charles river

FINAL REPORT

Test Facility Study No. 5002033

A 1-month (3 doses) Study of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat with a 2-Week Recovery Period

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USA

TEST FACILITY:
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QUALITY ASSURANCE STATEMENT

Study Number: 5002033

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**
06-Apr-2017	Final Study Plan	10-Apr-2017	10-Apr-2017
10-Apr-2017	Study Schedule	10-Apr-2017	10-Apr-2017
19-Apr-2017	Addition of Study Plan to Provantis	19-Apr-2017	19-Apr-2017
19-Apr-2017	Dose Preparation	19-Apr-2017	19-Apr-2017
19-Apr-2017	Study Plan Amendment 1	19-Apr-2017	19-Apr-2017
21-Apr-2017	Draize Evaluation	28-Apr-2017	28-Apr-2017
05-May-2017	Study Plan Amendment 2	05-May-2017	05-May-2017
19-May-2017	Blood Collection	19-May-2017	19-May-2017
19-May-2017	Necropsy	19-May-2017	19-May-2017
24-May-2017	Tissue Trimming	24-May-2017	24-May-2017
28-Jun-2017	Study Plan Amendment 3	28-Jun-2017	28-Jun-2017
29-Jun-2017 - 10-Jul-2017	Data Review - Animal Care	11-Jul-2017	11-Jul-2017
29-Jun-2017 - 10-Jul-2017	Data Review - Formulations	11-Jul-2017	11-Jul-2017
29-Jun-2017 - 11-Jul-2017	Data Review - Technical Operations	11-Jul-2017	11-Jul-2017
29-Jun-2017 - 11-Jul-2017	Data Review - Technical Operations	11-Jul-2017	11-Jul-2017
29-Jun-2017 - 11-Jul-2017	Data Review - Shipping/Receiving	11-Jul-2017	11-Jul-2017
29-Jun-2017 - 11-Jul-2017	Data Review - Clinical Pathology	11-Jul-2017	11-Jul-2017
29-Jun-2017 - 11-Jul-2017	Data Review - Veterinary Services	11-Jul-2017	11-Jul-2017
29-Jun-2017 - 11-Jul-2017	Draft Report - Materials and Methods	11-Jul-2017	11-Jul-2017
29-Jun-2017 - 11-Jul-2017	Draft Phase Report - Ophthalmology	11-Jul-2017	11-Jul-2017
29-Jun-2017 - 11-Jul-2017	Report Preparation	11-Jul-2017	11-Jul-2017
04-Jul-2017 - 05-Jul-2017	Data Review - Analytical Chemistry	06-Jul-2017	06-Jul-2017
05-Jul-2017	Draft Phase Report - Dose Formulation Analysis	05-Jul-2017	05-Jul-2017
16-Aug-2017	Data Review - Bioanalysis & Immunology	17-Aug-2017	17-Aug-2017
16-Aug-2017	Final Phase Report - Immunology	17-Aug-2017	17-Aug-2017
06-Sep-2017 - 07-Sep-2017	Data Review - Necropsy	07-Sep-2017	07-Sep-2017
06-Sep-2017 - 07-Sep-2017	Data Review - Shipping/Receiving	07-Sep-2017	07-Sep-2017
06-Sep-2017 - 07-Sep-2017	Data Review - Histology	08-Sep-2017	08-Sep-2017
06-Sep-2017 - 07-Sep-2017	Report Preparation	07-Sep-2017	07-Sep-2017
07-Sep-2017	Draft Phase Report - Pathology	08-Sep-2017	08-Sep-2017

QUALITY ASSURANCE STATEMENT - Study Number: 5002033

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
25-Sep-2017	Study Plan Amendment 4	25-Sep-2017	25-Sep-2017
25-Sep-2017	Draft Report - Results	26-Sep-2017	26-Sep-2017
05-Oct-2017	Final Report	05-Oct-2017	05-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 Final Report has been reviewed to assure that it accurately describes the materials and methods, and that the reported results accurately reflect the raw data.

(b) (6)

(b) (6)

11 Oct 2017
Date

COMPLIANCE STATEMENT

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

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

Exceptions to GLPs included the following study elements:

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

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

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

(b) (6)

(b) (6)

Date: 11 Oct 2017

1. RESPONSIBLE PERSONNEL

1.1. Test Facility

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

1.2. Individual Scientists (IS) at Test Facility

Analytical Chemistry (Concentration and Particle size Analysis)	(b) (6) CR MTL, Senneville, QC
Ophthalmology	(b) (6) CR MTL, Senneville, QC
Biomarkers (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1)	(b) (6) CR MTL, Senneville, QC
Immunology (Purity Analysis)	(b) (6) CR MTL, Senneville, QC
Pathology	(b) (6) (b) (6) CR MTL, Senneville, QC

1.3. PIs at Sponsor-designated Test Site

ATA analysis	(b) (4), (b) (6)

2. SUMMARY

The objectives of this study were to determine the potential toxicity of mRNA-1653, when given by intramuscular injection for 1 month (3 doses) to Sprague Dawley rat and to evaluate the potential reversibility of any findings following a 2 week recovery period.

The study design was as follows:

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL)	Dose Concentration (µg/mL)	No. of Animals			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1653	10	200	50	10	10	-	-
3	mRNA-1653	50	200	250	10	10	-	-
4	mRNA-1653	150	200	750	10	10	5	5

[a] = 10/sex/groups 1 to 4 necropsied 1 day following the last dose.
[b] = The remaining 5/sex/groups 1 to 4 necropsied 2 weeks following the last dose.

The following parameters and endpoints were evaluated in this study: clinical observations consisting of twice daily examinations for mortality/moribundity and weekly detailed examinations; local irritation assessment 24- and 72-hour postdose on dosing days, weekly on non- dosing weeks and recovery period; weekly body weights and food consumption measurements; ophthalmic examinations prior to dose initiation and during Week 4; body temperature on Days 1 and 29 predose, 6 and 24 hours postdose; clinical pathology assessment (hematology, coagulation, and clinical chemistry) at termination; cytokine analysis (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) on Days 1, 15 and 29 at 6 hours postdose and on Day 43; Anti-Therapeutic Antibody (ATA) analysis for neutralizing antibodies prior to dose initiation and at study termination; gross necropsy findings, organ weights, and histopathologic examinations.

There were no mRNA-1653-related ophthalmic changes.

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

mRNA-1653-treated main study and recovery animals had significant detectable antibody responses against hMPV/A2 and PIV/3 strain of virus.

The primary mRNA-1653-related findings were related to local inflammation. The injection site inflammation generally occurred with a dose-related increased incidence/severity at 10, 50 and 150 µg/dose. Very slight to severe edema was noted at the injection site, following dosing of males and females (peaking 24 hours postdose and generally decreasing by 72 hours postdose). Although sporadic in occurrence, very slight to mild, and (on rare occasions) moderate to severe erythema was noted at each dose occasion but was only considered mRNA-1653-related at 150 µg/dose. Additionally, swelling (soft or firm) and localized skin redness was noted at the injection site following the second and occasionally present upon third dose at 150 µg/dose level. Macroscopically, at the injection site, observations of firmness and swelling were correlated with microscopic changes noted as minimal to marked mixed cell inflammation at ≥ 10 µg/dose. Microscopic changes at the injection site consisted of mostly neutrophils, but also including macrophages and lymphocytes present in connective and subcutaneous tissues. Edema, necrotic

debris, hemorrhage and/or rare degenerated myofibers were also occasionally present. The popliteal, inguinal and iliac lymph nodes of animals dosed at ≥ 10 µg/dose exhibited increased incidence and severity of minimal to moderate mixed cell inflammation was which correlated macroscopically with enlargement. Minimal to mild mixed cell inflammation was also noted in the sciatic nerve (also present in surrounding connective tissue) of animals at ≥ 10 µg/dose. The lymph nodes and sciatic nerve inflammatory changes were regarded as secondary to the injection site inflammation. mRNA-1653-related microscopic findings were still noted in the popliteal lymph node, injection site and sciatic nerve of recovery animals. The popliteal lymph node mixed cell inflammation occurred with a decreased incidence and severity indicating partial recovery. The sciatic nerve and injection site was characterized by mononuclear cell infiltration present in lower numbers compared to the mixed cell inflammation observed in the main study animals indicating a partial recovery. Clinical signs (i.e. edema, soft swelling, and erythema) observed at the injection site including gross pathology findings (firm abnormal consistency, swelling and thick) and inguinal and iliac lymph nodes enlargement were not present in the recovery study animals indicating complete recovery of those findings.

mRNA-1653-related systemic changes indicative of inflammation were observed in animals given ≥ 10 µg/dose and included minimally to mildly increased hematopoiesis of the myeloid lineage in the bone marrow. This change was considered a reactive response to the pronounced inflammation observed at the injection site. Additional systemic findings included increases in absolute and/or relative spleen weights in males at ≥ 50 µg/dose and females at ≥ 10 µg/dose without correlating histopathology, and minimal to mild decreased cellularity of the splenic periarteriolar lymphoid sheath often associated with an increase in macrophages in both sexes at all dose levels tested. Clinical pathology changes suggestive of inflammation were also observed in males and/or females given mRNA-1653 at all doses (unless noted otherwise) and included: minimal to marked increases in neutrophil, eosinophil and large unstained cell counts with concomitant increases in white blood cell counts, minimal decreases in lymphocyte counts and platelet counts starting at 10 µg/dose, minimal increases in activated partial thromboplastin time and mild increases in fibrinogen, starting at 10 µg/dose, minimal increases in globulin, minimal decreases in albumin, with concomitant decreases in A/G ratio. Minimal increases in body temperature postdose and increases in MCP-1, IP-10 and MIP-1α at 150 µg/dose were suggestive of inflammation. At the end of the 2-week recovery period, all aforementioned organ weight and microscopic observations were considered fully reversed. Clinical pathology parameters returned to normal levels for most recovery animals and were considered fully recovered.

In the liver, a minimal to mild hepatocellular vacuolation was noted in Reference and Test Item-dosed animals. Increased incidence and severity were noted at 150 µg/dose and considered mRNA-1653. Liver weights (relative to body weights) were higher in a statistically significant manner in females given 150 µg/dose without any microscopic correlations.

When compared to controls, following each dose, a tendency towards dose-dependent lower mean body weight gains was noted in males given ≥ 10 µg/dose and in females given ≥ 50 µg/dose; these changes were only cumulative at 150 µg/dose and associated with a slightly reduced food consumption at that dose. The body weight and food consumption changes were generally comparable or rebounded during the 2-week recovery period.

In conclusion, administration of mRNA-1653 by intramuscular injection for 1 month (3 doses) was clinically well tolerated (no mortality, no major decreases in body weight/food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to

150 µg/dose. Starting at 10 µg/dose, generally dose-dependent changes in clinical signs at the injection site, clinical pathology parameters, cytokines, consistent with an inflammatory response at the injection site, were noted. Dose-related target organ effects were limited to the injection site, the bone marrow, the inguinal, popliteal and/or ileac lymph nodes, the connective tissue surrounding the sciatic nerve, the spleen and the liver of animals given mRNA-1653. At the end of the 2-week recovery period, all changes were fully recovered with exception of the injection site, popliteal lymph node, and the connective tissue surrounding the sciatic nerve which were considered to be partially recovered.

3. INTRODUCTION

The objectives of this study were to determine the potential toxicity of mRNA-1653, when given by intramuscular injection for 1 month (3 doses) to Sprague Dawley rat and to evaluate the potential reversibility of any findings.

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

- OECD Guideline 407. *Repeated Dose 28-day Oral Toxicity Study in Rodents*.
- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S3a. *Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.
- ICH Harmonised Tripartite Guideline S8. *Notes for Guidance on Immunotoxicity Testing of Human Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, and *Guidelines for General Pharmacology Studies*, and *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.
- Appendix to Director General Notification, No. 12-Nousan-8147, 24 Nov 2000, Agricultural Production Bureau, Ministry of Agriculture, Forestry and Fisheries of Japan (JMAFF).

The Study Director signed the study plan on 05 Apr 2017, and dosing was initiated on 19 Apr 2017. The in-life phase of the study was completed on 01 Jun 2017. The experimental start date was 05 Apr 2017, and the experimental completion date will be the date the pathology report is signed. The study plan, the last amended study plan, and deviations are presented in Appendix 1.

4. MATERIALS AND METHODS

4.1. Test and Reference Items

4.1.1. Test Item

Identification:	mRNA-1653
Supplier:	Moderna Therapeutics, Inc.
Lot No.:	MTDP 17038
Concentration:	2.2 mg/mL
Expiration Date:	An end-of-use analysis of the bulk Test Item was performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	Off-white nanoparticle suspension
Storage Conditions:	Kept in a freezer set to maintain -20°C

4.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Supplier:	Gibco
Batch (Lot) Number:	1854892
Expiration Date:	30 Dec 2018
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

4.3. Test and Reference Item Characterization

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

4.4. Reserve Samples

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

4.5. Test and Reference Item Inventory and Disposition

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

4.6. Dose Formulation and Analysis

4.6.1. 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.

Any residual volumes were discarded. Details of the preparation and dispensing of the Reference Item have been retained in the Study Records.

4.6.2. 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. Stock vials were used only once.

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

4.6.3. 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	Concentration	Homogeneity	Sampling From
Day 1[b]	All groups	2 and 4[a] (see Appendix 1)	Preparation vessel
Day 29[b]	All groups	N/A	Preparation vessel

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

Samples to be analyzed were submitted as soon as possible following preparation.

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

4.6.3.1. Analytical Method

Analyses were performed by IEX-HPLC using a validated analytical procedure (CR MTL Study No. 1801997).

4.6.3.2. Concentration Analysis

Duplicate sets of samples (0.5 mL) for each sampling time point were sent to the analytical laboratory; the remaining samples were retained at the Test Facility as backup samples. Concentration results were considered acceptable if mean sample concentration results were within or equal to ± 15% of theoretical concentration. Each individual sample concentration result was considered acceptable if it was within or equal to ± 20%. After acceptance of the analytical results, backup samples were discarded.

4.6.3.3. Homogeneity Analysis

Duplicate sets of samples (0.5 mL) for each sampling time point were sent to the analytical laboratory; the remaining samples were retained at the Test Facility as backup samples. Homogeneity results were considered acceptable if the relative standard deviation of the mean value at each sampling location was ≤ 5%. After acceptance of the analytical results, backup samples were discarded.

4.6.3.4. Stability Analysis

No stability analysis was performed for concentration used on this study however end of use stability analysis on the bulk Test Item was performed at the end of the dosing period.

4.7. Test System

4.7.1. Receipt

On 05 Apr 2017, 110 Crl:CD(SD) Sprague-Dawley rats were received from Charles River Canada Inc., St. Constant, QC. At the initiation of dosing, the animals were 8 weeks old.

4.7.2. 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.

4.7.3. Animal Identification

At study assignment, each animal was identified using a subcutaneously implanted electronic identification chip.

4.7.4. Environmental Acclimation

An acclimation period of 14 or 15 days was allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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

Healthy 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 at extremes of body weight range were not assigned to groups.

No animals were replaced during this study.

The alternate animals were released from the study on Day 2. The disposition of all animals was documented in the study records.

4.7.6. Husbandry

4.7.6.1. 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. The room in which the animals were kept was documented in the study records.

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

4.7.6.2. Environmental Conditions

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

4.7.6.3. Food

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

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

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

4.7.6.4. Water

Municipal tap water after treatment by reverse osmosis and ultraviolet irradiation was freely available to each animal via an automatic watering system.

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

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

4.7.6.5. 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.

4.7.6.6. 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.

4.8. Experimental Design

Text Table 3
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL)	Dose Concentration (µg/mL)	Animal Numbers			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	1001-1010	1501-1510	1011-1015	1511-1515
2	mRNA-1653	10	200	50	2001-2010	2501-2510	-	-
3	mRNA-1653	50	200	250	3001-3010	3501-3510	-	-
4	mRNA-1653	150	200	750	4001-4010	4501-4510	4011-4015	4511-4515

[a] = 10/sex/groups 1 to 4 necropsied 1 day following the last dose.
[b] = The remaining 5/sex/groups 1 to 4 necropsied 2 weeks following the last dose.

4.8.1. Administration of Test Materials

The Test and Reference Items were administered to Groups 1 to 4 animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, and 29. The dose volume for each animal was constant. The volume for each dose was administered using a syringe/needle within the demarcated area. The injection site was alternated on each dosing occasion.

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

4.8.2. Justification of Route and Dose Levels

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

The doses selected were based upon tolerability data of various lipid nanoparticle formulations in rats, which were expected to drive toxicities observed. The mid and low dose levels were chosen based upon observed efficacy with this modified mRNA construct in a lipid nanoparticle formulation. Doses with this test material or similarly formulated material up to 1 mg/kg (sponsor internal data) were well-tolerated in rats.

4.9. In-life Procedures, Observations, and Measurements

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

4.9.1. Mortality/Moribundity Checks

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

4.9.2. Clinical Observations

4.9.2.1. Detailed Clinical Observations

A detailed clinical observation was performed weekly during the dosing and recovery periods, and at least every two weeks during the predosing period. The animals were removed from the cage during observation.

4.9.3. Local Irritation Assessment

All animals had the dose injection site examined for signs of erythema/edema on days of dosing; at least 24 and 72 hours post-dose (end of each group) and weekly when there is no dosing and during recovery period. Examinations were also performed following Day 29 dosing. No assessment was performed on main animals at 72 hours postdose as animals were sent to necropsy on Day 30. Observations were scored according to the Local Irritation Assessment scoring table as follows:

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

Any other abnormalities were recorded as they were observed.

4.9.4. Body Weights

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

4.9.5. Food Consumption

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

4.10. Ophthalmic Examinations

All animals were subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations once prestudy and again during Week 4 of dosing. The mydriatic used was 1% tropicamide.

4.11. Body Temperature

Body temperature was recorded via subcutaneous implanted transponder on Day 1 and Day 29 at predose, 6 and 24 hours post dose (end of each group). When body temperature was significantly above normal range (36.0°C to 38.0°C) the temperature was monitored daily until return to normal.

4.12. Laboratory Evaluations

4.12.1. Clinical Pathology

4.12.1.1. Sample Collection

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

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

Text Table 4
Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry
1 to 4[a]	Day 30	X	X	X
1 and 4	Day 43	X	X	X

X = Sample collected.
[a] Samples collected from those animals scheduled for euthanasia on Day 30.

4.12.1.2. Hematology

Blood samples were analyzed for the parameters specified in Text Table 5.

Text Table 5
Hematology Parameters

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

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

4.12.1.3. Coagulation

Blood samples 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	Prothrombin time
Fibrinogen	Sample Quality

4.12.1.4. Clinical Chemistry

Blood samples 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

4.12.2. Bone Marrow Smear Evaluation

Bone marrow smears were collected and prepared as described Section 4.14.9.

4.12.3. Cytokines Analysis

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

Text Table 8
Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	
Timepoints			**Sample Type**	
Day	**Hours**	**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 (processing)			CR SHB	CR SHB

X = Sample collected; N/A = not applicable
* The assay validation of IFN-α did not work appropriately and serum samples analysis was not conducted.

The samples for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 were analyzed by the Biomarkers department at CR MTL. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 was conducted using a qualified multiplex Luminex method (non-GLP). 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.

Any residual/retained samples were discarded prior to report finalization, following Study Director approval.

4.13. Anti-Therapeutic Antibody (ATA) Sample Collection, Processing, and Analysis

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

Samples 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). 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 (b) (4)

The samples were analyzed for rat anti-HMPV antibodies using a qualified neutralizing antibody assay method.

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

4.14. Terminal Procedures

Terminal procedures are summarized in Text Table 9.

Text Table 9
Terminal Procedures

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

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

4.14.1. Unscheduled Deaths

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

4.14.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia had a terminal body weight recorded, samples for clinical pathology, anti-therapeutic antibodies and cytokines were collected (as appropriate), and were euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. When possible, 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.

4.14.3. Necropsy

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

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

4.14.4. Organ Weights

The organs identified in Text Table 10 were weighed at necropsy for all scheduled euthanasia animals. Paired organs were weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ to body weight ratio (using the terminal body weight) and organ to brain weight ratios were calculated.

Text Table 10
Organs Weighed at Necropsy

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

[a] Paired organ weight.

4.14.5. 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

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

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

4.14.6. Histology

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

4.14.7. Histopathology

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

4.14.8. Peer Review

An on-site pathology peer review was conducted by (b) (6) from Moderna Therapeutics Cambridge, MA.

4.14.9. Bone Marrow Smear Analysis

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

5. CONSTRUCTED VARIABLES

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

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

6. STATISTICAL ANALYSIS

Numerical data collected on scheduled occasions for the listed variables were analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation were reported whenever possible. Inferential statistics were performed according to the matrix below when possible, but excluded semi-quantitative data, and any group with less than 3 observations.

Text Table 12
Statistical Matrix

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

The following pairwise comparisons were made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

6.1. Parametric/Non-Parametric

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

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

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

7. COMPUTERIZED SYSTEMS

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

Text Table 13
Critical Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	8	In-life; clinical pathology; postmortem
Dispense	8	Test Material receipt, accountability and/or formulation activities.
In-house reporting software Nevis 2012 (using SAS)	Nevis 2 (SAS 9.2)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
SRS (CR MTL in-house application built with SAS and SAS system for Windows)	1.4	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7.0 / 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
Dynamics (Wyatt)	7.1.9.3	Data acquisition for particle size analysis for the Test Item using DLS
(b) (4)	1.1.0.11	Test Item purity data acquisition
Bio Plex Manager (Bio-Rad)	Version 6.1	Cytokine data collection

8. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, documentation, study plan, samples, specimens, and final reports from this study were archived at the Test Facility by no later than the date of final report issue. At least one year after issue of the draft report, the Sponsor will be contacted.

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

All raw data and the final report (original) related to the ATA analysis will be retained at the Sponsor designated Test Site.

9. RESULTS

9.1. Dose Formulation Analyses

(Appendix 3)

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

9.2. End of Use Bulk Test Item Analysis

(Appendix 3 and Appendix 16)

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

9.3. Mortality

(Appendix 4)

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

9.4. Clinical Observations

(Table 1 and Appendix 5)

Following the second and/or third (last) dosing occasion, a dose-related (in severity; from slight to severe) firm swelling was noted on the injection site. Soft swelling (slight to moderate in severity) was also noted at the injection site of individual females given ≥ 50 µg/dose, following the second dose. In addition, skin redness at the injection site was noted in individual males and females given 150 µg/dose, following the last dose.

During the recovery period, firm swelling (slight) was still noted on Day 39 and redness, still noted for a few animals on Day 43, as such, these findings were considered partially reversed. Soft swelling was not observed during the 2-week recovery period.

