement : bilateral (G)]

LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G) | LYMPH NODE : Enlargement : iliac 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; minimal [THYMUS : Focus; dark : 1, right lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, QUADRICEPS; 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

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : >10 (TGL)
LYMPH NODE, INGUINAL : Enlargement : left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : right (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
SITE, INJECTION : Thick : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, POPLITEAL : Infiltration, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : right (G)]

NO CORRELATE : No correlating lesion [LIVER : Focus; pale : >10 (G) | LYMPH NODE, INGUINAL : Enlargement : left (G)]

SITE, INJECTION : Inflammation; mild [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G) | SITE, INJECTION : Thick : left (G)]

SPLEEN : Decreased cellularity; lymphoid, minimal, periarteriolar lymphoid sheath

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; MUSCLE, QUADRICEPS; 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

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

HEART : Infiltration, mononuclear cell; minimal
LIVER : Infiltration, lymphocytic; 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; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

NERVE, OPTIC : One of a pair 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

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, 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

GLAND, MAMMARY - Not Present In Section.
SKIN - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Infiltration, mononuclear cell; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; 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, QUADRICEPS; 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:

GALT - Not Present In Section.

Appendix 17

5002045 - Individual Animal Data Gross and Histopathology Findings

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:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SITE, INJECTION : Infiltration, mononuclear cell; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; 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, QUADRICEPS; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 18

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PEER-REVIEW STATEMENT

Study Number: 5002045

Study Title: **A 1-Month (3 doses) Intramuscular Injection Toxicity Study of mRNA-1706 in Sprague-Dawley Rats with a 2-Week Recovery Period**.

EXPERIMENTAL DESIGN:

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animals Nos.			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	1001-1003, 1104, 1005-1010	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	4001-4004, 4105, 4006-4010	4501-4510	4011-4015	4511-4515

- = Not applicable

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, 1006, 1012, 1503, 4001, 4004, 4008, 4502, 4506, and 4509.
3. The following organs from all animals in all Groups were reviewed: Eyes (males only), Injection sites, Liver and Spleen.
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)
(b) (6)

Date : February 23 2017

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

Date : 28 FEB 2017