9.5. Local Irritation Assessment

(Appendix 6)

Very slight to severe edema was noted at the injection site following dosing of males and females at ≥ 10 µg/dose. The incidence and severity of these findings were dose-dependent. The apex of severity was noted 24 hours postdose and generally decreased 72 hours postdose.

Sporadic, generally very slight to mild erythema, and on rare occasions, moderate to severe erythema, noted at the injection site, was considered mRNA-1653-related only at 150 µg/dose and occurred at a higher incidence and severity 72 hours postdose.

With the exception of one male, edema and erythema were no longer observed at the end of the recovery period, and as such, they were considered completely reversed.

9.6. Body Weights and Body Weight Gains

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

When compared to controls, following each dose, a tendency towards dose-dependent lower mean body weight gains was noted in males given ≥ 10 µg/dose and in females given ≥ 50 µg/dose; these changes sometimes reached statistical significance. The changes were only cumulative at 150 µg/dose; from Days -1 to 28, when compared to controls, the body weight changes were 0.85X for males and 0.79X, for females. The body weight changes were generally comparable or rebounded during the 2-week recovery period.

9.7. Food Consumption

(Table 4 and Appendix 9)

The weekly food consumption appeared slightly noticeably lower in animals given mRNA-1653, and, more consistently at 150 µg/dose. The food consumption changes were generally comparable or rebounded during the 2-week recovery period.

9.8. Ophthalmic Examinations

(Appendix 14)

There were no mRNA-1653-related ocular changes observed during the course of the study. The findings noted were age-related or incidental in origin and to be expected in this population of animals.

9.9. Body Temperature

(Table 5 and Appendix 10)

When compared to controls, the mean body temperature appeared minimally increased in males and females given ≥ 10 µg/dose, 6 and/or 24 hours post Day 1 and Day 29 doses. These generally statistically-significant changes were considered mRNA-1653-related.

9.10. Hematology

(Table 6 and Appendix 11)

mRNA-1653-related hematology changes were noted for males and females starting at 10 µg/dose and included increases in neutrophil (NEUT), eosinophil (EOS) and/or large unstained cell (LUC) counts (with concomitant increases in white blood cell [WBC] counts) and decreases in lymphocyte (LYMPH), platelet (PLT) and reticulocyte (RETIC) counts. These changes are illustrated in Text Table 14.

Text Table 14
Hematology Changes

Dose (µg/dose)	10		50		150	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
WBC						
Day 30	1.4	**1.6**	**1.9**	**1.7**	**2.0**	**1.6**
Day 43					1.0	1.0
NEUT						
Day 30	**5.7**	7.8	**11.2**	**13.0**	**12.6**	**14.0**
Day 43					1.1	1.2
LYMPH						
Day 30	0.8	-	**0.7**	**0.7**	**0.7**	**0.6**
Day 43					1.0	0.9
EOS						
Day 30	**2.8**	**3.2**	**3.4**	**4.6**	**4.3**	**3.9**
Day 43					1.0	1.2
LUC						
Day 30	**3.0**	1.7	**2.4**	1.3	1.7	1.2
Day 43					1.1	0.8
PLT						
Day 30	-	0.9	-	**0.9**	**-**	**0.7**
Day 43					-	1.0
RETIC						
Day 30	**0.8**	-	**0.7**	**-**	**0.7**	-
Day 43					**1.3**	-

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

Mild to moderate increases in WBC counts (up to 2.0X and 1.7X controls, respectively) were noted in males and females given ≥ 10 µg/dose, mainly due to minimal to marked increases in NEUT, LUC (up to 12.6X and 3.0X controls for males and 14.0X and 1.7X controls for females) and/or EOS (up to 4.3X controls for males and up to 4.6X controls for females). Minimal decreases in LYMPH counts were noted for males at ≥ 10 µg/dose and females at ≥ 50 µg/dose (down to 0.7X and 0.6X controls, respectively).

Minimal decreases in PLT were noted in females at ≥ 10 µg/dose (down to 0.7X controls).

Minimal decreases in RETIC were noted in males at ≥ 10 µg/dose (down to 0.7X controls).

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

Any other differences in hematology parameters, including those attaining statistical significance, were judged to be due to individual or biological variation or lacked true dose relationship and therefore were considered not mRNA-1653-related.

9.11. Coagulation

(Table 7 and Appendix 12)

mRNA-1653-related increases in activated partial thromboplastin time (APTT) and in fibrinogen (FIB) were noted in males and females starting at 10 µg/dose. The changes are illustrated in Text Table 15.

Text Table 15
Coagulation Changes

Dose (µg/dose)	10		50		150	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
APTT						
Day 30	-	1.1	**1.1**	**1.1**	**1.2**	**1.3**
Day 43					1.0	1.1
FIB						
Day 30	**2.0**	**1.6**	**2.1**	**2.1**	**2.3**	**2.2**
Day 43					0.9	1.1

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

Minimal increases in APTT were noted for males given ≥ 50 µg/dose and females given ≥ 10 µg/dose (up to 1.2X controls for males and 1.3X controls for females). Mild increases in FIB were noted for males and females given ≥ 10 µg/dose (up to 2.3X controls for males and up to 2.2X controls for females. At the end of the 2-week recovery period, changes were near to fully recovered.

Any other differences in the coagulation parameters were judged to be due to individual or biological variability or lacked true dose relationship and therefore were considered not mRNA-1653-related.

9.12. Clinical Chemistry

(Table 8 and Appendix 13)

mRNA-1653-related decreases in albumin (ALB) and increases in globulin (GLOB) were noted for males and females; these changes were reflected by overall decrease in A/G ratio. The changes are illustrated in Text Table 16.

Text Table 16
Clinical Chemistry Changes

Dose (µg/dose)	10		50		150	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
ALB						
Day 30	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**
Day 43					1.0	**0.9**
GLOB						
Day 30	**1.3**	**1.2**	**1.4**	**1.2**	**1.4**	**1.3**
Day 43					1.0	**1.2**
A/G						
Day 30	**0.7**	**0.8**	**0.6**	**0.7**	**0.6**	**0.7**
Day 43					**0.9**	**0.9**

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

Minimal decreases in ALB and minimal increases in GLOB were noted for males and females given ≥ 10 µg/dose (0.9X controls and up to 1.4X controls for each parameter) and affected the A/G ratio (down to 0.6X controls in males and down to 0.7X controls in females). At the end of the 2-week recovery period, changes were near to fully recovered.

Any other differences in the clinical chemistry parameters, including those attaining statistical significance, were judged to be due to individual or biological variability or lacked true dose relationship and therefore were considered not mRNA-1653-related.

9.13. Cytokines

(Appendix 15)

When compared to controls, mRNA-1653-related increases in MCP-1 and IP-10 were observed at 150 µg/dose on Days 1, 15 and 29, 6 hours postdose. The magnitude of increases observed were higher for IP-10, ranging from 5.2 to 10.4X for males, and from 7.0 to 17.5X for females, and were apparent for all animals at all dosing timepoints. The increases in MCP-1 were observed for all animals at almost all dosing timepoints, but the magnitude of increases was lower, ranging from 1.2 to 3X for males and from 1.2 to 6.4X for females. Following the 2-week recovery period (i.e. Day 43), the level of both MCP-1 and IP-10 were back to the normal range values for all animals.

mRNA-1653-related slight increases in MIP-1α were observed on Days 1 and 15, 6 hours postdose, for some animals, at a similar incidence and magnitude in both genders given 150 µg/dose. Such increases were not observed on Day 29, 6 hours postdose and at the recovery timepoint (i.e. Day 43). These increases were considered to be related due to similar incidence, magnitude and pattern observed in the mRNA-1653 dosed group.

No mRNA-1653 changes were observed in IL-1β, TNF-α and IL-6.

9.14. Anti-Therapeutic Antibody (ATA)

(Appendix 17)

The Day 30 samples from mRNA-1653-treated Main Study animals had detectable antibody responses against hMPV/A2 and PIV/3 strain of virus. The Day 43 samples from Recovery Study animals previously given 150 µg/dose had higher antibody titers compared to Day 30 titers, indicative of the booster effect on Day 30.

9.15. Gross Pathology

(Appendix 18)

9.15.1. Terminal Necropsy (Day 30)

Gross pathology findings related to mRNA-1653 were seen in the injection site and the popliteal lymph node and are summarized in Text Table 17.

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

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**150**	**0**	**10**	**50**	**150**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Injection Site (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency; firm	0	8	10	9	0	6	10	10
Swelling	0	4	6	10	0	1	6	9
Thick	0	0	0	3	0	0	1	1
Popliteal Lymph Node (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	4	1	0	0	1	3
Lymph Node, Inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	1	1	3	0	0	0	3
Lymph Node[a] (No. Examined)	0	1	1	3	0	0	2	4
Enlargement	0	1	1	3	0	0	2	4

a: Iliac lymph node

At the injection site, firm abnormal consistency, swelling and/or thick was observed in both sexes at 10, 50 and/or 150 µg/dose. Swelling occurred with a dose-related increased incidence. These injection site changes correlated microscopically with mixed cell inflammation.

In the lymph nodes (popliteal, inguinal and iliac), enlargement occurred in both sexes at 10, 50 and/or 150 µg/dose. Enlargement correlated microscopically with perinodal mixed cell inflammation.

Other gross findings observed were considered incidental, of the nature observed in this strain and age of rats, and/or were of similar incidence in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1653-related.

9.15.2. Recovery Necropsy (Day 43)

(Appendix 18)

Following the 2-week recovery period, the mRNA-1653-related popliteal lymph node enlargement observed at the terminal necropsy was still present in females at 150 µg/dose and are summarized in Text Table 18. Other mRNA-1653-related gross findings observed at the terminal necropsy at the injection site (firm abnormal consistency, swelling and thick) and in the inguinal and iliac lymph nodes (enlargement) were not observed in recovery animals.

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

	Males		Females	
Group	**1**	**4**	**1**	**4**
Dose (µg/dose)	**0**	**150**	**0**	**150**
No. Animals Examined	**5**	**5**	**5**	**5**
Popliteal Lymph Node (No. Examined)	5	5	5	5
Enlargement	0	0	0	2

Other gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1653-related.

9.16. Organ Weights

(Appendix 18)

9.16.1. Terminal Necropsy (Day 30)

The organ weight changes related to mRNA-1653 were increases in liver and spleen weights, and are summarized in Text Table 19.

Text Table 19
Summary of Organ Weight Data – Terminal Necropsy (Day 30)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**10**	**50**	**150**	**10**	**50**	**150**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Terminal Body Weight	-6.0	-5.2	**-10.4**	-1.0	-4.2	-6.0
Liver (No. Weighed)[a]	10	10	10	10	10	10
Absolute value	-	-	-	0.47	-1.69	2.72
% of body weight	-	-	-	1.71	2.40	**9.34**
% of brain weight	-	-	-	-2.08	-0.97	2.68
Spleen (No. Weighed)	10	10	10	10	10	10
Absolute value	3.65	15.17	14.79	**24.86**	**31.14**	**21.37**
% of body weight	10.27	**21.80**	**27.58**	**26.40**	**37.21**	**28.66**
% of brain weight	1.96	15.35	15.47	**21.44**	**32.18**	**21.17**

[a] All values expressed as percent difference of control (Group 1) means.
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – $P \leq 0.05$; refer to data tables for actual significance levels and tests used.
- = Not Test Item-related

Liver weights (relative to body weights) were higher in a statistically significant manner in females given150 µg/dose. The higher liver weights had no microscopic correlations.

Statistically-significant higher (absolute and/or relative to body and/or brain weights) spleen weights occurred in males given ≥ 50 µg/dose and females given ≥ 10 µg/dose. These spleen weight changes had no microscopic correlation.

There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or secondary to the lower terminal body weight, and therefore, not mRNA-1653-related.

9.16.2. Recovery Necropsy (Day 43)

Following the 2-week recovery period, mRNA-1653-related higher liver weight changes observed for Main Study animals were still present in females at 150 µg/dose; these changes had no microscopic correlations. These liver weight changes are summarized in Text Table 20. The higher spleen weights observed for Main Study animals were not present in recovery animals.

Text Table 20
Summary of Organ Weight Data – Recovery Necropsy (Day 43)

	Males	Females
Group	**4**	**4**
Dose (µg/dose)	**150**	**150**
No. Animals per Group	**5**	**5**
Terminal Body Weight	-2.0	-4.4
Liver (No. Weighed)[a]	5	5
Absolute value	-	8.62
% of body weight	-	**13.45**
% of brain weight	-	6.93

[a] All values expressed as percent difference of control (Group 1) means.
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – P ≤ 0.05; refer to data tables for actual significance levels and tests used.
- = Not Test Item-related

There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or secondary to the lower terminal body weight, and therefore, not mRNA-1653-related.

9.17. Histopathology

(Appendix 18)

9.17.1. Terminal Necropsy (Day 30)

mRNA-1653-related microscopic changes were noted at the injection site, liver, bone marrow, spleen, lymph nodes (popliteal, inguinal and iliac) and sciatic nerve which are summarized in Text Table 21.

Text Table 21
Summary of Microscopic Findings – Terminal Necropsy (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**150**	**0**	**10**	**50**	**150**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Injection Site (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(1)[a]	(10)	(10)	(10)	(3)	(9)	(10)	(10)
Minimal	1	1	-	-	2	1	-	-
Mild	-	1	1	-	1	4	-	-
Moderate	-	8	5	5	-	4	6	5
Marked	-	-	4	5	-	-	4	5
Liver (No. Examined)	10	10	10	10	10	10	10	10
Vacuolation, hepatocellular	(1)	(1)	(2)	(7)	(2)	(1)	(2)	(9)
Minimal	1	1	2	3	2	1	2	5
Mild	-	-	-	4	-	-	-	4
Bone Marrow (No. Examined)	10	10	10	10	10	10	10	10
Increased hematopoiesis: myeloid	0	10	10	10	0	10	10	10
Minimal	-	10	7	3	-	10	8	5
Mild	-	-	3	7	-	-	2	5
Popliteal Lymph Node (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(0)	(9)	(8)	(10)	(0)	(10)	(9)	(9)
Minimal	-	1	3	2	-	3	1	4
Mild	-	8	5	7	-	7	6	3
Moderate	-	-	-	1	-	-	2	2
Inguinal Lymph Node (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(0)	(2)	(1)	(4)	(0)	(0)	(0)	(6)
Minimal	-	2	1	3	-	-	-	2
Mild	-	-	-	1	-	-	-	4
Lymph Node[b] (No. Examined)	0	1	1	3	0	0	2	4
Inflammation, mixed cell	(0)	(1)	(1)	(2)	(0)	(0)	(2)	(4)
Minimal	-	1	1	1	-	-	1	-
Mild	-	-	-	1	-	-	1	4
Sciatic Nerve (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(0)	(9)	(10)	(10)	(0)	(10)	(10)	(7)
Minimal	-	8	9	9	-	9	9	6
Mild	-	1	1	1	-	1	1	1
Spleen (No. Examined)	10	10	10	10	10	10	10	10
Decreased cellularity; periarteriolar lymphoid sheath	(0)	(2)	(4)	(7)	(0)	(1)	(2)	(7)
Minimal	-	2	4	3	-	1	2	6
Mild	-	-	-	4	-	-	-	1
Increased macrophages; periarteriolar lymphoid sheath	(0)	(0)	(3)	(5)	(0)	(0)	(2)	(7)
Minimal	-	-	3	5	-	-	2	7

[a] Numbers in parentheses represent the number of animals with the finding.
[b] Iliac lymph node

At the injection site, there was a minimal to marked mixed cell inflammation in both sexes given Reference and Test items. The exacerbation of the mixed cell inflammation was considered mRNA-1653-related at ≥ 10 µg/dose, based on the increased incidence and severity compared to controls. The change occurred with an apparent dose-related increase in severity and was characterized by an infiltration of mostly neutrophils but also macrophages and lymphocytes in the intramuscular connective tissue and subcutis; edema, necrotic debris, hemorrhage and/or rare

degenerated myofibers were also present. The injection site mixed cell inflammation correlated macroscopically with firm abnormal consistency, swelling and/or thick.

In the lymph nodes (popliteal, inguinal and/or iliac), minimal to moderate perinodal mixed cell inflammation was seen in both sexes at ≥ 10 µg/dose. Mixed cell inflammation occurred generally with an increased incidence and severity in the popliteal lymph node. The lymph node inflammation correlated macroscopically with enlargement. Minimal to mild mixed cell inflammation was also noted in the sciatic nerve of animals at ≥ 10 µg/dose in connective tissue surrounding the nerve. The lymph nodes and sciatic nerve inflammatory changes were regarded as secondary to the injection site inflammation.

In the liver, there was minimal to mild hepatocellular vacuolation in both sexes given the Reference and Test Items. The increased incidence and severity observed at 150 µg/dose was considered mRNA-1653-related; it consisted of the presence of intracytoplasmic microvesicles with enlarged hepatocytes.

In the bone marrow, there was minimal to mild increased hematopoiesis of the myeloid lineage in both sexes at ≥ 10 µg/dose; this change was likely a reactive response to the inflammation observed at the injection site.

In the spleen, there was minimal to mild decreased cellularity of the periarteriolar lymphoid sheath often associated with an increase in macrophages in both sexes at 10, 50 and/or 150 µg/dose.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1653-related.

9.17.2. Recovery Necropsy (Day 43)

Following the 2-week recovery period, mRNA-1653-related microscopic changes were mixed cell inflammation around the popliteal lymph node and mononuclear cell infiltration around the sciatic nerve and at the injection site. The popliteal lymph node mixed cell inflammation occurred with a decreased incidence and/or severity indicating partial recovery. The sciatic nerve and injection site mononuclear cell infiltration had a low number of cells compared to the mixed cell inflammation observed in Main Study animals, indicating partial recovery. The incidence of these microscopic findings is presented in Text Table 22. Other mRNA-1653-related microscopic findings observed in Main Study animals in the liver (hepatocellular vacuolation), inguinal and iliac lymph nodes (mixed cell inflammation), bone marrow (increased hematopoiesis, myeloid) and spleen (decreased cellularity and increased macrophages in the periarteriolar lymphoid sheath) were not present following the 2-week recovery period, indicating reversibility.

Text Table 22
Summary of Microscopic Findings – Recovery Necropsy (Day 43)

	Males		Females	
Group	**1**	**4**	**1**	**4**
Dose (µg/dose)	**0**	**150**	**0**	**150**
No. Animals Examined	**5**	**5**	**5**	**5**
Injection Site (No. Examined)	5	5	5	5
Infiltration, mononuclear cell	(0)[a]	(5)	(0)	(5)
Minimal	-	4	-	5
Mild	-	1	-	-
Popliteal Lymph Node (No. Examined)	5	5	5	5
Inflammation, mixed cell	(0)	(3)	(0)	(5)
Minimal	-	3	-	5
Nerve, sciatic (No. Examined)	5	5	5	5
Infiltration, mononuclear cell	(0)	(5)	(0)	(4)
Minimal	-	5	-	4

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

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1653-related.

10. CONCLUSION

In conclusion, administration of mRNA-1653 by intramuscular injection for 1 month (3 doses) was clinically well tolerated (no mortality, no major decreases in body weight/food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 150 µg/dose. Starting at 10 µg/dose, generally dose-dependent changes in clinical signs at the injection site, clinical pathology parameters, cytokines, consistent with an inflammatory response at the injection site, were noted. Dose-related target organ effects were limited to the injection site, the bone marrow, the inguinal, popliteal and/or ileac lymph nodes, the connective tissue surrounding the sciatic nerve, the spleen and the liver of animals given mRNA-1653. At the end of the 2-week recovery period, all changes were fully recovered with exception of the injection site, popliteal lymph node, and the connective tissue surrounding the sciatic nerve which were considered to be partially recovered.

Figure 1

Summary of Body Weights - Males

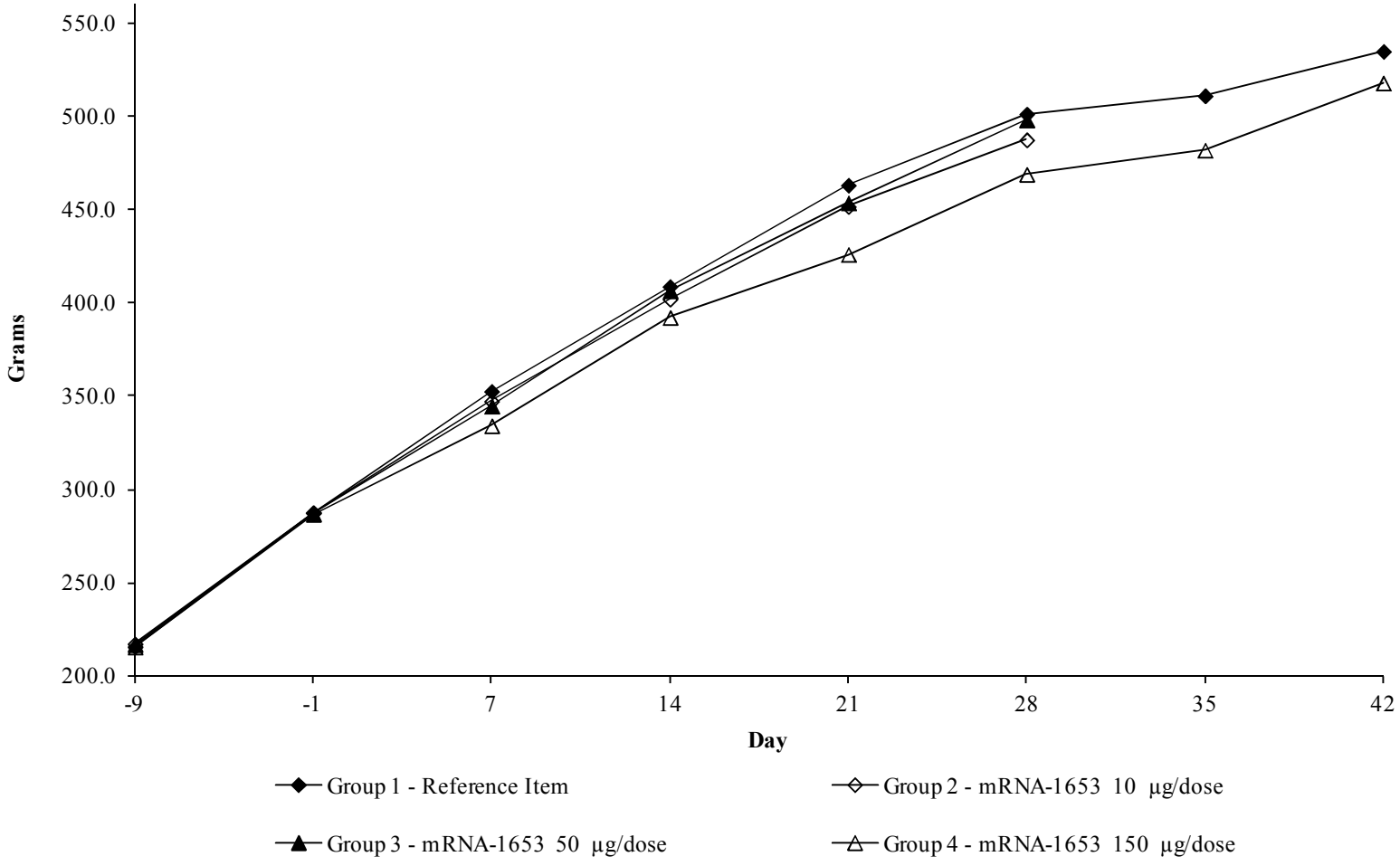

Figure 2

Summary of Body Weights - Females

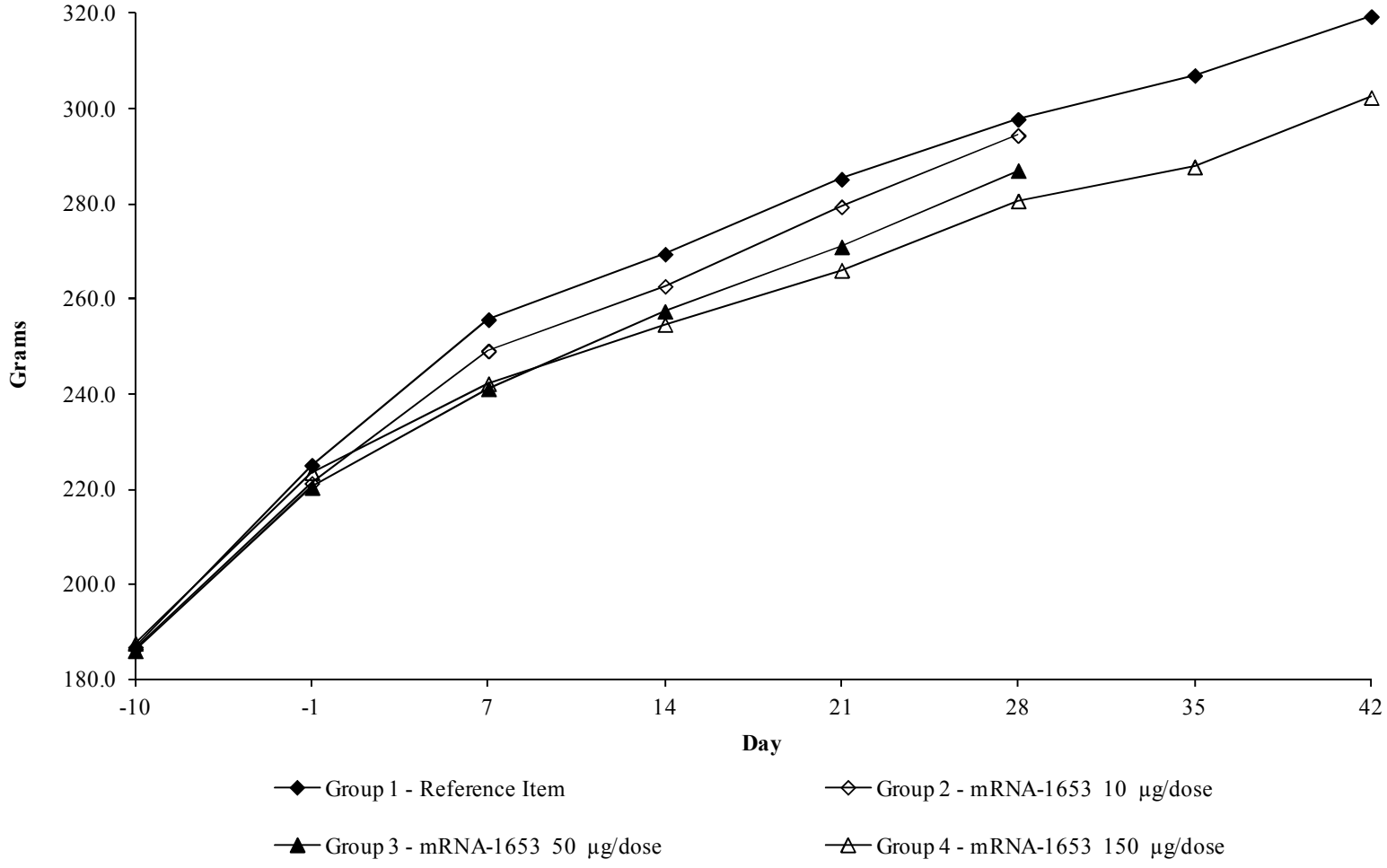

Table 1

Summary of Clinical Observations

5002033

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	10 ug/dose	50 ug/dose	150 ug/dose
Hunched Posture				
Number of Observations	.	.	.	2
Number of Animals	.	.	.	2
Days from - to	.	.	.	30 30
Swollen Firm				
Number of Observations	2	10	10	19
Number of Animals	1	10	10	15
Days from - to	32 39	30 30	30 30	30 39
Skin, Red				
Number of Observations	.	.	.	9
Number of Animals	.	.	.	5
Days from - to	.	.	.	30 43
Skin, Lesion				
Number of Observations	.	1	.	.
Number of Animals	.	1	.	.
Days from - to	.	-4 -4	.	.
Skin, Lesion w/ Discharge				
Number of Observations	.	1	.	.
Number of Animals	.	1	.	.
Days from - to	.	2 2	.	.
Skin, Scab				
Number of Observations	9	1	3	9
Number of Animals	4	1	2	6
Days from - to	-4 30	4 4	-4 30	11 30
Fur, Erected				
Number of Observations	.	.	.	2
Number of Animals	.	.	.	2
Days from - to	.	.	.	30 30

Table 1

Summary of Clinical Observations

5002033

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	10 ug/dose	50 ug/dose	150 ug/dose
Fur, Staining, Red				
Number of Observations	3	5	4	2
Number of Animals	1	3	4	2
Days from - to	-4 11	-4 30	30 30	30 30
Fur, Thin Cover				
Number of Observations	10	6	3	6
Number of Animals	2	2	2	3
Days from - to	-4 39	-4 11	25 30	11 39
Malocclusion				
Number of Observations	.	3	.	.
Number of Animals	.	1	.	.
Days from - to	.	18 30	.	.
Tail, Bent				
Number of Observations	.	3	.	.
Number of Animals	.	1	.	.
Days from - to	.	18 30	.	.

Table 1

Summary of Clinical Observations

5002033

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	10 ug/dose	50 ug/dose	150 ug/dose
Abnormal Gait				
Number of Observations	.	.	6	.
Number of Animals	.	.	1	.
Days from - to	.	.	16 25	.
Activity Decreased				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	2 2
Teeth Grinding				
Number of Observations	.	.	5	.
Number of Animals	.	.	1	.
Days from - to	.	.	17 25	.
Uncoordinated				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	16 16	.
Hunched Posture				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	2 2
Limited Usage				
Number of Observations	.	.	5	.
Number of Animals	.	.	1	.
Days from - to	.	.	16 25	.
Post Puncture Swelling				
Number of Observations	2	.	.	.
Number of Animals	1	.	.	.
Days from - to	18 25	.	.	.

Table 1

Summary of Clinical Observations

5002033

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	10 ug/dose	50 ug/dose	150 ug/dose
Swollen Soft				
Number of Observations	.	.	8	3
Number of Animals	.	.	3	3
Days from - to	.	.	16 25	18 18
Swollen Firm				
Number of Observations	.	10	17	31
Number of Animals	.	10	10	15
Days from - to	.	30 30	16 30	18 39
Skin, Brown				
Number of Observations	.	.	3	.
Number of Animals	.	.	1	.
Days from - to	.	.	16 18	.
Skin, Red				
Number of Observations	11	3	7	12
Number of Animals	3	3	2	8
Days from - to	4 39	4 25	16 30	18 39
Skin, Lesion				
Number of Observations	.	.	2	.
Number of Animals	.	.	1	.
Days from - to	.	.	17 18	.
Skin, Scab				
Number of Observations	5	.	8	4
Number of Animals	3	.	2	4
Days from - to	-4 30	.	16 30	18 30
Fur, Erected				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	2 2

Table 1

Summary of Clinical Observations

5002033

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	10 ug/dose	50 ug/dose	150 ug/dose
Fur, Staining, Red				
Number of Observations	9	2	4	2
Number of Animals	5	1	2	1
Days from - to	-4 39	25 30	16 30	25 30
Fur, Thin Cover				
Number of Observations	6	.	4	8
Number of Animals	3	.	3	5
Days from - to	4 30	.	4 30	18 39
Skin Staining				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	-4 -4	.	.	.
Teeth, Clear				
Number of Observations	.	1	.	2
Number of Animals	.	1	.	2
Days from - to	.	30 30	.	30 30

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		Day -9	-1	7	14	21	28	35	42
1M	Mean	215.67	287.67	352.67	408.87	463.20	501.33	511.20	535.00
	SD	11.00	15.31	21.25	27.77	33.85	38.08	30.95	35.16
	N	15	15	15	15	15	15	5	5
2M	Mean	217.30	287.50	347.30	402.20	451.90	487.60	--	--
	SD	7.35	9.25	15.34	21.45	29.12	36.44	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	0.76	-0.06	-1.52	-1.63	-2.44	-2.74	--	--
3M	Mean	217.00	287.10	344.70	406.50	453.70	498.10	--	--
	SD	7.99	13.62	23.13	32.54	42.48	48.17	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	0.62	-0.20	-2.26	-0.58	-2.05	-0.64	--	--
4M	Mean	215.67	286.73	334.27	392.33	426.07b	469.07	482.00	518.00
	SD	10.61	12.75	15.66	17.55	18.80	21.58	29.57	33.32
	N	15	15	15	15	15	15	5	5
	%Diff G1	0.00	-0.32	-5.22	-4.04	-8.02	-6.44	-5.71	-3.18

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

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		Day -10	-1	7	14	21	28	35	42
1F	Mean	186.87	225.07	255.67	269.47	285.20	297.80	307.00	319.40
	SD	7.54	10.75	11.90	11.01	13.01	11.62	9.67	10.92
	N	15	15	15	15	15	15	5	5
2F	Mean	186.50	221.30	249.10	262.70	279.40	294.40	--	--
	SD	4.17	11.48	15.93	17.63	18.54	23.46	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	-0.20	-1.67	-2.57	-2.51	-2.03	-1.14	--	--
3F	Mean	186.10	220.40	241.10a	257.40	271.00	287.00	--	--
	SD	4.65	6.62	9.49	12.95	16.97	21.90	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	-0.41	-2.07	-5.70	-4.48	-4.98	-3.63	--	--
4F	Mean	187.67	223.53	242.20a	254.67a	266.07b	280.67	287.80	302.40
	SD	7.03	11.51	13.42	12.27	13.39	16.59	26.20	25.34
	N	15	15	15	15	15	15	5	5
	%Diff G1	0.43	-0.68	-5.27	-5.49	-6.71	-5.75	-6.25	-5.32

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-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	72.00	65.00	56.20	54.33	38.13	213.67	37.20
	SD	7.34	8.12	8.38	8.03	8.37	28.78	6.65
	N	15	15	15	15	15	15	5
2M	Mean	70.20	59.80	54.90	49.70	35.70	200.10	--
	SD	7.04	9.73	9.24	8.83	9.33	33.08	--
	N	10	10	10	10	10	10	--
3M	Mean	70.10	57.60	61.80	47.20	44.40	211.00	--
	SD	9.55	12.49	9.99	12.01	8.40	38.25	--
	N	10	10	10	10	10	10	--
4M	Mean	71.07	47.53c	58.07	33.73f	43.00	182.33a	21.40h
	SD	6.68	5.13	5.09	4.20	6.11	13.32	5.37
	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)
g=p≤0.05,h=p≤0.01,i=p≤0.001 (T-test)

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		Day Change 35 - 42	Day Change 28 - 42
1M	Mean	23.80	61.00
	SD	10.18	13.32
	N	5	5
2M	Mean	--	--
	SD	--	--
	N	--	--
3M	Mean	--	--
	SD	--	--
	N	--	--
4M	Mean	36.00a	57.40
	SD	5.87	9.42
	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-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	38.20	30.60	13.80	15.73	12.60	72.73	8.80
	SD	6.39	2.82	4.41	5.06	5.18	5.31	5.26
	N	15	15	15	15	15	15	5
2F	Mean	34.80	27.80	13.60	16.70	15.00	73.10	--
	SD	9.58	7.91	3.69	3.20	7.80	15.99	--
	N	10	10	10	10	10	10	--
3F	Mean	34.30	20.70b	16.30	13.60	16.00	66.60	--
	SD	6.20	4.57	6.06	9.65	8.77	19.10	--
	N	10	10	10	10	10	10	--
4F	Mean	35.87	18.67c	12.47	11.40	14.60	57.13c	7.20
	SD	7.36	5.96	5.63	5.87	5.51	10.80	6.38
	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)

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		Day Change 35 - 42	Day Change 28 - 42
1F	Mean	12.40	21.20
	SD	5.94	5.76
	N	5	5
2F	Mean	--	--
	SD	--	--
	N	--	--
3F	Mean	--	--
	SD	--	--
	N	--	--
4F	Mean	14.60	21.80
	SD	8.20	3.11
	N	5	5

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		Day (From/To)						
		-7/1	1/8	8/15	15/22	22/29	29/36	36/42
1M	Mean	30.93	33.55	34.37	35.72	36.81	33.16	32.32
	SD	1.69	2.23	2.05	2.56	2.73	2.96	1.81
	N	15	15	15	15	15	5	5
2M	Mean	30.74	32.11	33.91	33.41	35.89	--	--
	SD	0.87	0.89	1.56	1.81	1.77	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	-0.62	-4.28	-1.33	-6.47	-2.51	--	--
3M	Mean	30.77	31.75	35.60	34.48	37.64	--	--
	SD	1.81	2.09	3.11	2.73	2.93	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	-0.53	-5.36	3.59	-3.47	2.25	--	--
4M	Mean	30.49	29.21	34.25	31.67	35.25	30.64	34.18
	SD	0.45	1.14	1.48	1.82	1.14	0.49	0.16
	N	15	15	15	15	15	5	5
	%Diff G1	-1.42	-12.94	-0.35	-11.33	-4.26	-7.60	5.75

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		Day (From/To)						
		-7/1	1/8	8/15	15/22	22/29	29/36	36/42
1F	Mean	21.63	23.08	25.52	22.99	23.63	22.66	22.42
	SD	1.01	1.21	4.80	0.93	1.48	0.77	0.71
	N	15	15	15	15	15	5	5
2F	Mean	21.20	22.60	23.23	23.00	23.70	--	--
	SD	1.69	1.19	1.62	1.21	1.91	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	-1.97	-2.08	-8.97	0.03	0.28	--	--
3F	Mean	20.81	21.45	22.09	21.63	22.36	--	--
	SD	0.70	0.66	1.38	1.89	2.59	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	-3.78	-7.06	-13.44	-5.93	-5.39	--	--
4F	Mean	22.31	20.99	23.07	21.03	23.42	23.38	24.22
	SD	0.61	0.58	1.21	0.41	1.12	0.38	1.53
	N	15	15	15	15	15	5	5
	%Diff G1	3.14	-9.07	-9.59	-8.52	-0.90	3.18	8.03

Table 5

Summary of Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1 (pr)	Day 1 (p)	Day 2	Day 3	Day 29 (pr)	Day 29 (p)	Day 30
1M	Mean	36.94	37.67	36.81	--	36.62	37.96	36.26
	SD	0.45	0.53	0.31	--	0.41	0.40	0.31
	N	15	15	15	--	15	15	15
2M	Mean	36.72	38.57c	37.32a	--	36.62	38.22	36.89a
	SD	0.53	0.58	0.45	--	0.21	0.44	0.59
	N	10	10	10	--	10	10	10
	%Diff G1	-0.60	2.38	1.39	--	0.00	0.68	1.74
3M	Mean	36.86	39.12c	38.29c	36.95z	36.79	38.13	36.97b
	SD	0.36	0.36	0.61	0.21	0.50	0.44	0.57
	N	10	10	10	2	10	10	10
	%Diff G1	-0.22	3.84	4.03	--	0.46	0.45	1.96
4M	Mean	36.90	39.13c	38.56c	36.90z	36.68	38.88c	37.90c
	SD	0.32	0.32	0.47	0.14	0.24	0.53	0.63
	N	15	15	15	2	15	15	15
	%Diff G1	-0.11	3.88	4.76	--	0.16	2.42	4.52

Significantly different from control group 1 value :a=p≤0.05,b=p≤0.01,c=p≤0.001 (Dunnett)
Group excluded from statistical analysis (N<3): z

Table 5

Summary of Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1 (pr)	Day 1 (p)	Day 2	Day 3	Day 29 (pr)	Day 29 (p)	Day 30
1F	Mean	37.13	37.89	37.79	--	38.43	38.42	38.37
	SD	0.47	0.45	0.52	--	0.32	0.47	0.50
	N	15	15	15	--	15	15	15
2F	Mean	37.41	38.00	38.05	--	38.85	38.10	38.60
	SD	0.84	0.52	0.47	--	0.49	0.85	0.48
	N	10	10	10	--	10	10	10
	%Diff G1	0.75	0.30	0.70	--	1.10	-0.83	0.61
3F	Mean	37.38	38.95f	38.40d	--	38.60	38.80	38.53
	SD	0.33	0.59	0.31	--	0.42	0.56	0.78
	N	10	10	10	--	10	10	10
	%Diff G1	0.66	2.81	1.62	--	0.45	0.99	0.43
4F	Mean	37.36	39.38f	39.11f	37.32	38.56	39.25b	38.93d
	SD	0.49	0.35	0.65	0.60	0.47	0.55	0.32
	N	15	15	15	9	15	15	15
	%Diff G1	0.61	3.94	3.51	--	0.35	2.15	1.46

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

Table 6

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	8.500	0.865	7.245	0.213	0.074	0.019	0.087
	SD	2.067	0.318	1.817	0.095	0.023	0.010	0.040
	N	10	10	10	10	10	10	10
2M	Mean	11.700	4.919f	6.074	0.222	0.207a	0.016	0.261f
	SD	2.139	1.585	1.473	0.081	0.143	0.008	0.106
	N	10	10	10	10	10	10	10
	%Diff G1	37.647	468.671	-16.163	4.225	179.730	-15.789	200.000
3M	Mean	15.415f	9.665f	5.054d	0.216	0.251c	0.020	0.210e
	SD	2.831	2.786	1.092	0.065	0.096	0.007	0.084
	N	10	10	10	10	10	10	10
	%Diff G1	81.353	1017.341	-30.242	1.408	239.189	5.263	141.379
4M	Mean	16.911f	10.926f	5.367d	0.156	0.321c	0.018	0.151
	SD	4.324	3.204	2.102	0.047	0.102	0.018	0.096
	N	10	10	10	10	10	10	8
	%Diff G1	98.953	1163.121	-25.921	-26.761	333.784	-5.263	73.851

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

Table 6

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.821	14.40	42.89	54.90	18.41	33.54	12.42
	SD	0.357	0.44	1.26	1.77	0.61	0.60	0.30
	N	10	10	10	10	10	10	10
2M	Mean	7.496	13.84a	41.13	54.92	18.49	33.68	13.06b
	SD	0.309	0.38	1.35	2.06	0.75	0.39	0.54
	N	10	10	10	10	10	10	10
	%Diff G1	-4.155	-3.89	-4.10	0.04	0.43	0.42	5.15
3M	Mean	7.492	13.97	41.67	55.63	18.66	33.53	13.19b
	SD	0.299	0.54	1.78	1.39	0.52	0.47	0.37
	N	10	10	10	10	10	10	10
	%Diff G1	-4.207	-2.99	-2.84	1.33	1.36	-0.03	6.20
4M	Mean	7.731	14.15	41.98	54.37	18.32	33.69	13.73c
	SD	0.371	0.39	1.16	1.69	0.68	0.58	0.57
	N	10	10	10	10	10	10	10
	%Diff G1	-1.151	-1.74	-2.12	-0.97	-0.49	0.45	10.55

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

Table 6

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1087.3	258.03
	SD	115.6	13.62
	N	10	10
2M	Mean	1105.2	213.03c
	SD	123.5	14.21
	N	10	10
	%Diff G1	1.6	-17.44
3M	Mean	1167.6	194.65c
	SD	104.9	27.14
	N	10	10
	%Diff G1	7.4	-24.56
4M	Mean	1071.0	170.99c
	SD	144.2	11.48
	N	10	10
	%Diff G1	-1.5	-33.73

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

Table 6

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	6.188	0.487	5.393	0.149	0.071	0.006	0.083
	SD	1.534	0.157	1.605	0.045	0.013	0.005	0.029
	N	10	10	10	10	10	10	10
2F	Mean	9.770e	3.822	5.425	0.138	0.228b	0.015d	0.143
	SD	2.754	1.406	1.498	0.056	0.091	0.007	0.072
	N	10	10	10	10	10	10	10
	%Diff G1	57.886	684.805	0.593	-7.383	221.127	150.000	72.289
3F	Mean	10.586f	6.332c	3.710d	0.095	0.329c	0.009	0.105
	SD	2.822	1.993	1.095	0.043	0.188	0.010	0.065
	N	10	10	10	10	10	10	10
	%Diff G1	71.073	1200.205	-31.207	-36.242	363.380	50.000	26.506
4F	Mean	10.160e	6.586c	3.100e	0.092	0.276c	0.007	0.098
	SD	2.034	1.244	1.358	0.097	0.106	0.007	0.055
	N	10	10	10	10	10	10	10
	%Diff G1	64.189	1252.361	-42.518	-38.255	288.732	16.667	18.072

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

Table 6

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.372	13.56	40.04	54.37	18.41	33.88	11.10
	SD	0.257	0.58	1.38	0.70	0.37	0.41	0.50
	N	10	10	10	10	10	10	10
2F	Mean	7.111	13.10	38.46	54.16	18.41	34.03	11.65
	SD	0.435	0.64	1.79	1.96	0.61	0.60	0.52
	N	10	10	10	10	10	10	10
	%Diff G1	-3.540	-3.39	-3.95	-0.39	0.00	0.44	4.95
3F	Mean	7.291	13.65	39.50	54.22	18.72	34.53e	12.12b
	SD	0.170	0.41	0.99	1.34	0.46	0.37	0.50
	N	10	10	10	10	10	10	10
	%Diff G1	-1.099	0.66	-1.35	-0.28	1.68	1.92	9.19
4F	Mean	7.599	13.89	40.89	53.83	18.28	33.98	12.32c
	SD	0.192	0.43	1.55	1.95	0.51	0.45	0.18
	N	10	10	10	10	10	10	10
	%Diff G1	3.079	2.43	2.12	-0.99	-0.71	0.30	10.99

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

Table 6

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1189.2	181.32
	SD	171.8	40.10
	N	10	10
2F	Mean	1117.4	192.08
	SD	152.9	21.21
	N	10	10
	%Diff G1	-6.0	5.93
3F	Mean	1034.5a	183.84
	SD	117.7	37.86
	N	10	10
	%Diff G1	-13.0	1.39
4F	Mean	876.3c	173.38
	SD	99.2	36.80
	N	10	10
	%Diff G1	-26.3	-4.38

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

Table 6

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	8.374	1.112	6.916	0.188	0.104	0.020	0.040
	SD	3.554	0.360	3.077	0.077	0.034	0.017	0.023
	N	5	5	5	5	5	5	5
4M	Mean	8.326	1.228	6.760	0.176	0.108	0.014	0.042
	SD	1.710	0.453	1.679	0.044	0.044	0.005	0.008
	N	5	5	5	5	5	5	5
	%Diff G1	-0.573	10.432	-2.256	-6.383	3.846	-30.000	5.000

Table 6

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.882	14.26	42.10	53.44	18.06	33.78	12.54
	SD	0.242	0.36	0.86	1.01	0.54	0.43	0.51
	N	5	5	5	5	5	5	5
4M	Mean	7.456a	13.72	40.98	54.94a	18.38	33.46	14.66c
	SD	0.275	0.81	2.16	1.05	0.58	0.42	0.33
	N	5	5	5	5	5	5	5
	%Diff G1	-5.405	-3.79	-2.66	2.81	1.77	-0.95	16.91

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

Table 6

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1184.8	218.66
	SD	24.6	30.40
	N	5	5
4M	Mean	1200.4	275.72a
	SD	123.8	26.93
	N	5	5
	%Diff G1	1.3	26.10

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

Table 6

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	7.124	1.506	5.302	0.188	0.066	0.006	0.054
	SD	2.283	0.857	2.208	0.046	0.021	0.009	0.034
	N	5	5	5	5	5	5	5
4F	Mean	6.972	1.732	4.906	0.200	0.078	0.008	0.044
	SD	1.668	0.959	1.486	0.101	0.039	0.004	0.019
	N	5	5	5	5	5	5	5
	%Diff G1	-2.134	15.007	-7.469	6.383	18.182	33.333	-18.519

Table 6

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.026	13.02	37.70	53.66	18.56	34.56	11.12
	SD	0.242	0.44	1.37	1.96	0.62	0.62	0.47
	N	5	5	5	5	5	5	5
4F	Mean	6.980	12.50	36.64	52.56	17.92	34.08	12.98c
	SD	0.300	0.61	1.37	2.00	0.74	0.45	0.22
	N	5	5	5	5	5	5	5
	%Diff G1	-0.655	-3.99	-2.81	-2.05	-3.45	-1.39	16.73

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

Table 6

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1204.2	159.92
	SD	169.6	18.25
	N	5	5
4F	Mean	1224.2	166.28
	SD	173.2	36.33
	N	5	5
	%Diff G1	1.7	3.98

Table 7

Summary of Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	17.45	16.21	302.8
	SD	0.93	0.81	20.5
	N	10	10	10
2M	Mean	16.64	16.84	613.6c
	SD	0.72	0.44	89.7
	N	10	10	10
	%Diff G1	-4.64	3.89	102.6
3M	Mean	17.02	18.37c	647.2c
	SD	0.61	1.04	38.8
	N	10	10	10
	%Diff G1	-2.46	13.33	113.7
4M	Mean	17.01	19.37c	697.8c
	SD	0.95	0.71	58.9
	N	10	10	10
	%Diff G1	-2.52	19.49	130.4

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

Table 7

Summary of Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.81	15.29	280.4
	SD	0.71	1.18	35.5
	N	10	10	10
2F	Mean	17.83	16.42	454.6c
	SD	0.66	1.09	88.9
	N	10	10	10
	%Diff G1	0.11	7.39	62.1
3F	Mean	17.88	17.11b	590.6c
	SD	0.58	0.72	138.0
	N	10	10	10
	%Diff G1	0.39	11.90	110.6
4F	Mean	18.39	19.23c	604.7c
	SD	1.07	1.14	66.3
	N	10	10	10
	%Diff G1	3.26	25.77	115.7

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

Table 7

Summary of Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	17.96	15.74	323.2
	SD	0.74	0.72	46.8
	N	5	5	5
4M	Mean	17.82	15.68	301.0
	SD	0.45	0.80	27.9
	N	5	5	5
	%Diff G1	-0.78	-0.38	-6.9

Table 7

Summary of Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.70	15.40	234.0
	SD	0.85	1.90	25.6
	N	5	5	5
4F	Mean	17.96	16.28	262.4
	SD	0.61	1.19	12.6
	N	5	5	5
	%Diff G1	1.47	5.71	12.1

Table 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	64.3	37.6	148.3	2.0	257.0	0.083	13.4
	SD	11.8	4.4	19.5	0.0	184.3	0.011	1.7
	N	10	10	10	10	10	10	10
2M	Mean	75.5	37.6	132.6	2.0	385.6	0.096	14.8
	SD	18.6	6.2	19.9	0.0	244.1	0.031	1.8
	N	10	10	10	10	10	10	10
	%Diff G1	17.4	0.0	-10.6	0.0	50.0	15.663	10.4
3M	Mean	85.7	40.5	147.5	2.0	345.4	0.105	15.6a
	SD	39.4	9.9	17.7	0.0	346.8	0.026	2.0
	N	10	10	10	10	10	10	10
	%Diff G1	33.3	7.7	-0.5	0.0	34.4	26.506	16.4
4M	Mean	82.4	36.0	143.2	2.0	459.9	0.098	13.6
	SD	31.2	5.1	27.8	0.0	360.3	0.026	2.1
	N	10	10	10	10	10	10	10
	%Diff G1	28.1	-4.3	-3.4	0.0	78.9	18.072	1.5

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

Table 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	209.1	75.3	70.3	5.79	3.83	1.96
	SD	0.05	31.0	5.3	48.0	0.22	0.16	0.18
	N	10	10	10	10	10	10	10
2M	Mean	0.34	162.6b	70.6	49.0	6.04	3.41c	2.63c
	SD	0.05	36.0	12.6	12.9	0.28	0.15	0.20
	N	10	10	10	10	10	10	10
	%Diff G1	-5.56	-22.2	-6.2	-30.3	4.32	-10.97	34.18
3M	Mean	0.37	168.7a	73.8	52.5	6.08a	3.36c	2.72c
	SD	0.05	26.6	15.2	12.1	0.18	0.11	0.14
	N	10	10	10	10	10	10	10
	%Diff G1	2.78	-19.3	-2.0	-25.3	5.01	-12.27	38.78
4M	Mean	0.39	167.7a	73.3	62.6	6.05	3.28c	2.77c
	SD	0.06	24.3	12.4	10.5	0.29	0.12	0.21
	N	10	10	10	10	10	10	10
	%Diff G1	8.33	-19.8	-2.7	-11.0	4.49	-14.36	41.33

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

Table 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.98	10.95	7.92	140.1	5.09	100.2
	SD	0.22	0.21	0.49	1.6	0.36	1.7
	N	10	10	10	10	10	10
2M	Mean	1.31a	11.17	8.43	140.1	5.14	100.4
	SD	0.10	0.26	0.31	1.6	0.38	2.5
	N	10	10	10	10	10	10
	%Diff G1	-33.84	2.01	6.44	0.0	0.98	0.2
3M	Mean	1.24c	11.12	8.63	140.2	5.47	100.2
	SD	0.07	0.14	0.77	1.7	0.30	2.0
	N	10	10	10	10	10	10
	%Diff G1	-37.37	1.55	8.96	0.1	7.47	0.0
4M	Mean	1.18c	11.15	9.20c	140.3	5.69e	100.0
	SD	0.09	0.22	0.85	1.6	0.37	1.6
	N	10	10	10	10	10	10
	%Diff G1	-40.40	1.83	16.16	0.1	11.79	-0.2

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

Table 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	86.1	37.6	83.1	2.0	232.3	0.087	14.6
	SD	41.3	10.1	17.2	0.0	126.1	0.036	1.9
	N	10	10	10	10	10	10	10
2F	Mean	78.9	41.4	80.2	2.0	302.7	0.059	17.4
	SD	19.0	11.8	18.2	0.0	153.3	0.035	3.0
	N	10	10	10	10	10	10	10
	%Diff G1	-8.4	10.1	-3.5	0.0	30.3	-32.184	19.2
3F	Mean	103.8	36.6	89.8	2.0	610.4	0.077	16.5
	SD	24.4	9.1	20.0	0.0	394.5	0.026	4.0
	N	10	10	10	10	10	10	10
	%Diff G1	20.6	-2.7	8.1	0.0	162.8	-11.494	13.0
4F	Mean	92.3	51.4	107.1a	2.0	280.8	0.061	15.3
	SD	46.4	41.3	14.5	0.0	218.9	0.011	3.0
	N	10	10	10	10	10	10	10
	%Diff G1	7.2	36.7	28.9	0.0	20.9	-29.885	4.8

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

Table 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	186.4	79.9	53.9	6.27	4.31	1.96
	SD	0.06	31.1	12.5	19.1	0.39	0.27	0.18
	N	10	10	10	10	10	10	10
2F	Mean	0.39	168.8	76.1	40.9	6.31	3.97a	2.34b
	SD	0.07	32.5	15.5	8.8	0.26	0.24	0.25
	N	10	10	10	10	10	10	10
	%Diff G1	2.63	-9.4	-4.8	-24.1	0.64	-7.89	19.39
3F	Mean	0.43	140.9b	71.7	42.3	6.38	3.94a	2.44c
	SD	0.05	26.2	16.3	5.7	0.39	0.27	0.28
	N	10	10	10	10	10	10	10
	%Diff G1	13.16	-24.4	-10.3	-21.5	1.75	-8.58	24.49
4F	Mean	0.41	147.3a	70.2	53.7	6.26	3.79c	2.47c
	SD	0.06	21.2	19.1	12.5	0.31	0.30	0.17
	N	10	10	10	10	10	10	10
	%Diff G1	7.89	-21.0	-12.1	-0.4	-0.16	-12.06	26.02

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

Table 8

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.22	11.03	7.28	140.9	4.66	101.5
	SD	0.18	0.31	0.63	1.7	0.26	1.4
	N	10	10	10	10	10	10
2F	Mean	1.72f	11.07	7.39	139.8	4.87	101.3
	SD	0.27	0.28	0.60	1.2	0.33	2.0
	N	10	10	10	10	10	10
	%Diff G1	-22.52	0.36	1.51	-0.8	4.51	-0.2
3F	Mean	1.63f	11.00	7.69	138.8b	4.87	99.2
	SD	0.23	0.42	0.40	0.6	0.38	2.3
	N	10	10	10	10	10	10
	%Diff G1	-26.58	-0.27	5.63	-1.5	4.51	-2.3
4F	Mean	1.55f	11.10	7.78	139.8	4.96	100.4
	SD	0.18	0.18	0.79	1.4	0.42	3.2
	N	10	10	10	10	10	10
	%Diff G1	-30.18	0.63	6.87	-0.8	6.44	-1.1

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

Table 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	112.8	44.8	124.6	2.0	806.0	0.070	15.8
	SD	36.8	4.7	17.9	0.0	488.9	0.023	1.5
	N	5	5	5	5	5	5	5
4M	Mean	93.6	47.6	152.4	2.0	458.0	0.050	14.0
	SD	12.4	5.5	26.6	0.0	214.3	0.016	1.7
	N	5	5	5	5	5	5	5
	%Diff G1	-17.0	6.3	22.3	0.0	-43.2	-28.571	-11.4

Table 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	Mean	0.32	176.4	77.6	84.2	6.00	3.82	2.18
	SD	0.04	30.3	16.1	30.7	0.28	0.19	0.15
	N	5	5	5	5	5	5	5
4M	Mean	0.36	200.8	64.8	64.2	6.12	3.82	2.30
	SD	0.05	40.2	6.1	22.4	0.13	0.08	0.07
	N	5	5	5	5	5	5	5
	%Diff G1	12.50	13.8	-16.5	-23.8	2.00	0.00	5.50

Table 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.76	10.18	8.04	141.6	5.38	102.2
	SD	0.15	0.13	0.83	1.1	0.26	2.2
	N	5	5	5	5	5	5
4M	Mean	1.66	10.18	7.80	141.2	5.28	102.4
	SD	0.05	0.29	0.77	0.8	0.28	1.3
	N	5	5	5	5	5	5
	%Diff G1	-5.68	0.00	-2.99	-0.3	-1.86	0.2

Table 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	35.0	65.8	2.0	412.6	0.066	16.6
	SD	12.8	5.1	10.4	0.0	197.0	0.026	2.8
	N	5	5	5	5	5	5	5
4F	Mean	104.0	44.2	78.0	2.0	433.0	0.054	17.0
	SD	37.9	14.0	13.2	0.0	303.0	0.018	4.7
	N	5	5	5	5	5	5	5
	%Diff G1	20.9	26.3	18.5	0.0	4.9	-18.182	2.4

Table 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	0.40	190.2	70.8	67.6	6.24	4.40	1.84
	SD	0.00	40.9	7.4	17.8	0.15	0.07	0.13
	N	5	5	5	5	5	5	5
4F	Mean	0.40	211.2	75.2	71.2	6.66	4.52	2.14b
	SD	0.07	14.1	11.1	13.2	0.38	0.35	0.09
	N	5	5	5	5	5	5	5
	%Diff G1	0.00	11.0	6.2	5.3	6.73	2.73	16.30

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

Table 8

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.42	10.66	6.82	140.0	4.72	101.8
	SD	0.22	0.22	0.23	1.0	0.15	1.3
	N	5	5	5	5	5	5
4F	Mean	2.10a	10.62	6.74	138.6a	4.90	100.0
	SD	0.17	0.20	0.43	0.5	0.32	1.4
	N	5	5	5	5	5	5
	%Diff G1	-13.22	-0.38	-1.17	-1.0	3.81	-1.8

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

Appendix 1

FINAL STUDY PLAN

Test Facility Study No. 5002033

A 1-month (3 doses) Study of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat 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

05 April 2017

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Appendix 1

1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1653, when given by intramuscular injection for 1 month (3 doses) to Sprague Dawley rat and to evaluate the potential reversibility of any findings.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity; Toxicokinetics
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 Apr 2017 (First date of study-specific data collection)
Experimental Completion Date:	12 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	05 Apr 2017
Initiation of Dosing:	19 Apr 2017
Completion of In-life:	19 May 2017 (main study animals) 01 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	28 Jul 2017
Audited Draft Report:	05 Sep 2017
Final Report:	12 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

Appendix 1

- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- OECD Guideline 417. *Toxicokinetics*.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S3a. *Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.
- ICH Harmonised Tripartite Guideline S8. *Notes for Guidance on Immunotoxicity Testing of Human Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, and *Guidelines for General Pharmacology Studies*, and *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 at a laboratory that follows FDA Good Manufacturing Practice (GMP) regulations.
- 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/were not 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.

Appendix 1

- 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.

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

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

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Appendix 1

Tel: (b) (6)
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	(b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Immunology (Cytokine Analysis)	(b) (6) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Pathology	To be included by amendment

Appendix 1

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

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

PIs at Sponsor-designated Test Site(s)

ATA analysis (b) (4), (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(s)

Identification:	mRNA-1653
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	To be included by amendment
Concentration:	To be included by amendment
Retest Date:	Concomitant assessment, ongoing
Physical Description:	To be included by amendment
Storage Conditions:	Kept in a freezer set to maintain -20°C

Appendix 1

8.2. Reference Item(s)

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 Item, and this information is available to the appropriate regulatory agencies should it be requested.

8.4. Analysis of Test Item

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

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

The second vial will be transferred 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 Items, a reserve sample (1 mL or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

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8.6. Test and Reference Item Inventory and Disposition

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

Shipping Contact

(b) (6)
Moderna Therapeutics
500 Technology Square, 8th Floor
Cambridge MA 02139, USA
Tel: (b) (6)
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.

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

10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1801997).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis:	Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Backup Samples:	Triplicate top, middle, and bottom samples (duplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On days where only concentration analysis is required, the formulation will only be sampled from the middle.
Sampling Containers:	Appropriate sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.

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

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	55
Number of Females Ordered:	55
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	150 to 175 g (males) 125 to 175 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.

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11.2. Animal Identification

At study assignment, each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 10 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 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

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Humidity:	30% to 70%
Light Cycle:	12 hours light and 12 hours dark (except during designated procedures)

12.3. Food

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

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

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

12.4. Water

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

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

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

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

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consultation with the Sponsor representative when such treatment does not impact fulfillment of the study objectives. If the condition of the animal(s) warrants significant therapeutic intervention or alterations in study procedures, the Sponsor representative will be contacted, when possible, to discuss appropriate action. If the condition of the animal(s) is such that emergency measures must be taken, the Study Director and/or clinical veterinarian will attempt to consult with the Sponsor representative prior to responding to the medical crisis, but the Study Director and/or veterinarian has authority to act immediately at his/her discretion to alleviate suffering. The Sponsor representative will be fully informed of any such events.

13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (mg/dose)	Dose Volume (µl)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1653	10	200	50	10	10	-	-
3	mRNA-1653	50	200	250	10	10	-	-
4	mRNA-1653	150	200	750	10	10	5	5

[a] = 10/sex/groups 1 to 4 necropsied 1 day following the last dose.
[b] = The remaining 5/sex/groups 1 to 4 necropsied 2 weeks following the last dose.

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to Groups 1 to 4 animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29. The dose volume for each animal will be based constant volume. The volume for each dose will be administered using a syringe/needle within the demarcated area. The injection site will be alternated on each dosing occasion.

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. Justifications of route and dose levels

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

The doses selected are based upon tolerability data of various lipid nanoparticle formulation(s) in rats, which is expected to drive toxicities observed. The mid and low dose levels were chosen based upon observed efficacy with this modified mRNA construct in a lipid nanoparticle formulation. Doses with this test material or similarly formulated material up to 1 mg/kg (sponsor internal data) were well-tolerated in rats.

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14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

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

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

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: Weekly during the dosing and recovery periods, and at least every 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 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

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Notable dermal lesion (maximized)	M
Edema (Swelling)	
No edema	0
Very slight edema	1
Slight edema	2
Moderate edema	3
Severe edema	4

Any other abnormalities will be recorded as they are observed.

14.4. Body Weights

Frequency: Weekly during the dosing and recovery periods, and at least every 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 during Week 4 of dosing. During Week 2 of the recovery period if Test-Item related findings are observed during the dosing period.

Procedure: All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be 1% tropicamide.

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

14.7. Body Temperature

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

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

15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

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

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

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry
1 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

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

15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Clinical Chemistry Parameters

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

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

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (ATTACHMENT A).

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

15.2. Cytokines Analysis

Blood will be collected from the jugular vein of all recovery animals and preterminally euthanized animals (recovery animals only). After collection, blood samples for serum will be

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allowed to clot at ambient room temperature and blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	(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 qualified multiplex Luminex method (non-GLP). A qualified ELISA method (non-GLP) 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).

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Time Points:	Before initiation of dosing and at study termination (on Day 30 for main animals and on Day 43 for recovery animals).
Target Volume:	0.5 mL
Anticoagulant:	None, collected in serum separator tubes
Processing:	To serum

Samples will be mixed gently and allowed to clot at room temperature until centrifugation which will be carried out as soon as practical (not exceeding 60 minutes after collection). The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (4), (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-HMPVantibodies using a qualified neutralizing antibody assay method.

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

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

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section 15.

These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo necropsy, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

Animals found dead or euthanized before the initiation of dosing will be subject to necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy and tissues will be retained (as per Tissue Collection and

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Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

17.3. Pathology Peer Review

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

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

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

18. CONSTRUCTED VARIABLES

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

19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method Parametric/ Non-Parametric
Body Weight	X
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
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
Bio-Plex Manager	Data acquisition and regression for Luminex data
Softmax Pro GxP	Data collection and regression for Elisa methods
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

21. AMENDMENTS AND DEVIATIONS

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

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

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date

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

23. REPORTING

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

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

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

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

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TEST FACILITY APPROVAL

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

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

Date: 05 Apr 2017

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

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

Date: 05 Apr 2017

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SPONSOR APPROVAL

The Study Plan was approved by the Sponsor by email on 05 April 2017. The signature below confirms the approval of the Study Plan by the Sponsor Representative

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

Date: 30Sep17

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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[1] 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	including femorotibial joint
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, other	-	X	X	X	Lymph node draining the administration sites: popliteal (bilateral) and inguinal (bilateral)
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. Both sites.
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.

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STUDY PLAN AMENDMENT 01

Test Facility Study No. 5002033

A 1-month (3 doses) Study of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat 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: 05 Apr 2017

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

Item or Section(s)	Justification
Amendment 1	**Date: 19-Apr-2017**
4. REGULATORY COMPLIANCE	To remove non applicable exception.
7. RESPONSIBLE PERSONNEL	To include clarification for analytical chemistry IS and to include IS for pathology and immunology (purity).
8.1. Test Item(s)	To include missing information.
8.4. Analysis of Test Item	To remove encapsulation analysis as not required for this study and to include transfer condition for purity analysis.
10.3. Sample Collection and Analysis	To remove Ph, osmolality and density column as not required for this study.
13. EXERIMENTAL DESIGN	To update units for dose levels and concentrations.
13.1. Administration of Test and Reference Items	To include clarification.
22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS	To include clarification for archives location.
ATTACHMENT A	To remove footnote for nasal cavities.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1653, when given by intramuscular injection for 1 month (3 doses) to Sprague Dawley rat and to evaluate the potential reversibility of any findings.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity; Toxicokinetics
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 Apr 2017 (First date of study-specific data collection)
Experimental Completion Date:	12 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	05 Apr 2017
Initiation of Dosing:	19 Apr 2017
Completion of In-life:	19 May 2017 (main study animals) 01 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	28 Jul 2017
Audited Draft Report:	05 Sep 2017
Final Report:	12 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- OECD Guideline 417. *Toxicokinetics*.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S3a. *Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.
- ICH Harmonised Tripartite Guideline S8. *Notes for Guidance on Immunotoxicity Testing of Human Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, and *Guidelines for General Pharmacology Studies*, and *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 at a laboratory that follows FDA Good Manufacturing Practice (GMP) regulations.**~~
- 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/were not conducted in compliance with the GLP or GMP regulations.

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- 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.

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

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

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

(b) (6)
Charles River Laboratories Montreal ULC

Appendix 1

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

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

Pathology ~~**To be included by amendment**~~
(b) (6)
Preclinical Services, Montreal
Montreal Site (PCS-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (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

PIs at Sponsor-designated T
(b) (4), (b) (6)

ATA analysis

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)

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- 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(s)

Identification:	mRNA-1653
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	**MTDP 17038** ~~**To be included by amendment**~~
Concentration:	**2.2 mg/mL** ~~**To be included by amendment**~~
Retest Date:	Concomitant assessment, ongoing
Physical Description:	**White to off-white lipid nanoparticle dispersion** ~~**To be included by amendment**~~
Storage Conditions:	Kept in a freezer set to maintain -20°C

8.2. Reference Item(s)

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 Item, and this information is available to the appropriate regulatory agencies should it be requested.

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8.4. Analysis of Test Item

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

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

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

Purity~~, and~~ Particle size~~, 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 Items, a reserve sample (1 mL or 1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

8.6. Test and Reference Item Inventory and Disposition

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

Shipping Contact
(b) (6)
Moderna Therapeutics
500 Technology Square, 8th Floor
Cambridge MA 02139, USA
Tel: (b) (6)
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

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

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

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

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

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

10.2. Preparation of Test Item

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

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

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

10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

Interval	Concentration	Homogeneity	~~pH, Osmolality and Density~~	Sampling From
Day 1[b]	All groups	2 to 4[a]	~~All groups~~	Preparation vessel
Day 29[b]	All groups	N/A	~~N/A~~	Preparation vessel

N/A = Not applicable.

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1801997).

10.3.1.1. Concentration and Homogeneity Analysis

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

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	55

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Number of Females Ordered:	55
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	150 to 175 g (males) 125 to 175 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

At study assignment, each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 10 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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

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

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

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

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

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

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12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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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.

13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (~~m~~ µg/dose)	Dose Volume (µl)	Dose Concentration (~~m~~ µg/mL)	No. of Animals			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1653	10	200	50	10	10	-	-
3	mRNA-1653	50	200	250	10	10	-	-
4	mRNA-1653	150	200	750	10	10	5	5

[a] = 10/sex/groups 1 to 4 necropsied 1 day following the last dose.
[b] = The remaining 5/sex/groups 1 to 4 necropsied 2 weeks following the last dose.

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13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to Groups 1 to 4 animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29. The dose volume for each animal will be ~~based~~ constant ~~volume~~. The volume for each dose will be administered using a syringe/needle within the demarcated area. The injection site will be alternated on each dosing occasion.

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. Justifications of route and dose levels

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

The doses selected are based upon tolerability data of various lipid nanoparticle formulation(s) in rats, which is expected to drive toxicities observed. The mid and low dose levels were chosen based upon observed efficacy with this modified mRNA construct in a lipid nanoparticle formulation. Doses with this test material or similarly formulated material up to 1 mg/kg (sponsor internal data) were well-tolerated in rats.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

Frequency:	Twice daily, once in the morning and once in the afternoon, throughout the study.
Procedure:	Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

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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 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

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.

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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 during Week 4 of dosing. During Week 2 of the recovery period if Test-Item related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be 1% tropicamide.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

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

15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

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

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

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry
1 to 4[a]	Day 30	X	X	X

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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

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

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Clinical Chemistry Parameters

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

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

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (ATTACHMENT A).

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

15.2. Cytokines Analysis

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

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Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			None (SST)	EDTA
Centrifugation setting			(b) (4)	(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 qualified multiplex Luminex method (non-GLP). A qualified ELISA method (non-GLP) 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).

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Target Volume: 0.5 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Samples will be mixed gently and allowed to clot at room temperature until centrifugation which will be carried out as soon as practical (not exceeding 60 minutes after collection). The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)) at (b) (4) The resultant serum will be separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.
Samples will be shipped on dry ice to:

Shipping Contact
(b) (4), (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-HMPVantibodies using a qualified neutralizing antibody assay method.

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

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

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16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section 15.

These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo necropsy, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

Animals found dead or euthanized before the initiation of dosing will be subject to necropsy and limited tissue retention (standard diagnostic tissue list). Any animal replaced after the start of dosing will be subject to necropsy and tissues will be retained (as per Tissue Collection and

Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

17.3. Pathology Peer Review

A 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

	Statistical Method
Variables for Inferential Analysis	**Parametric/ Non-Parametric**
Body Weight	X
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Organ Weights	X
Body Weight 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
Bio-Plex Manager	Data acquisition and regression for Luminex data
Softmax Pro GxP	Data collection and regression for Elisa methods
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

21. AMENDMENTS AND DEVIATIONS

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

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

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date

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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.

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

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

23. REPORTING

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

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

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

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

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AMENDMENT APPROVAL

(b) (6)

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

Date: 19 Apr 2017

As authorized by the Sponsor on 18 Apr 2017

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ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	X	Level 4[1] 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	including femorotibial joint
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, other	-	X	X	X	Lymph node draining the administration sites: popliteal (bilateral) and inguinal (bilateral)
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. Both sites.
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.

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STUDY PLAN AMENDMENT 02

Test Facility Study No. 5002033

A 1-month (3 doses) Study of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat 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: 05 Apr 2017

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

Item or Section(s)	Justification
Amendment 1	**Date: 19-Apr-2017**
4. REGULATORY COMPLIANCE	To remove non applicable exception.
7. RESPONSIBLE PERSONNEL	To include clarification for analytical chemistry IS and to include IS for pathology and immunology (purity).
8.1. Test Item(s)	To include missing information.
8.4. Analysis of Test Item	To remove encapsulation analysis as not required for this study and to include transfer condition for purity analysis.
10.3. Sample Collection and Analysis	To remove Ph, osmolality and density column as not required for this study.
13. EXERIMENTAL DESIGN	To update units for dose levels and concentrations.
13.1. Administration of Test and Reference Items	To include clarification.
22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS	To include clarification for archives location.
ATTACHMENT A	To remove footnote for nasal cavities.
Amendment 2	**Date: 01-May-2017**
ATTACHMENT A	To include description for footnote “a” and to remove evaluation for nasal cavity based on comments column.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1653, when given by intramuscular injection for 1 month (3 doses) to Sprague Dawley rat and to evaluate the potential reversibility of any findings.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity; Toxicokinetics
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 Apr 2017 (First date of study-specific data collection)
Experimental Completion Date:	12 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	05 Apr 2017
Initiation of Dosing:	19 Apr 2017
Completion of In-life:	19 May 2017 (main study animals) 01 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	28 Jul 2017
Audited Draft Report:	05 Sep 2017
Final Report:	12 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- OECD Guideline 417. *Toxicokinetics*.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S3a. *Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.
- ICH Harmonised Tripartite Guideline S8. *Notes for Guidance on Immunotoxicity Testing of Human Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, and *Guidelines for General Pharmacology Studies*, and *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/were not 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

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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.

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

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

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

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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) (b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Immunology (Purity Analysis)	(b) (6) 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) Address as cited for Test Facility

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

Pathology (b) (6)
Preclinical Services, Montreal
Montreal Site (PCS-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (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

PIs at Sponsor-designated Test Site(s)

ATA analysis (b) (4), (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

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8. TEST AND REFERENCE ITEMS

8.1. Test Item(s)

Identification:	mRNA-1653
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP 17038
Concentration:	2.2 mg/mL
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C

8.2. Reference Item(s)

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 Item, and this information is available to the appropriate regulatory agencies should it be requested.

8.4. Analysis of Test Item

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

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

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

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

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

8.5. Reserve Samples

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

8.6. Test and Reference Item Inventory and Disposition

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

Shipping Contact
(b) (6)
Moderna Therapeutics
500 Technology Square, 8th Floor
Cambridge MA 02139, USA
Tel: (b) (6)
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.

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10.2. Preparation of Test Item

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

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

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

10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1801997).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis: Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On days where only concentration analysis is required, the formulation will only be sampled from the middle.

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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.

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	55
Number of Females Ordered:	55
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	150 to 175 g (males) 125 to 175 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.

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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

At study assignment, each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 10 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 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

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will be arranged on the racks in group order. Where possible, control group animals will be housed on a separate rack from the Test Item treated animals.

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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

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

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examinations and recommended therapeutic treatments, if any, will be documented in the study records.

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

13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (~~m~~ µg/dose)	Dose Volume (µl)	Dose Concentration (~~m~~ µg/mL)	No. of Animals			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1653	10	200	50	10	10	-	-
3	mRNA-1653	50	200	250	10	10	-	-
4	mRNA-1653	150	200	750	10	10	5	5

[a] = 10/sex/groups 1 to 4 necropsied 1 day following the last dose.
[b] = The remaining 5/sex/groups 1 to 4 necropsied 2 weeks following the last dose.

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to Groups 1 to 4 animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29. The dose volume for each animal will be constant. The volume for each dose will be administered using a syringe/needle within the demarcated area. The injection site will be alternated on each dosing occasion.

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.

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13.2. Justifications of route and dose levels

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

The doses selected are based upon tolerability data of various lipid nanoparticle formulation(s) in rats, which is expected to drive toxicities observed. The mid and low dose levels were chosen based upon observed efficacy with this modified mRNA construct in a lipid nanoparticle formulation. Doses with this test material or similarly formulated material up to 1 mg/kg (sponsor internal data) were well-tolerated in rats.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

Frequency:	Twice daily, once in the morning and once in the afternoon, throughout the study.
Procedure:	Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

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

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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

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 during Week 4 of dosing. During Week 2 of the recovery period if Test-Item related findings are observed during the dosing period.

Procedure: All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be 1% tropicamide.

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

14.7. Body Temperature

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

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

15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

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

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

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry
1 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

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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

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Clinical Chemistry Parameters

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

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

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15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (ATTACHMENT A).

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

15.2. Cytokines Analysis

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

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	(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 qualified multiplex Luminex method (non-GLP). A qualified ELISA method (non-GLP) 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

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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

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) (4), (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-HMPVantibodies using a qualified neutralizing antibody assay method.

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

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

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

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section 15.

These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo necropsy, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered

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formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

17.3. Pathology Peer Review

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

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

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

18. CONSTRUCTED VARIABLES

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

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19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

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

The following pairwise comparisons will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

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

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20. COMPUTERIZED SYSTEMS

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

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

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
Bio-Plex Manager	Data acquisition and regression for Luminex data
Softmax Pro GxP	Data collection and regression for Elisa methods
Watson LIMS	Biomarker data analysis
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

21. AMENDMENTS AND DEVIATIONS

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

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

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22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date of final report issue. All materials generated by Charles River from this study will be transferred to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

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

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

23. REPORTING

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

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

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

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

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AMENDMENT APPROVAL

(b) (6) Date: 01 May 2017

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

As authorized by the Sponsor on 01 May 2017

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ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	X	~~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	including femorotibial joint
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, other	-	X	X	X	Lymph node draining the administration sites: popliteal (bilateral) and inguinal (bilateral)
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. Both sites.
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

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STUDY PLAN AMENDMENT 03

Test Facility Study No. 5002033

A 1-month (3 doses) Study of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat 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: 05 Apr 2017

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

Item or Section(s)	Justification
Amendment 1	**Date: 19-Apr-2017**
4. REGULATORY COMPLIANCE	To remove non applicable exception.
7. RESPONSIBLE PERSONNEL	To include clarification for analytical chemistry IS and to include IS for pathology and immunology (purity).
8.1. Test Item(s)	To include missing information.
8.4. Analysis of Test Item	To remove encapsulation analysis as not required for this study and to include transfer condition for purity analysis.
10.3. Sample Collection and Analysis	To remove Ph, osmolality and density column as not required for this study.
13. EXERIMENTAL DESIGN	To update units for dose levels and concentrations.
13.1. Administration of Test and Reference Items	To include clarification.
22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS	To include clarification for archives location.
ATTACHMENT A	To remove footnote for nasal cavities.
Amendment 2	**Date: 01-May-2017**
ATTACHMENT A	To include description for footnote “a” and to remove evaluation for nasal cavity based on comments column.
Amendment 3	
7. RESPONSIBLE PERSONNEL	To include clarification for immunology analysis and to include a biomarker IS.
15.2. Cytokines Analysis	To include clarification for cytokine analysis.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1653, when given by intramuscular injection for 1 month (3 doses) to Sprague Dawley rat and to evaluate the potential reversibility of any findings.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity; Toxicokinetics
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 Apr 2017 (First date of study-specific data collection)
Experimental Completion Date:	12 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	05 Apr 2017
Initiation of Dosing:	19 Apr 2017
Completion of In-life:	19 May 2017 (main study animals) 01 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	28 Jul 2017
Audited Draft Report:	05 Sep 2017
Final Report:	12 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- OECD Guideline 417. *Toxicokinetics*.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S3a. *Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.
- ICH Harmonised Tripartite Guideline S8. *Notes for Guidance on Immunotoxicity Testing of Human Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, and *Guidelines for General Pharmacology Studies*, and *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/were not 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

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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.

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

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

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

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) (b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Immunology (Purity Analysis)	(b) (6) 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**~~ **IFN-α** Analysis)	(b) (6) Address as cited for Test Facility

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	Tel: (b) (6) E-mail: (b) (6)
Biomarkers (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1)	(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)
Pathology	(b) (6) Preclinical Services, Montreal Montreal Site (PCS-MTL) 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) Fax: (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

PIs at Sponsor-designated Test Site(s)

ATA analysis	(b) (4), (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

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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(s)

Identification:	mRNA-1653
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP 17038
Concentration:	2.2 mg/mL
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C

8.2. Reference Item(s)

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.

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

8.4. Analysis of Test Item

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

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

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

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

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

8.5. Reserve Samples

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

8.6. Test and Reference Item Inventory and Disposition

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

Shipping Contact
(b) (6)
Moderna Therapeutics
500 Technology Square, 8th Floor
Cambridge MA 02139, USA
Tel: (b) (6)
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

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

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

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

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

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

10.2. Preparation of Test Item

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

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

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

10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1801997).

10.3.1.1. Concentration and Homogeneity Analysis

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

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	55

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Number of Females Ordered:	55
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	150 to 175 g (males) 125 to 175 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

At study assignment, each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 10 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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

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

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

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

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

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

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12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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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.

13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (~~m~~ µg/dose)	Dose Volume (µl)	Dose Concentration (~~m~~ µg/mL)	No. of Animals			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1653	10	200	50	10	10	-	-
3	mRNA-1653	50	200	250	10	10	-	-
4	mRNA-1653	150	200	750	10	10	5	5

[a] = 10/sex/groups 1 to 4 necropsied 1 day following the last dose.
[b] = The remaining 5/sex/groups 1 to 4 necropsied 2 weeks following the last dose.

Appendix 1

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to Groups 1 to 4 animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29. The dose volume for each animal will be constant. The volume for each dose will be administered using a syringe/needle within the demarcated area. The injection site will be alternated on each dosing occasion.

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. Justifications of route and dose levels

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

The doses selected are based upon tolerability data of various lipid nanoparticle formulation(s) in rats, which is expected to drive toxicities observed. The mid and low dose levels were chosen based upon observed efficacy with this modified mRNA construct in a lipid nanoparticle formulation. Doses with this test material or similarly formulated material up to 1 mg/kg (sponsor internal data) were well-tolerated in rats.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

Frequency:	Twice daily, once in the morning and once in the afternoon, throughout the study.
Procedure:	Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

Appendix 1

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 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

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.

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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 during Week 4 of dosing. During Week 2 of the recovery period if Test-Item related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be 1% tropicamide.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

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

15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

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

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

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry
1 to 4[a]	Day 30	X	X	X

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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

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

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Clinical Chemistry Parameters

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

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

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (ATTACHMENT A).

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

15.2. Cytokines Analysis

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

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Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			(b) (4)	(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 **(processing)**			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 **for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1** will be analyzed by the ~~Immunology~~ **Biomarkers** department **at CR MTL**. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 will be conducted using a qualified multiplex Luminex method (non-GLP). 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.

A qualified ELISA method (non-GLP) will be used for the analysis of IFN-α **by the Immunology department at CR SHB**. **The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.**

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

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

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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

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) (4), (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-HMPVantibodies using a qualified neutralizing antibody assay method.

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

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

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Appendix 1

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section 15.

These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo necropsy, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

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16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

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

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

17.3. Pathology Peer Review

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

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

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

18. CONSTRUCTED VARIABLES

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

19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method Parametric/ Non-Parametric
Body Weight	X
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
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
Bio-Plex Manager	Data acquisition for Luminex data
Softmax Pro GxP	Data collection and regression for Elisa methods
Watson LIMS	Biomarkers data regression
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

21. AMENDMENTS AND DEVIATIONS

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

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

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date

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of final report issue. All materials generated by Charles River from this study will be transferred to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

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

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

23. REPORTING

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

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

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

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24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

Appendix 1

AMENDMENT APPROVAL

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

As authorized by the Sponsor on 15 Jun 2017

Appendix 1

ATTACHMENT A

Tissue Collection and Preservation

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Animal identification	-	X	-	-	-
Artery, aorta	-	X	X	X	-
Body cavity, nasal	-	X	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	including femorotibial joint
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, other	-	X	X	X	Lymph node draining the administration sites: popliteal (bilateral) and inguinal (bilateral)
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. Both sites.
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

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STUDY PLAN AMENDMENT 04

Test Facility Study No. 5002033

A 1-month (3 doses) Study of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat 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: 05 Apr 2017

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

Item or Section(s)	Justification
Amendment 1	**Date: 19-Apr-2017**
4. REGULATORY COMPLIANCE	To remove non applicable exception.
7. RESPONSIBLE PERSONNEL	To include clarification for analytical chemistry IS and to include IS for pathology and immunology (purity).
8.1. Test Item(s)	To include missing information.
8.4. Analysis of Test Item	To remove encapsulation analysis as not required for this study and to include transfer condition for purity analysis.
10.3. Sample Collection and Analysis	To remove Ph, osmolality and density column as not required for this study.
13. EXERIMENTAL DESIGN	To update units for dose levels and concentrations.
13.1. Administration of Test and Reference Items	To include clarification.
22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS	To include clarification for archives location.
ATTACHMENT A	To remove footnote for nasal cavities.
Amendment 2	**Date: 01-May-2017**
ATTACHMENT A	To include description for footnote “a” and to remove evaluation for nasal cavity based on comments column.
Amendment 3	**Date: 15-Jun-2017**
7. RESPONSIBLE PERSONNEL	To include clarification for immunology analysis and to include a biomarker IS.
15.2. Cytokines Analysis	To include clarification for cytokine analysis.
Amendment 4	
7. RESPONSIBLE PERSONNEL	To remove the IS for immunology (cytokine IFN-α Analysis) as analysis will not be conducted.
15.2 Cytokine Analysis	To remove IFN-α from the list of cytokine to be analyzed as we were not able to appropriately validate an assay for the analysis.

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1. OBJECTIVE(S)

The objectives of this study are to determine the potential toxicity of mRNA-1653, when given by intramuscular injection for 1 month (3 doses) to Sprague Dawley rat and to evaluate the potential reversibility of any findings.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity; Toxicokinetics
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 Apr 2017 (First date of study-specific data collection)
Experimental Completion Date:	12 Sep 2017 (Last date data are collected from the study)
Animal Arrival:	05 Apr 2017
Initiation of Dosing:	19 Apr 2017
Completion of In-life:	19 May 2017 (main study animals) 01 Jun 2017 (recovery animals) (Last date of necropsy)
Unaudited Draft Report:	28 Jul 2017
Audited Draft Report:	05 Sep 2017
Final Report:	12 Sep 2017 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- OECD Guideline 417. *Toxicokinetics*.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- ICH Harmonised Tripartite Guideline S3a. *Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*.
- ICH Harmonised Tripartite Guideline S8. *Notes for Guidance on Immunotoxicity Testing of Human Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Nonclinical Pharmacokinetic Studies*, and *Guidelines for General Pharmacology Studies*, and *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/were not 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

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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.

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

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

5.2. Test Facility-designated Subcontractor(s)

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

- Ophthalmology

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

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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) (b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Immunology (Purity Analysis)	(b) (6) Charles River Laboratories Montreal ULC Senneville Site (CR-MTL) 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
~~**Immunology (IFN-α Analysis)**~~	(b) (6) ~~**Address as cited for Test Facility**~~

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

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

Pathology (b) (6)
Preclinical Services, Montreal
Montreal Site (PCS-MTL)
22022 Transcanadienne
Senneville, QC H9X 3R3
Canada
Tel: (b) (6)
Fax: (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

PIs at Sponsor-designated Test Site(s)

ATA analysis (b) (4), (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

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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(s)

Identification:	mRNA-1653
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP 17038
Concentration:	2.2 mg/mL
Retest Date:	Concomitant assessment, ongoing
Physical Description:	White to off-white lipid nanoparticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C

8.2. Reference Item(s)

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.

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

8.4. Analysis of Test Item

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

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

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

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

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

8.5. Reserve Samples

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

8.6. Test and Reference Item Inventory and Disposition

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

Shipping Contact
(b) (6)
Moderna Therapeutics
500 Technology Square, 8th Floor
Cambridge MA 02139, USA
Tel: (b) (6)
Cell: (b) (6)
E-mail: (b) (6)

9. SAFETY

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

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10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

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

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

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

10.2. Preparation of Test Item

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

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

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

10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1801997).

10.3.1.1. Concentration and Homogeneity Analysis

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

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Crl:CD(SD) Sprague-Dawley rat
Source:	Charles River Canada Inc., St. Constant, QC, Canada
Number of Males Ordered:	55

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Number of Females Ordered:	55
Target Age at Arrival:	4 to 8 weeks
Target Weight at Arrival:	150 to 175 g (males) 125 to 175 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

At study assignment, each animal will be identified using a subcutaneously implanted electronic identification chip.

11.3. Environmental Acclimation

A minimum acclimation period of 10 days will be allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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

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

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

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

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

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

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12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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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.

13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (~~m~~ µg/dose)	Dose Volume (µl)	Dose Concentration (~~m~~ µg/mL)	No. of Animals			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1653	10	200	50	10	10	-	-
3	mRNA-1653	50	200	250	10	10	-	-
4	mRNA-1653	150	200	750	10	10	5	5

[a] = 10/sex/groups 1 to 4 necropsied 1 day following the last dose.
[b] = The remaining 5/sex/groups 1 to 4 necropsied 2 weeks following the last dose.

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13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to Groups 1 to 4 animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29. The dose volume for each animal will be constant. The volume for each dose will be administered using a syringe/needle within the demarcated area. The injection site will be alternated on each dosing occasion.

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. Justifications of route and dose levels

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

The doses selected are based upon tolerability data of various lipid nanoparticle formulation(s) in rats, which is expected to drive toxicities observed. The mid and low dose levels were chosen based upon observed efficacy with this modified mRNA construct in a lipid nanoparticle formulation. Doses with this test material or similarly formulated material up to 1 mg/kg (sponsor internal data) were well-tolerated in rats.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all main study and recovery animals. These data will be included in an appendix to the study report, but not used in the evaluation of the results, unless considered appropriate by the Study Director. During the study, additional evaluations to those described below and/or scheduled, and considered necessary by the Study Director and/or Veterinarian to assess health status will be conducted and duly documented. More frequent observations may be undertaken if considered appropriate.

14.1. Mortality/Moribundity Checks

Frequency:	Twice daily, once in the morning and once in the afternoon, throughout the study.
Procedure:	Animals will be observed for general health/mortality and moribundity. Animals will not be removed from cage during observation, unless necessary for identification or confirmation of possible findings.

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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 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

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.

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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 during Week 4 of dosing. During Week 2 of the recovery period if Test-Item related findings are observed during the dosing period.
Procedure:	All animals will be subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used will be 1% tropicamide.
Evaluation:	A report will be included as an appendix to the Final Report.

14.7. Body Temperature

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

15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

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

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

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry
1 to 4[a]	Day 30	X	X	X

Appendix 1

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

15.1.4. Clinical Chemistry

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Appendix 1

Clinical Chemistry Parameters

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

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

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (ATTACHMENT A).

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

15.2. Cytokines Analysis

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

Appendix 1

Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			None (SST)	EDTA
Centrifugation setting			(b) (4)	(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 (processing)			CR-SHB	CR-SHB

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

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

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

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

~~**A qualified ELISA method (non-GLP) will be used for the analysis of IFN-α by the Immunology department at CR SHB. The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.**~~

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

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

Appendix 1

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

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) (4), (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-HMPVantibodies using a qualified neutralizing antibody assay method.

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

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

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Appendix 1

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main study or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of clinical pathology parameters and antibody analysis will be obtained if possible as specified in Section 15.

These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo necropsy, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

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, anti-therapeutic antibodies and cytokines will be collected (as appropriate), and will be euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. When possible, the animals will be euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, will be necropsied throughout the day. Animals will be fasted overnight before their scheduled necropsy.

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

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

Appendix 1

17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. 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

Appendix 1

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method Parametric/ Non-Parametric
Body Weight	X
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Organ Weights	X
Body Weight 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.

Appendix 1

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
Bio-Plex Manager	Data acquisition for Luminex data
Softmax Pro GxP	Data collection and regression for Elisa methods
Watson LIMS	Biomarkers data regression
Dynamics (Wyatt)	Data acquisition for particle size analysis of the test item using DLS
(b) (4)	Data acquisition
Excel	Data analyses and tabulation

21. AMENDMENTS AND DEVIATIONS

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

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

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, study plan, retained samples and specimens, and interim (if applicable) and final reports will be archived by no later than the date

Appendix 1

of final report issue. All materials generated by Charles River from this study will be transferred to CR MTL archive. One year after issue of the draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

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

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

23. REPORTING

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

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

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

Appendix 1

24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

Appendix 1

AMENDMENT APPROVAL

(b) (6)

(b) (6)

Date: 20Sep 2017

(b) (6)

As authorized by the Sponsor on 19 Sep 2017

Appendix 1

ATTACHMENT A

Tissue Collection and Preservation

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

Appendix 1

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[a]	Comment
Large intestine, rectum	-	X	X	X	-
Larynx	-	X	-	-	-
Liver	X	X	X	X	-
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, other	-	X	X	X	Lymph node draining the administration sites: popliteal (bilateral) and inguinal (bilateral)
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. Both sites.
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. Minor SOP deviations that did not impact the quality or integrity of the study have been included at the discretion of the Study Director.

None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Formulations and Dosing

- The Day 1 dose formulation samples from Group 3 (mid dose) were collected from the middle of the preparation vessel instead of the top middle, and bottom. Formulations of the high and low dose were homogeneous and therefore the Group 3 formulation was also considered homogeneous.

Postmortem and Pathology

- Two miscellaneous tissues were not available for the microscopic evaluation. Those missing tissues were noted in one male and one female. As only two missing tissues were missing, the absence was considered to have no adverse impact on the pathologist`s interpretation and on the pathology outcome.

Appendix 2

moderna
messenger therapeutics

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

Summary of Analysis

Document number	mRNA 1653 TA COT
Date of Document Generation	14 Sep 2017
Revision	003
Product name	**mRNA 1653 test article**
Product description	mRNA 1653 LNP in 93mM Tris, 7% PG, 1mM DTPA, pH 7.4
Lot No.	**MTDP 17038**
mRNA Drug Substances	CX-001049 lot MTDS 16003 and CX-001366 lot MTDS 16015
Date of Manufacture	30-Mar-2017
Time Point	T = Initial

Test	Method	Testing Reference	Acceptance Criteria	Results
RNA Content	(b) (4)	Notebook: 2017_04_14-(b) (6)	(b) (4)	
Identity CX-001049	RT-qPCR	Report MPW171350		
Identity CX-001366	RT-qPCR	Report MPW171350		
CX-001049 to CX-001366 Ratio	RT-qPCR ($2^{\Delta\Delta C_T}$)	Report MPW171350		
Endotoxin	USP 85 (b) (4)	Report 0417-024	(b) (4)	
Bioburden (TAMC) (TYMC)	USP 61	Report 957262-S01		

(b) (4)

Data Approved: (b) (6) (b) (6) Date: 14-Sep-2017

Doc: mRNA1653 TA COT

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Appendix 2

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

eurofins | Advantar

Revised Summary of Analysis[3] *DATE: 15 September 2017*

[2]Part II Release Testing for mRNA-1653 LNP Drug Product Lot # MTDP17038

Protocol Number: MRA-C0020-RTP0003.00 **Document Number:** MRA-C0020-RTR0006.01 (CPR17211)	**Date Received at Eurofins Advantar:** April 7, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1653 in a white to off-white lipid nanoparticle dispersion (93 mM Tris Buffer, 7% PG, and 1mM DTPA, pH 7.4)[3]
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17038	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Appearance (MRA-C0000-GTM0016.00)	White to off-white dispersion, no visible particulates	04/27/2017	Conforms (CPR15052, Page 10)
Purity (MRA-C0000-GTM0019.01)	(b) (4)	04/26/2017	(b) (4)
Related Impurities (MRA-C0000-GTM0019.01)		04/26/2017	
Encapsulated RNA (MRA-C0000-GTM0014.00)		04/27/2017	
Osmolality (mOsm/Kg) (USP <785>) USP39NF34 Supplement 2		05/08/2017	
Lipid Identification		05/22/2017	
SM102	Matches retention time of standard		Conforms
PEG2000-DMG	Matches retention time of standard		Conforms
Cholesterol	Matches retention time of standard		Conforms
DSPC	Matches retention time of standard		Conforms
(UHPLC-CAD)			(CPR15052, ADR D1)
Lipid Content	Lipid (mg/mL)	05/22/2017	(b) (4)
SM102	Report results		
PEG2000-DMG	Report results		
Cholesterol	Report results		
DSPC	Report results		
(UHPLC-CAD)			

Appendix 2

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

eurofins | Advantar

Revised Summary of Analysis[3] ***DATE: 15 September 2017***

[2]Part II Release Testing for mRNA-1653 LNP Drug Product Lot # MTDP17038

Protocol Number: MRA-C0020-RTP0003.00 **Document Number:** MRA-C0020-RTR0006.01 (CPR17211)	**Date Received at Eurofins Advantar:** April 7, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1653 in a white to off-white lipid nanoparticle dispersion (93 mM Tris Buffer, 7% PG, and 1mM DTPA, pH 7.4)[3]
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17038	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Lipid Impurities (UHPLC-CAD)	(b) (4)	05/22/2017	(b) (4)
Mean Particle Size (nm) (MRA-C0000-GTM0015.02)		04/26/2017	
Polydispersity (MRA-C0000-GTM0015.02)		04/26/2017	
pH (MRA-C0000-GTM0017.01)		04/27/2017	
Particulate matter[1] (USP <788> Method 2)		04/13/2017	
Residual Solvents, ethanol (MRA-C0000-GTM0018.01) (USP <467>)		05/04/2017	

[1] Testing performed at Nelson Laboratories.
[2] Part I included AEX, Bacterial Endotoxins, and Bioburden.

(b) (4)

The data generated at Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Advantar has archived the raw data.

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

09/15/2017
Date

Appendix 3

FINAL REPORT

Study Phase: Analytical Chemistry

Test Facility Study No. 5002033

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

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Appendix 3

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Appendix 3

1. SUMMARY

Dose formulation samples have been analyzed by Ion Exchange High Performance Liquid Chromatography (IEX-HPLC) for the determination of mRNA-1653.

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-1653 in dose formulations (phosphate-buffered saline (PBS) pH 7.2) in the bulk test item from Study 5002033.

For the work detailed in this report, the analytical phase experimental start date was 21 Apr 2017, and the analytical phase experimental completion date was 25 May 2017.

3. EXPERIMENTAL DESIGN

3.1. Dose Formulation Analysis

Analysis of dose formulations was carried out with regard to concentration and homogeneity.

On Day 1 of the study, duplicate samples were collected from the top, middle and bottom strata of Group 2 and 4 for concentration and homogeneity verification while duplicate samples were collected from the middle strata of Group 1 and 3. Duplicate samples were also collected from the middle strata of all Groups for concentration verification on Day 29 of the study. The samples were shipped on ice packs, stored refrigerated upon receipt and analyzed within the established stability.

3.2. Bulk Test Item Analysis

Analysis of the bulk test item was carried out with regard to concentration and particle size analysis.

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

Appendix 3

4. MATERIALS AND METHODS

4.1. Materials

4.1.1. Reference Standard

Identification:	CX-001049 mRNA
Physical Description:	Clear, colorless solution
Batch/Lot No.:	MTDS16003
Concentration:	2.05 mg/mL (used for calculations)
Retest Date:	Jul 2018
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

4.1.2. Reference Material (Bulk Test Item)

Identification:	mRNA-1653
Physical Description:	White to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP17038
Concentration:	2.2 mg/mL (used for calculations)
Date of manufacture:	30 Mar 2017
Retest Date:	1 year after date of manufacture
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

4.1.3. Characterization of Reference Standard and Reference Material

The Sponsor provided the documentation for the identity, strength, purity, composition, and stability for the reference standard and reference material. Copies of the supplied Summary of Analysis (SoA) or equivalent documentation are presented in Appendix 2.

Appendix 3

4.1.4. Inventory and Disposition of Reference Standard and Reference Material

Records of the receipt, distribution, and storage of the reference standard and reference material were maintained. All unused Sponsor-supplied reference standard and reference material were retained for use on subsequent studies for the Sponsor.

4.2. Methods

4.2.1. Analytical Procedures

The method for concentration analysis is documented in Analytical Procedure AP.5002033.SP.02 (Appendix 1) and was previously validated under Study Nos. 1801997. Concentration stability data were generated by the department of Analytical Chemistry, Charles River, CR MTL for 1 day and 5 days, for formulation samples stored at ambient temperature and in a refrigerator set to maintain 4°C, respectively, over the concentration range of 0.0100 – 2.20 mg/mL, under Study No. 1801997.

The method for particle size analysis is documented in Analytical Procedure AP.5002033.DLS.01 (Appendix 1).

4.3. Computerized Systems

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

Text Table 1
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Empower 3 (Waters Corporation)	Build 3471 SR1	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
Dynamics (Wyatt)	7.1.9.3	Data acquisition for particle size analysis for the test item using DLS
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

5. RESULTS AND DISCUSSIONS

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

Appendix 3

5.1. Dose Formulation Analysis

All study samples analyzed had mean concentrations within or equal to the acceptance criteria of ± 15% (individual values within or equal to ± 20%) of their theoretical concentrations. Results are presented in Table 1.

For homogeneity, the RSD of concentrations for all samples in each group tested was within the acceptance criteria of ≤ 5%. Results are presented in Table 1.

5.2. Bulk Test Item Analysis

The concentration and the particle size was measured. Concentration and particle size results were consistent with the initial Certificate of Analysis provided by the Sponsor. Results are presented in Table 2 and Table 3.

6. CONCLUSION

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

The bulk Test Item analysis demonstrated that the test item was suitable for use during the study period.

Appendix 3

7. REPORT APPROVAL

(b) (6)

(b) (6) Date: 02 Oct 2017

Appendix 3

Table 1 Study Samples - Concentration and Homogeneity

Occasion (Sampling Date)	Group	Theoretical Concentration (mg/mL)	Sampling Location	Measured Concentration (mg/mL)	Percent of Theoretical	RSD (%)
Day 1 (19 Apr 2017)	1	(b) (4)	Middle	ND	-	-
				ND	-	
			Mean	ND	-	
	2		Top	(b) (4)		
			Middle			
			Bottom			
			Mean			
	3		Middle			
			Mean			
	4		Top			
			Middle			
			Bottom			
			Mean			
Day 29 (18 May 2017)	1		Middle	ND	-	-
				ND	-	
			Mean	ND	-	
	2		Middle	(b) (4)		-
			Mean			
	3		Middle			-
			Mean			
	4		Middle			-
			Mean			

ND = None detected.

Appendix 3

Table 2 Bulk Test Item - Concentration

Occasion (Analysis Date)	Theoretical Concentration (mg/mL)	Measured Concentration (mg/mL)	Percent of Theoretical	Mean Measured Concentration (mg/mL)
End of study (25 May 2017)	(b) (4)			

Table 3 Bulk Test Item - Particle Size Analysis

Occasion (Analysis Date)	Theoretical Diameter (nm)	Measured Diameter (nm)	PD Index	% Difference Between Duplicate	Mean Measured Diameter (nm)
End of study (25 May 2017)	(b) (4)				

Appendix 3

Appendix 1
Analytical Procedures

Appendix 3

Analytical Procedure (AP.5002033.SP.02)

Determination of mRNA-1653 in Dose Formulations by Ion Exchange High Performance Chromatography Using Ultraviolet/Visible Detection

Reference Standard, Reference Material and Vehicle

Reference Standard	CX-001049 mRNA
Lot number	MTDS16003
Concentration (actual)	2.05 mg/mL
Reference Material	mRNA-1653
Description	White dispersion in lipid nanoparticles
Lot number	MTDP17038
Concentration (nominal)	2.2 mg/mL (to be used for calculations)
Vehicle	Phosphate-buffered Saline (PBS) pH 7.2

For storage conditions for reference standard and reference material supplied by the Sponsor, refer to the corresponding log sheets.

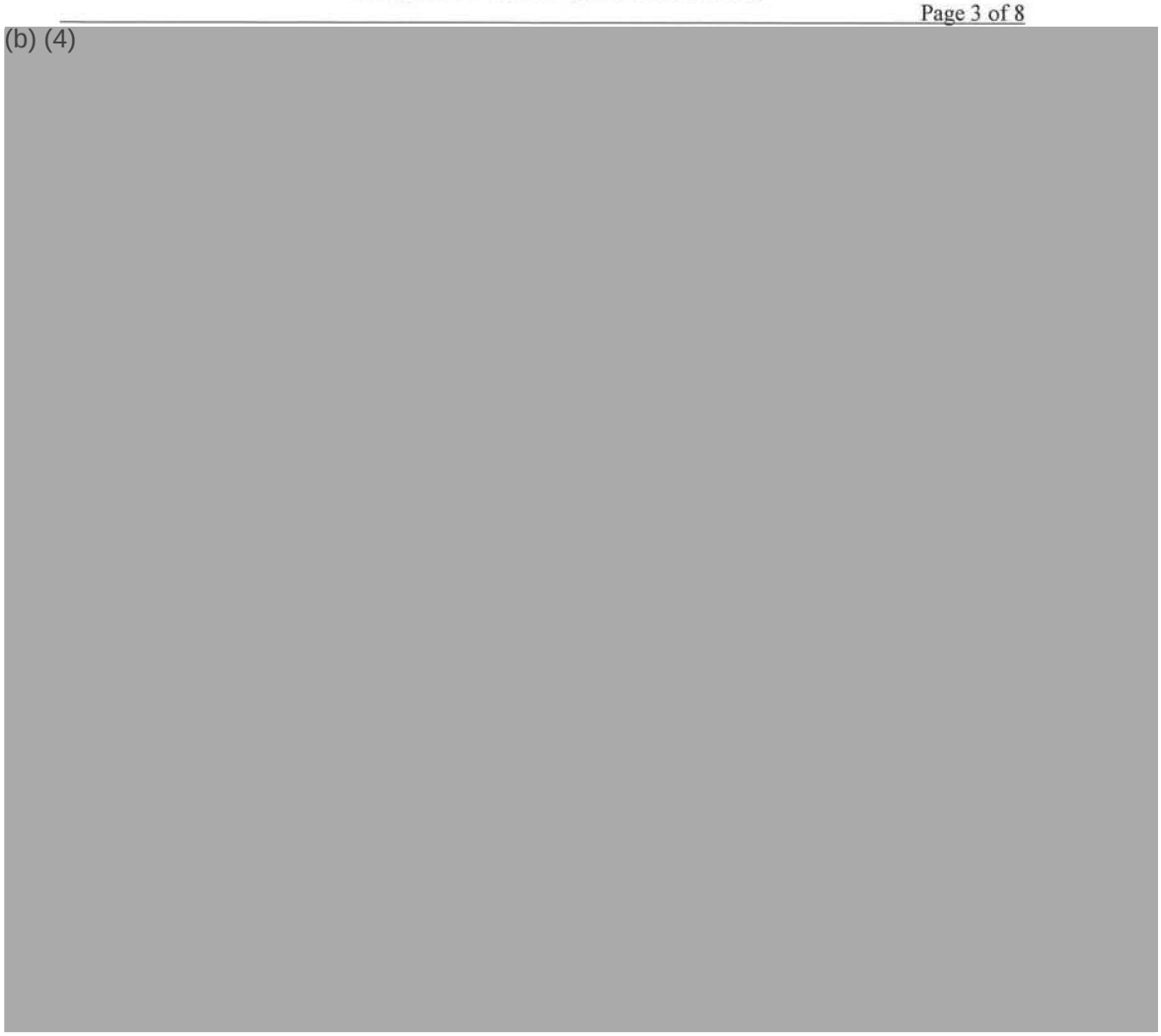
NOTES:

- ❑ Modifications may be made to the chromatographic conditions in order to optimize the chromatography.
- ❑ Solution volumes throughout this AP (including reagent solutions, blanks, standard stocks, standards and spiked samples) may be scaled up or down as long as the final concentration remains the same as specified in the procedure.
- ❑ Any changes made are to be documented in the raw data of the run.
- ❑ Unless otherwise indicated, information relating to the time of mixing/stirring, temperature or mixing method used in the preparation of solutions, diluents, mobile phases and vehicle will be considered non-critical. If a step is deemed critical, it will be noted within the procedure, and a positive entry will be made in the raw data
- ❑ **The compound is a mRNA, benchwork and handling should be performed under clean conditions to limit RNase contamination. When possible use RNase free tubes, pipette and repeater tips for reference standard/test item dilutions. DO NOT VORTEX, mix manually by inversion.**
- ❑ The method was previously validated under study 1801997.

Appendix 3

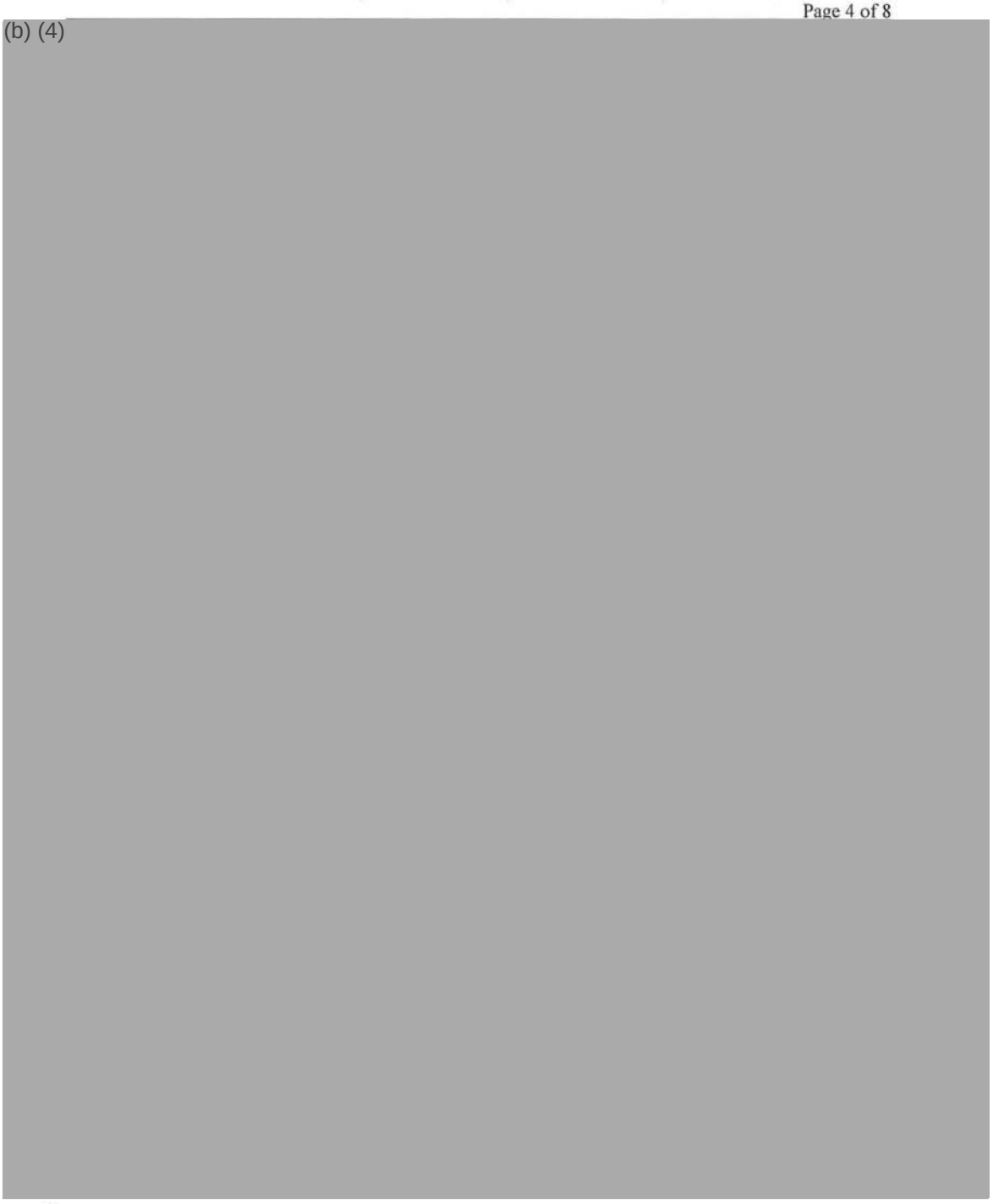
Appendix 3

(b) (4)



Appendix 3

(b) (4)

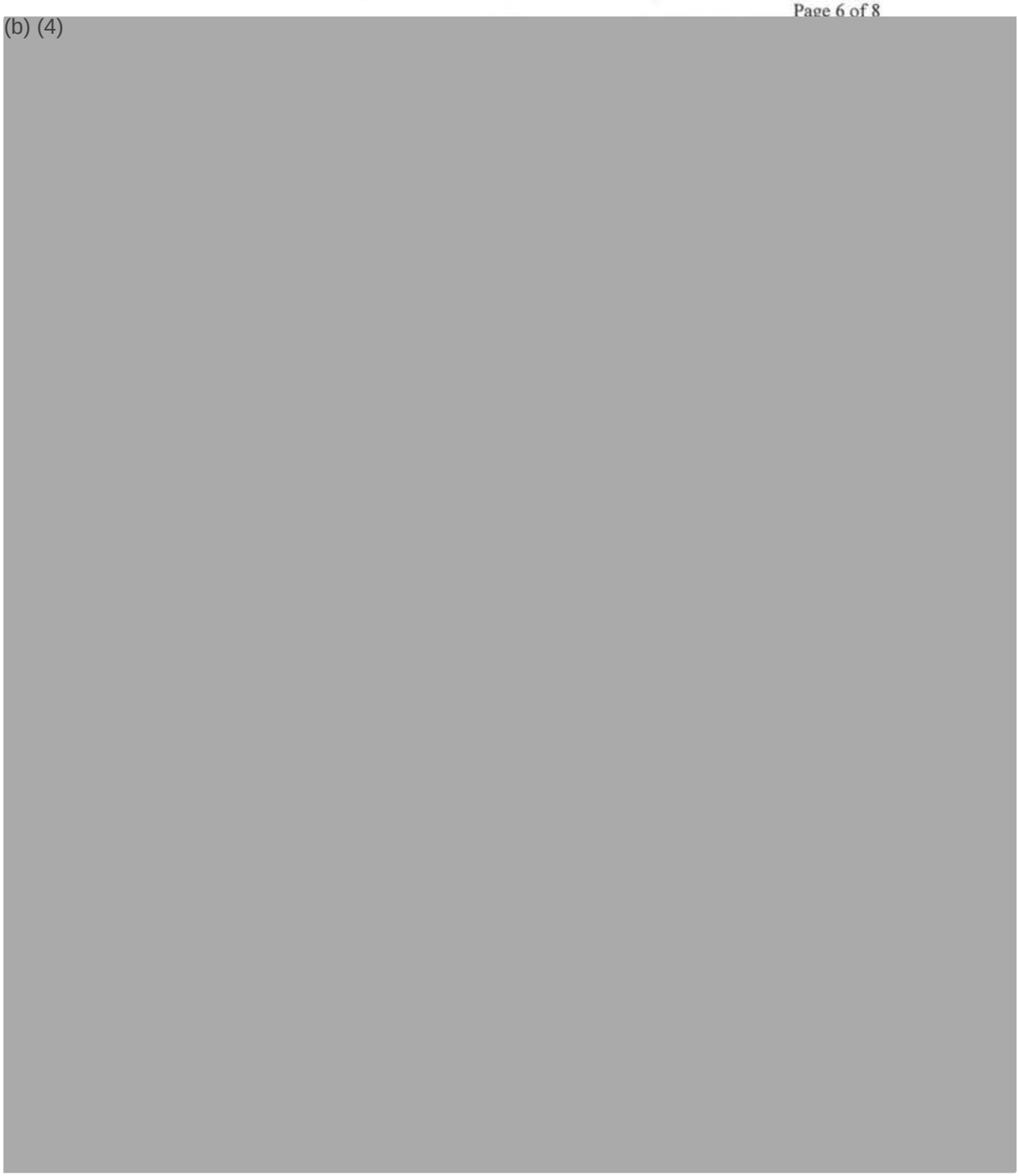


Appendix 3

(b) (4)

Appendix 3

(b) (4)



Appendix 3

(b) (4)

Acceptance criteria

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

Appendix 3

Analytical Procedure (AP.5002033.SP.02)

Page 8 of 8

AP Version Control

First update:
• Included missing expiry period and updated Test item name in AP title.

Verified by (b) (6) Date 21 Jul 2017

Approved by (b) (6) Date 24 Jul 2017

Authorized by (b) (6) Date 24-JUL-2017

Scientific Director ✓

Appendix 3

Analytical Procedure (AP.5002033.DLS.01)

Determination of the Particle Size Distribution of mRNA-1653 Drug Product by Dynamic Light Scattering (DLS) using Wyatt DynaPro NanoStar.

Bulk Test Item

Identity	mRNA-1653
Description	White dispersion in lipid nanoparticles
Lot number	MTDP 17038
Concentration (nominal)	2.2 mg/mL (to be used for calculations)

For storage conditions for test item supplied by the Sponsor, refer to the corresponding log sheets.

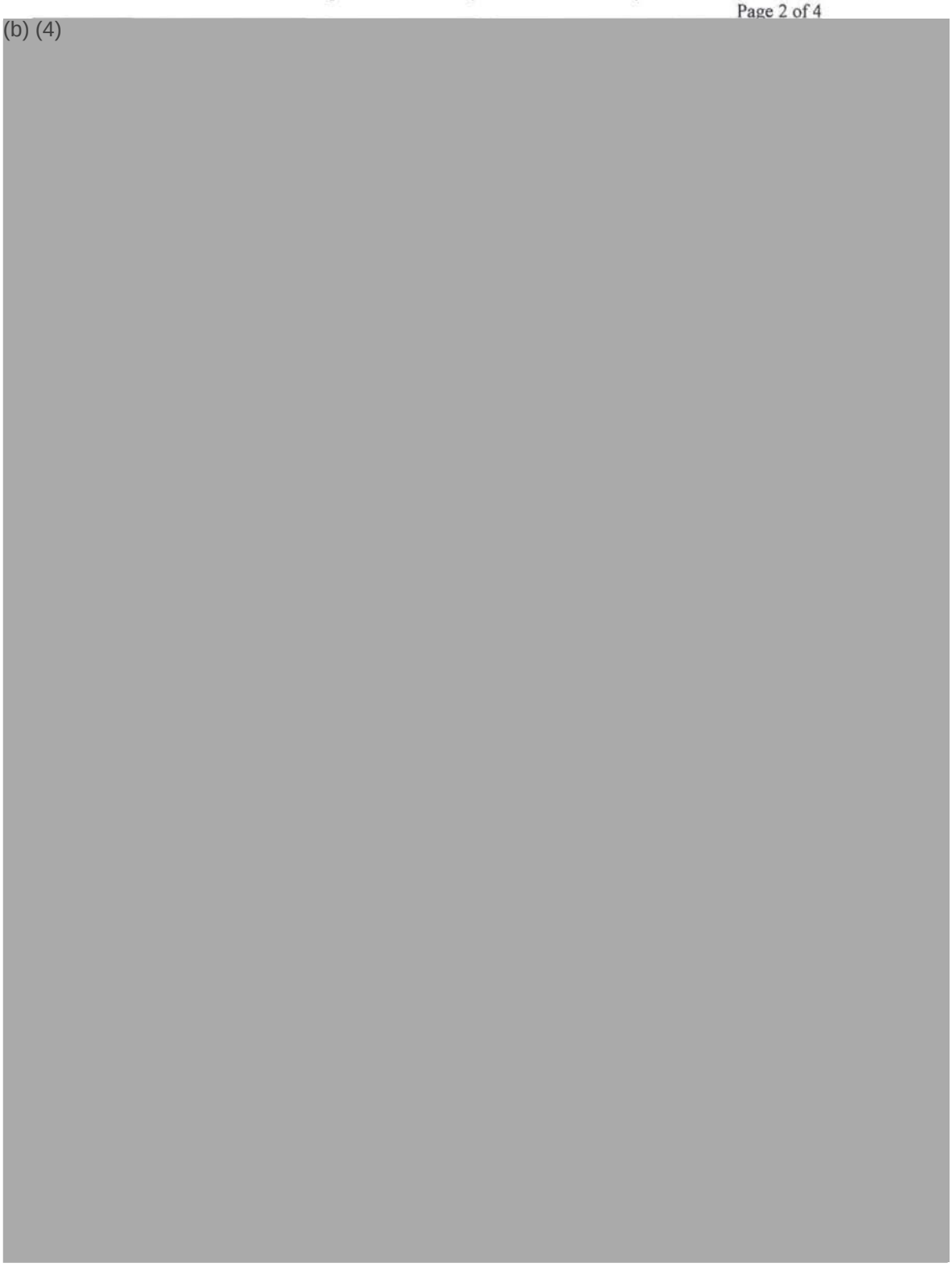
NOTES:

- ❑ Solution volumes throughout this AP may be scaled up or down as long as the final concentration remains the same as specified in the procedure.
- ❑ Any changes made are to be documented in the raw data of the run.
- ❑ Unless otherwise indicated, information relating to the time of mixing/stirring, temperature or mixing method used in the preparation of solutions will be considered non-critical. If a step is deemed critical, it will be noted within the procedure, and a positive entry will be made in the raw data
- ❑ **The compound is a mRNA, benchwork and handling should be performed under clean conditions to limit RNase contamination. When possible use RNase free tubes, pipette and repeater tips for test item dilutions. DO NOT VORTEX, mix manually by inversion.**
- ❑ Refer to SOP CAE-238 for operation of the Dynapro Nanostar DLS instrument with Dynamics software.

(b) (4)

Appendix 3

(b) (4)

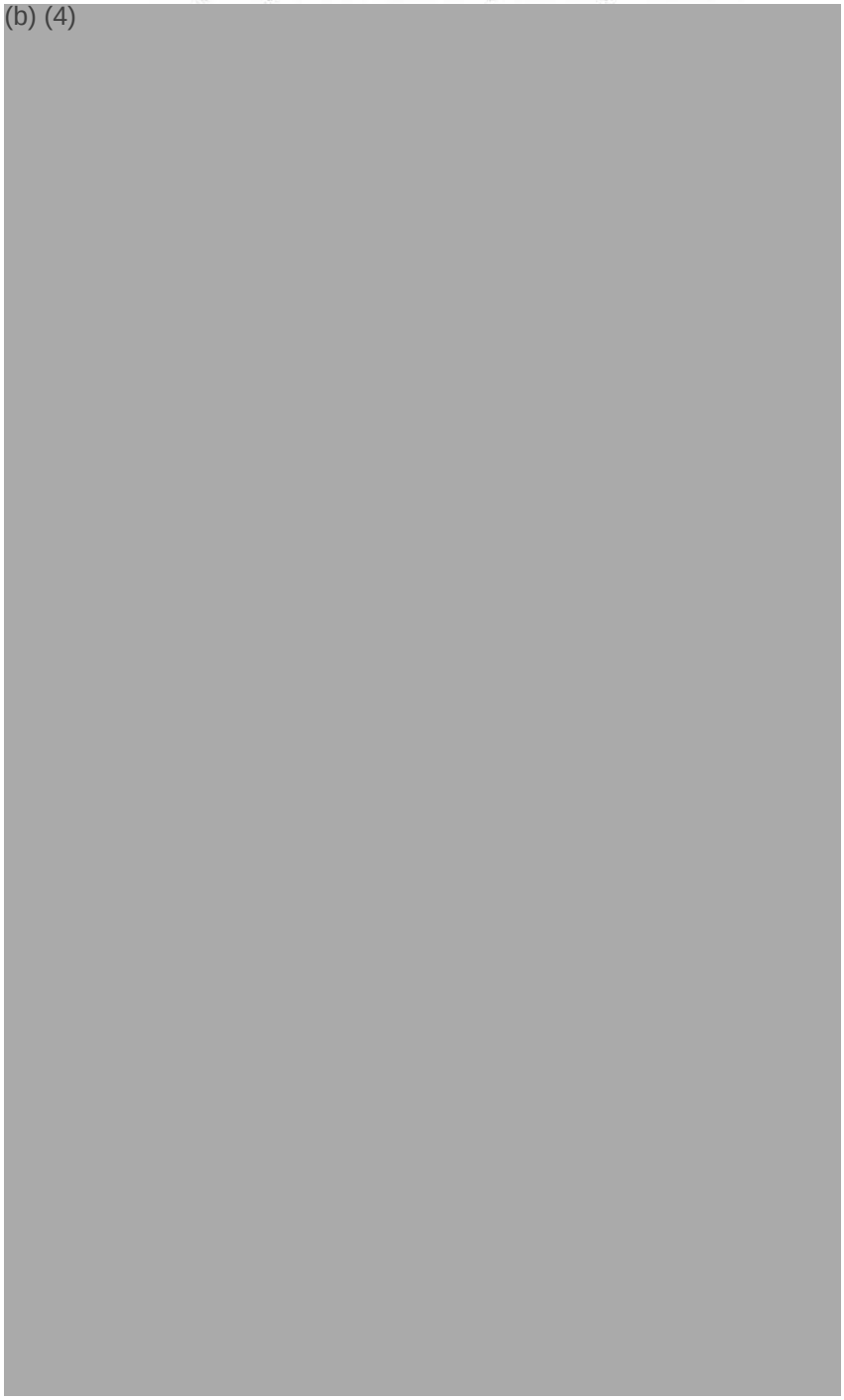


Appendix 3

Instrument Parameters for Sample Reading

Save all settings as a preset on location D:\Dynamics\Projects\5002033.

(b) (4)



Appendix 3

(b) (4)

[redacted]

AP Version Control

Initial version.

Verified by (b) (6) Date 24 May 2017.

Approved by (b) (6) Date 24 May 2017

Authorized by (b) (6) Date 25 May 2017

Scientific Director ☑

Appendix 3

Appendix 2
Certificates of Analysis

Appendix 3

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messenger therapeutics

200 Technology Square • Cambridge, MA 02139
Phone 617.714.6500 • Fax 617.583.1998

SUMMARY OF ANALYSIS

Sample Description:	**CX-001049** (former name MDPC-0010) (mRNA API)
mRNA length:	(b) (4)
Plasmid ID:	PL-006165
SSC:	33.09 µg/mL
Lot or Batch No:	**MTDS16003**
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	February 2016
Date of Analysis:	July 2016
Storage:	Shipping Temperature: ≤ -15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	July 2017

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Appearance	MRA-C0000-GTM0008.00	Clear, colorless solution, essentially free of visible particulates	Clear, colorless solution, essentially free of visible particulates	CPR11146 ADR C1
Identity by Sanger Sequencing	TSOP134.00	(b) (4)		209-TSOP134-076.00
Total RNA content	DSAD-TM-0019*	(b) (4)		2017_04_10-046-(b) (6)
Purity	MRA-C0000-GTM0001.02			CPR11147 ADR C16
Product related impurities	MRA-C0000-GTM0001.02			CPR11147 ADR C16
pH	USP<791>			CPR11146 ADR B1
Residual DNA template	qPCR TSOP344.01			209-TSOP344-072.00

CX-001049 Page 1 of 2 version 01

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Residual solvents TEA	MRA-C0000-GTM0005.02	(b) (4)	CPR11150 ADR P9
IPA	MRA-C0000-GTM0007.02		CPR11151 ADR B28
Ethanol	MRA-C0000-GTM0007.02		CPR11151 ADR B28
Hexylene glycol	MRA-C0000-GTM0007.02		CPR11152 P11
% Poly A tailed RNA (% Tailless RNA)	MRA-C0000-GTM0003.02		CPR11148 ADR A20
% 5' Capped	MRA-C0000-GTM0002.01		CPR11149 ADR B6
Bioburden	USP<61>		16-02274
Bacterial Endotoxins	USP<85>		PD Batch Record MTDS16003

(b) (4)

Signatures:

(b) (6)
Generated by: (b) (6) Date: 11 Apr 17

(b) (6)
Reviewed by: (b) (6) Date: 11 APR 20 17

CX-001049 Page 2 of 2 version 01

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SUMMARY OF ANALYSIS

Sample Description:	**CX-001049** (former name MDPC-0010) (mRNA API)
mRNA length:	(b) (4)
Plasmid ID:	PL-006165
SSC:	33.09 µg/mL
Lot or Batch No:	**MTDS16003**
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	February 2016
Date of Analysis:	July 2016
Storage:	Shipping Temperature: ≤ -15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	July 2018

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Appearance	MRA-C0000-GTM0008.00	Clear, colorless solution, essentially free of visible particulates	Clear, colorless solution, essentially free of visible particulates	CPR15943 P14
Identity by Sanger Sequencing	TSOP134.00	(b) (4)		209-TSOP134-076.00
Total RNA content	DSAD-TM-0019*			2017_04_10-046-(b) (6)
Purity	MRA-C0000-GTM0001.04			CPR15944 ADR C1
Product related impurities	MRA-C0000-GTM0001.04			CPR15944 ADR C1
pH	MRA-C0000-GTM0006.00			CPR15943 ADR C1
Residual DNA template	qPCR TSOP344.01			209-TSOP344-072.00

CX-001049 Page 1 of 2 version 03

Appendix 3

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Residual solvents TEA	MRA-C0000-GTM0005.02	(b) (4)	CPR11150 ADR P9
IPA	MRA-C0000-GTM0007.02		CPR11151 ADR B28
Ethanol	MRA-C0000-GTM0007.02		CPR11151 ADR B28
Hexylene glycol	MRA-C0000-GTM0009.02		CPR11152 P11
% Poly A tailed RNA (% Tailless RNA)	MRA-C0000-GTM0003.05		CPR15945 ADR C24
% 5' Capped	MRA-C0000-GTM0002.02		CPR15946 P18
Bioburden	USP<61>		16-02274
Bacterial Endotoxins	USP<85>		PD Batch Record MTDS16003

(b) (4)

Signatures:

(b) (6)

(b) (6)

(b) (6)

(b) (6)

Reviewed by:

31 July 2017
Date:

31 July 2017
Date:

CX-001049 Page 2 of 2 version 03

Appendix 3

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Summary of Analysis

Document number	mRNA 1653 TA COT
Date of Document Generation	21 Apr 2017
Revision	002
Product name	**mRNA 1653 test article**
Product description	mRNA 1653 LNP in 100mM Tris, 7% PG, 1mM DTPA, pH 7.4
Lot No.	**MTDP 17038**
mRNA Drug Substances	CX-001049 lot MTDS 16003 and CX-001366 lot MTDS 16015
Date of Manufacture	30-Mar-2017
Time Point	T = Initial

Test	Method	Testing Reference	Acceptance Criteria	Results
RNA Content	(b) (4)	Notebook: 2017_04_14-(b) (6)	(b) (4)	
Identity CX-001049	RT-qPCR	Report MPW171350		
Identity CX-001366	RT-qPCR	Report MPW171350		
CX-001049 to CX-001366 Ratio	RT-qPCR (2^ΔΔ C_T)	Report MPW171350		
Endotoxin	USP 85 (b) (4)	Report 0417-024		
Bioburden (TAMC) (TYMC)	USP 61	Report 957262-S01		

Data Approved: (b) (6) (b) (6) Date: 4-24-2017

Doc: mRNA1653 TA COT *Page 1 of 1*

Appendix 3

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

eurofins | Advantar

Summary of Analysis ***DATE: 14 July 2017***

[2]Part II Release Testing for mRNA-1653 LNP Drug Product Lot # MTDP17038

Protocol Number: MRA-C0020-RTP0003.00 **Document Number:** MRA-C0020-RTR0006.00 (CPR15057)	**Date Received at Eurofins Advantar:** April 7, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1653 in a white to off-white lipid nanoparticle dispersion (100mM Tris Buffer, 7% PG, and 1mM DTPA, pH 7.4)
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17038	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Appearance (MRA-C0000-GTM0016.00)	White to off-white dispersion, no visible particulates	04/27/2017	Conforms (CPR15052, Page 10)
Purity (MRA-C0000-GTM0019.01)	(b) (4)	04/26/2017	(b) (4)
Related Impurities (MRA-C0000-GTM0019.01)		04/26/2017	
Encapsulated RNA (MRA-C0000-GTM0014.00)		04/27/2017	
Osmolality (mOsm/Kg) (USP <785>) USP39NF34 Supplement 2		05/08/2017	
Lipid Identification		05/22/2017	
SM102	Matches retention time of standard		Conforms
PEG2000-DMG	Matches retention time of standard		Conforms
Cholesterol	Matches retention time of standard		Conforms
DSPC	Matches retention time of standard		Conforms
(UHPLC-CAD)			(CPR15052, ADR D1)
Lipid Content	Lipid (mg/mL)	05/22/2017	(b) (4)
SM102	Report results		
PEG2000-DMG	Report results		
Cholesterol	Report results		
DSPC	Report results		
(UHPLC-CAD)			

Appendix 3

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San Diego, CA 92121
Phone: (858) 228-778

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Summary of Analysis ***DATE: 14 July 2017***

[2]Part II Release Testing for mRNA-1653 LNP Drug Product Lot # MTDP17038

Protocol Number: MRA-C0020-RTP0003.00 **Document Number:** MRA-C0020-RTR0006.00 (CPR15057)	**Date Received at Eurofins Advantar:** April 7, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1653 in a white to off-white lipid nanoparticle dispersion (100mM Tris Buffer, 7% PG, and 1mM DTPA, pH 7.4)
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17038	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Lipid Impurities (UHPLC-CAD)	(b) (4)	05/22/2017	(b) (4)
Mean Particle Size (nm) (MRA-C0000-GTM0015.02)		04/26/2017	(b) (4)
Polydispersity (MRA-C0000-GTM0015.02)		04/26/2017	
pH (MRA-C0000-GTM0017.01)		04/27/2017	
Particulate matter [1] (USP <788> Method 2)		04/13/2017	(b) (4)
Residual Solvents, ethanol (MRA-C0000-GTM0018.01) (USP <467>)		05/04/2017	

[1] Testing performed at Nelson Laboratories.
[2] Part I included AEX, Bacterial Endotoxins, and Bioburden.

The data generated at Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Advantar has archived the raw data.

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

14 JUL 2017
Date

Appendix 4

Individual Animal Mortality Explanation Page

Abbreviation	Description	Abbreviation	Description
AD or ACCD	Accidental death	REC	Recovery euthanasia
FD	Found dead	REL	Released
INTM	Interim	TE or TERM	Terminal euthanasia
NR	Not recorded	UE or UNSC	Unscheduled euthanasia

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Removal Time represents the time the removal was entered into the Provantis system and may not be representative of the time of death.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 4

Individual Animal Mortality

5002033

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	18MAY2017	14:37	.	.	TERM
			1002	1001	30	5	18MAY2017	14:37	.	.	TERM
			1003	1001	30	5	18MAY2017	15:51	.	.	TERM
			1004	1004	30	5	18MAY2017	15:53	.	.	TERM
			1005	1004	30	5	18MAY2017	16:59	.	.	TERM
			1006	1004	30	5	18MAY2017	17:02	.	.	TERM
			1007	1007	30	5	18MAY2017	19:18	.	.	TERM
			1008	1007	30	5	18MAY2017	19:11	.	.	TERM
			1009	1009	30	5	18MAY2017	20:27	.	.	TERM
			1010	1009	30	5	18MAY2017	20:32	.	.	TERM
			1011	1011	43	7	31MAY2017	9:06	.	.	REC
			1012	1011	43	7	31MAY2017	9:47	.	.	REC
			1013	1011	43	7	31MAY2017	10:27	.	.	REC
			1014	1014	43	7	31MAY2017	11:25	.	.	REC
			1015	1014	43	7	31MAY2017	12:06	.	.	REC
1	0 ug/dose	Female	1501	1501	30	5	19MAY2017	14:50	.	.	TERM
			1502	1501	30	5	19MAY2017	14:32	.	.	TERM
			1503	1501	30	5	19MAY2017	16:00	.	.	TERM
			1504	1504	30	5	19MAY2017	15:51	.	.	TERM
			1505	1504	30	5	19MAY2017	17:10	.	.	TERM
			1506	1504	30	5	19MAY2017	17:03	.	.	TERM
			1507	1507	30	5	19MAY2017	19:19	.	.	TERM
			1508	1507	30	5	19MAY2017	19:11	.	.	TERM
			1509	1509	30	5	19MAY2017	20:22	.	.	TERM
			1510	1509	30	5	19MAY2017	20:25	.	.	TERM
			1511	1511	43	7	01JUN2017	10:55	.	.	REC
			1512	1511	43	7	01JUN2017	11:36	.	.	REC
			1513	1511	43	7	01JUN2017	12:13	.	.	REC
			1514	1514	43	7	01JUN2017	13:55	.	.	REC
			1515	1514	43	7	01JUN2017	14:30	.	.	REC
2	10 ug/dose	Male	2001	2001	30	5	18MAY2017	15:32	.	.	TERM
			2002	2001	30	5	18MAY2017	15:35	.	.	TERM
			2003	2001	30	5	18MAY2017	16:43	.	.	TERM
			2004	2004	30	5	18MAY2017	16:46	.	.	TERM
			2005	2004	30	5	18MAY2017	18:59	.	.	TERM

Appendix 4

Individual Animal Mortality

5002033

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
2	10 ug/dose	Male	2006	2004	30	5	18MAY2017	17:50	.	.	TERM
			2007	2007	30	5	18MAY2017	20:10	.	.	TERM
			2008	2007	30	5	18MAY2017	20:11	.	.	TERM
			2009	2009	30	5	18MAY2017	21:19	.	.	TERM
			2010	2009	30	5	18MAY2017	21:33	.	.	TERM
2	10 ug/dose	Female	2501	2501	30	5	19MAY2017	15:42	.	.	TERM
			2502	2501	30	5	19MAY2017	15:33	.	.	TERM
			2503	2501	30	5	19MAY2017	16:52	.	.	TERM
			2504	2504	30	5	19MAY2017	16:46	.	.	TERM
			2505	2504	30	5	19MAY2017	19:04	.	.	TERM
			2506	2504	30	5	19MAY2017	17:49	.	.	TERM
			2507	2507	30	5	19MAY2017	20:05	.	.	TERM
			2508	2507	30	5	19MAY2017	20:07	.	.	TERM
			2509	2509	30	5	19MAY2017	21:14	.	.	TERM
			2510	2509	30	5	19MAY2017	21:18	.	.	TERM
3	50 ug/dose	Male	3001	3001	30	5	18MAY2017	15:15	.	.	TERM
			3002	3001	30	5	18MAY2017	15:16	.	.	TERM
			3003	3001	30	5	18MAY2017	16:26	.	.	TERM
			3004	3004	30	5	18MAY2017	16:26	.	.	TERM
			3005	3004	30	5	18MAY2017	17:36	.	.	TERM
			3006	3004	30	5	18MAY2017	17:35	.	.	TERM
			3007	3007	30	5	18MAY2017	19:50	.	.	TERM
			3008	3007	30	5	18MAY2017	19:51	.	.	TERM
			3009	3009	30	5	18MAY2017	21:01	.	.	TERM
			3010	3009	30	5	18MAY2017	21:16	.	.	TERM
3	50 ug/dose	Female	3501	3501	30	5	19MAY2017	15:24	.	.	TERM
			3502	3501	30	5	19MAY2017	15:14	.	.	TERM
			3503	3501	30	5	19MAY2017	16:32	.	.	TERM
			3504	3504	30	5	19MAY2017	16:30	.	.	TERM
			3505	3504	30	5	19MAY2017	17:42	.	.	TERM
			3506	3504	30	5	19MAY2017	17:35	.	.	TERM
			3507	3507	30	5	19MAY2017	19:49	.	.	TERM
			3508	3507	30	5	19MAY2017	19:49	.	.	TERM
			3509	3509	30	5	19MAY2017	20:55	.	.	TERM

Appendix 4

Individual Animal Mortality

5002033

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
3	50 ug/dose	Female	3510	3509	30	5	19MAY2017	20:59	.	.	TERM
4	150 ug/dose	Male	4001	4001	30	5	18MAY2017	14:57	.	.	TERM
			4002	4001	30	5	18MAY2017	14:56	.	.	TERM
			4003	4001	30	5	18MAY2017	16:06	.	.	TERM
			4004	4004	30	5	18MAY2017	16:10	.	.	TERM
			4005	4004	30	5	18MAY2017	17:19	.	.	TERM
			4006	4004	30	5	18MAY2017	17:18	.	.	TERM
			4007	4007	30	5	18MAY2017	19:34	.	.	TERM
			4008	4007	30	5	18MAY2017	19:31	.	.	TERM
			4009	4009	30	5	18MAY2017	20:44	.	.	TERM
			4010	4009	30	5	18MAY2017	20:52	.	.	TERM
			4011	4011	43	7	31MAY2017	9:26	.	.	REC
			4012	4011	43	7	31MAY2017	10:06	.	.	REC
			4013	4011	43	7	31MAY2017	10:47	.	.	REC
			4014	4014	43	7	31MAY2017	11:46	.	.	REC
			4015	4014	43	7	31MAY2017	12:29	.	.	REC
4	150 ug/dose	Female	4501	4501	30	5	19MAY2017	15:07	.	.	TERM
			4502	4501	30	5	19MAY2017	14:56	.	.	TERM
			4503	4501	30	5	19MAY2017	16:16	.	.	TERM
			4504	4504	30	5	19MAY2017	16:07	.	.	TERM
			4505	4504	30	5	19MAY2017	17:26	.	.	TERM
			4506	4504	30	5	19MAY2017	17:17	.	.	TERM
			4507	4507	30	5	19MAY2017	19:34	.	.	TERM
			4508	4507	30	5	19MAY2017	19:31	.	.	TERM
			4509	4509	30	5	19MAY2017	20:39	.	.	TERM
			4510	4509	30	5	19MAY2017	20:42	.	.	TERM
			4511	4511	43	7	01JUN2017	11:17	.	.	REC
			4512	4511	43	7	01JUN2017	11:53	.	.	REC
			4513	4511	43	7	01JUN2017	13:39	.	.	REC
			4514	4514	43	7	01JUN2017	14:12	.	.	REC
			4515	4514	43	7	01JUN2017	14:50	.	.	REC

Appendix 5

Individual Clinical Observations Explanation Page

Abbreviation	Description	Abbreviation	Description
AM SIRT	Signs of ill health or reaction to treatment check in the morning	PM SIRT	Signs of ill health or reaction to treatment check in the afternoon
CSO	Cage side observation	PostRx #	Observation post dosing
DE	Detailed examination	PreRx #	Observation predosing
During Rx/R #	Observation during dosing	Unsc #	Unscheduled examination
Vet Aid	Anything observed by Vet Aid	#	Number to avoid using the same timeslot/animal/day

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Only animals with findings are presented in this appendix.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-4 DE	4 DE	11 DE	18 DE	25 DE	30 DE	32 DE	39 DE
1	m	1007	Skin, Scab	Tail	.	.	.	.	.	X	.	.
		1010	Skin, Scab	Hindlimb, Left	.	.	X	.	.	X	.	.
		1012	Swollen Firm	Treatment Site No.01	.	.	.	.	.	.	1	1
		1013	Skin, Scab	Dorsal Cervical	.	X	X	X	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	X	X	X	.	X	X
		1015	Skin, Scab	Sacral	.	X	.	.	.	.	.	.
			Skin, Scab	Interscapular	X	X	X	.	.	.	.	.
			Fur, Staining, Red	Interscapular	X	X	X	.	.	.	.	.
			Fur, Thin Cover	Interscapular	X	X	X	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	.	.	.	.	.	.	X	X

Severity Codes: X = Present; 1 = Slight

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-4 DE	2 Unsc	4 DE	11 DE	18 DE	25 DE	30 DE
2	m	2001	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1
		2002	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1
			Skin, Lesion w/ Discharge	Ventral Cervical	.	1	.	.	.	.	.
			Skin, Scab	Ventral Cervical	.	.	X	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	.	X	X	X	.	.	.
			Fur, Thin Cover	Ventral Cervical	.	X	X	X	.	.	.
		2003	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1
			Fur, Staining, Red	Muzzle	.	.	.	.	.	.	X
			Fur, Staining, Red	Forepaw, Right	.	.	.	.	.	.	X
			Fur, Staining, Red	Forepaw, Left	.	.	.	.	.	.	X
			Tail, Bent		.	.	.	.	X	X	X
		2004	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1
		2005	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1
			Skin, Lesion	Ventral Cervical	1	.	.	.	.	.	.
			Fur, Staining, Red	Ventral Cervical	X	.	.	.	.	.	.
			Fur, Thin Cover	Ventral Cervical	X	.	X	X	.	.	.
		2006	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1
			Malocclusion		.	.	.	.	X	X	X
		2007	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1
		2008	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1
		2009	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1
		2010	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	1

Severity Codes: X = Present; 1 = Slight

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-4 DE	4 DE	25 DE	30 DE
3	m	3001	Swollen Firm	Hindlimb, Left	.	.	.	2
		3002	Swollen Firm	Hindlimb, Left	.	.	.	2
		3003	Swollen Firm	Hindlimb, Left	.	.	.	2
			Fur, Staining, Red	Periorbital, Left	.	.	.	X
			Fur, Staining, Red	Muzzle	.	.	.	X
		3004	Swollen Firm	Hindlimb, Left	.	.	.	2
			Skin, Scab	Tail	.	.	.	X
		3005	Swollen Firm	Hindlimb, Left	.	.	.	2
		3006	Swollen Firm	Hindlimb, Left	.	.	.	2
			Fur, Staining, Red	Cranium	.	.	.	X
		3007	Swollen Firm	Hindlimb, Left	.	.	.	2
			Fur, Staining, Red	Muzzle	.	.	.	X
			Fur, Thin Cover	Forepaw, Right	.	.	.	X
			Fur, Thin Cover	Forepaw, Left	.	.	.	X
		3008	Swollen Firm	Hindlimb, Left	.	.	.	1
			Fur, Staining, Red	Periorbital, Right	.	.	.	X
			Fur, Thin Cover	Forepaw, Right	.	.	X	X
			Fur, Thin Cover	Forepaw, Left	.	.	X	X
		3009	Swollen Firm	Hindlimb, Left	.	.	.	2
			Skin, Scab	Dorsal Cervical	X	.	.	.
			Skin, Scab	Cranium	X	X	.	.
		3010	Swollen Firm	Hindlimb, Left	.	.	.	2

Severity Codes: X = Present; 1 = Slight; 2 = Moderate

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	11 DE	18 DE	25 DE	30 DE	32 DE	39 DE	43 DE
4	m	4001	Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
			Skin, Red	Hindlimb, Left	.	.	.	X	.	.	.
		4002	Hunched Posture		.	.	.	X	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
			Fur, Erected		.	.	.	X	.	.	.
		4003	Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
			Skin, Scab	Hindlimb, Right	.	X	.	.	.	.	.
		4004	Hunched Posture		.	.	.	X	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
			Skin, Scab	Cranium	.	.	.	X	.	.	.
			Fur, Erected		.	.	.	X	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	X	.	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	X	.	.	.
			Fur, Thin Cover	Cranium	.	.	.	X	.	.	.
		4005	Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
		4006	Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
			Fur, Staining, Red	Periorbital, Right	.	.	.	X	.	.	.
			Fur, Staining, Red	Muzzle	.	.	.	X	.	.	.
			Fur, Staining, Red	Forepaw, Right	.	.	.	X	.	.	.
			Fur, Staining, Red	Forepaw, Left	.	.	.	X	.	.	.
		4007	Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
			Fur, Staining, Red	Forepaw, Right	.	.	.	X	.	.	.
			Fur, Staining, Red	Forepaw, Left	.	.	.	X	.	.	.
			Fur, Staining, Red	Cranium	.	.	.	X	.	.	.
		4008	Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
			Skin, Scab	Tail	.	.	.	X	.	.	.
		4009	Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	X	X	.	.	.
		4010	Swollen Firm	Hindlimb, Left	.	.	.	3	.	.	.
			Skin, Scab	Tail	X	X	X	X	.	.	.
		4011	Swollen Firm	Treatment Site No.01	.	.	.	.	1	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	X	.
			Skin, Scab	Hindlimb, Right	.	.	X	.	.	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 150 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	11 DE	18 DE	25 DE	30 DE	32 DE	39 DE	43 DE
4	m	4012	Swollen Firm	Treatment Site No.01	.	.	.	.	1	1	.
			Skin, Scab	Dorsal Cervical	X	.	.	.	.	.	.
			Fur, Thin Cover	Dorsal Cervical	X	.	.	.	X	X	.
		4013	Swollen Firm	Treatment Site No.01	.	.	.	.	2	1	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	X	X
		4014	Swollen Firm	Treatment Site No.01	.	.	.	.	2	1	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	.	.
		4015	Swollen Firm	Treatment Site No.01	.	.	.	.	1	1	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	X	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 4 - 150 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-4 DE	4 DE	11 DE	18 DE	25 DE	30 DE	32 DE	39 DE
1	f	1501	Skin, Scab	Dorsal Cervical	X	.	.	.	.	.	.	.
		1504	Post Puncture Swelling	Hindlimb, Right	.	.	.	1	1	.	.	.
			Skin, Red	Hindlimb, Right	.	.	.	.	X	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	X	X	X	.	.
			Skin, Scab	Hindlimb, Right	.	.	.	.	.	X	.	.
			Skin, Scab	Hindlimb, Left	.	.	.	X	X	X	.	.
		1505	Fur, Staining, Red	Muzzle	X	.	.	.	.	.	.	.
			Fur, Staining, Red	Forepaw, Right	X	.	.	.	.	.	.	.
			Fur, Staining, Red	Forepaw, Left	X	.	.	.	.	.	.	.
		1506	Skin, Red	Tail	.	X	X	X	X	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	.	.	X	.	.
			Skin, Red	Hindpaw, Left	.	.	.	.	.	X	.	.
		1507	Fur, Thin Cover	Forepaw, Right	.	.	.	X	X	X	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	X	X	.	.
		1508	Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	X	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	X	.	.
		1509	Skin, Scab	Cranium	X	.	.	.	.	.	.	.
			Fur, Staining, Red	Periorbital, Right	X	.	.	.	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	.	.	X	X	.	.
			Fur, Thin Cover	Cranium	.	X	X	.	.	.	.	.
		1511	Fur, Staining, Red	Periorbital, Right	X	.	.	.	.	.	.	.
			Fur, Staining, Red	Muzzle	X	X	.	.	.	.	.	.
		1513	Fur, Staining, Red	Forepaw, Right	X	.	.	.	.	.	.	.
			Skin Staining	Pinna, Right	9	.	.	.	.	.	.	.
			Skin Staining	Pinna, Left	9	.	.	.	.	.	.	.
		1514	Fur, Staining, Red	Cranium	.	.	.	.	.	.	X	X
		1515	Skin, Red	Tail	.	.	.	.	X	.	X	X

Severity Codes: X = Present; 1 = Slight; 9 = Red

Group 1 - 0 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	4 DE	18 DE	25 DE	30 DE
2	f	2501	Swollen Firm	Hindlimb, Left	.	.	.	1
		2502	Swollen Firm	Hindlimb, Left	.	.	.	1
			Skin, Red	Lower Jaw	.	.	X	.
			Fur, Staining, Red	Ventral Cervical	.	.	X	X
			Fur, Staining, Red	Dorsal Cervical	.	.	X	X
		2503	Swollen Firm	Hindlimb, Left	.	.	.	1
		2504	Swollen Firm	Hindlimb, Left	.	.	.	1
			Skin, Red	Tail	X	.	.	.
		2505	Swollen Firm	Hindlimb, Left	.	.	.	1
			Teeth, Clear		.	.	.	X
		2506	Swollen Firm	Hindlimb, Left	.	.	.	1
		2507	Swollen Firm	Hindlimb, Left	.	.	.	1
			Skin, Red	Pinna, Right	.	X	.	.
		2508	Swollen Firm	Hindlimb, Left	.	.	.	1
		2509	Swollen Firm	Hindlimb, Left	.	.	.	1
		2510	Swollen Firm	Hindlimb, Left	.	.	.	1

Severity Codes: X = Present; 1 = Slight

Group 2 - 10 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	4 DE	11 DE	16 Unsc	17 Unsc	18 DE	19 Unsc	23 Unsc	25 DE	30 DE
3	f	3501	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2
		3502	Abnormal Gait		.	.	X	X	X	X	X	X	.
			Teeth Grinding		.	.	.	X	X	X	X	X	.
			Uncoordinated		.	.	2	.	.	.	.	.	.
			Limited Usage	Hindpaw, Right	.	.	.	1	2	.	.	.	.
			Limited Usage	Hindpaw, Left	.	.	2	2	2	.	2	1	.
			Swollen Soft	Hindpaw, Right	.	.	.	2	2	.	.	.	.
			Swollen Soft	Hindlimb, Left	.	.	1	1	2	.	.	.	.
			Swollen Soft	Forepaw, Right	.	.	.	.	.	1	2	1	.
			Swollen Firm	Hindpaw, Right	.	.	.	1	3	1	2	1	.
			Swollen Firm	Hindpaw, Left	.	.	3	3	3	.	2	1	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2
			Skin, Brown	Hindpaw, Left	.	.	X	X	X	.	.	.	.
			Skin, Red	Hindpaw, Right	.	.	.	X	X	X	X	X	.
			Skin, Red	Hindpaw, Left	.	.	X	X	X	.	.	.	.
			Skin, Lesion	Hindpaw, Left	.	.	.	1	1	.	.	.	.
			Skin, Scab	Tail	.	.	X	.	.	.	.	.	.
			Skin, Scab	Hindpaw, Right	.	.	.	.	.	X	X	X	.
			Skin, Scab	Hindpaw, Left	.	.	X	X	X	X	X	X	X
			Fur, Staining, Red	Muzzle	.	.	X	X	X	.	.	.	.
			Fur, Staining, Red	Forepaw, Right	.	.	.	.	X	.	.	.	.
			Fur, Staining, Red	Forepaw, Left	.	.	.	.	X	.	.	.	.
			Fur, Staining, Red	Cranium	.	.	X	X	X	.	.	.	.
		3503	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2
			Skin, Red	Hindlimb, Left	.	.	.	.	.	.	.	.	X
		3504	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2
			Fur, Staining, Red	Cranium	.	.	.	.	.	.	.	.	X
		3505	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2
			Fur, Thin Cover	Dorsal Thoracic	X	X	.	.	.	.	.	.	.
		3506	Swollen Firm	Hindlimb, Right	.	.	.	.	2	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2
			Fur, Thin Cover	Forelimb, Right	.	.	.	.	.	.	.	.	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	4 DE	11 DE	16 Unsc	17 Unsc	18 DE	19 Unsc	23 Unsc	25 DE	30 DE
3	f	3507	Swollen Soft	Hindlimb, Right	.	.	.	.	1	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2
		3508	Swollen Soft	Hindlimb, Right	.	.	.	.	1	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2
			Fur, Thin Cover	Forepaw, Right	.	.	.	.	.	.	.	.	X
			Fur, Thin Cover	Forepaw, Left	.	.	.	.	.	.	.	.	X
		3509	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2
			Skin, Scab	Hindlimb, Left	.	.	.	.	.	.	.	X	.
		3510	Swollen Firm	Hindlimb, Left	.	.	.	.	.	.	.	.	2

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe

Group 3 - 50 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2 Unsc	18 DE	25 DE	30 DE	32 DE	39 DE
4	f	4501	Swollen Firm	Hindlimb, Right	.	2	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.
			Skin, Red	Hindlimb, Right	.	X	X	.	.	.
		4502	Swollen Soft	Hindlimb, Right	.	Y	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	2	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	X	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	X	.	.
		4503	Swollen Firm	Hindlimb, Left	.	.	.	3	.	.
			Skin, Scab	Cranium	.	.	.	X	.	.
			Fur, Thin Cover	Cranium	.	.	.	X	.	.
		4504	Swollen Firm	Hindlimb, Right	.	2	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.
			Teeth, Clear		.	.	.	X	.	.
		4505	Swollen Soft	Hindlimb, Right	.	1	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.
			Fur, Thin Cover	Forepaw, Right	.	.	.	X	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	X	.	.
		4506	Swollen Firm	Hindlimb, Right	.	2	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.
			Fur, Thin Cover	Forepaw, Left	.	.	.	X	.	.
		4507	Swollen Firm	Hindpaw, Right	.	2	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.
			Teeth, Clear		.	.	.	X	.	.
		4508	Swollen Firm	Hindpaw, Right	.	2	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.
			Skin, Red	Hindlimb, Right	.	X	.	.	.	.
			Skin, Scab	Hindlimb, Right	.	X	.	.	.	.
		4509	Swollen Firm	Hindpaw, Right	.	2	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.
			Skin, Red	Hindlimb, Left	.	.	.	X	.	.

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe; Y = Yellow

Group 4 - 150 ug/dose

Appendix 5

Individual Clinical Observations

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2 Unsc	18 DE	25 DE	30 DE	32 DE	39 DE
4	f	4510	Swollen Firm	Hindpaw, Right	.	2	.	.	.	.
			Swollen Firm	Hindlimb, Left	.	.	.	3	.	.
			Skin, Red	Hindpaw, Right	.	.	.	X	.	.
			Skin, Red	Hindpaw, Left	.	.	.	X	.	.
			Skin, Red	Hindlimb, Left	.	.	.	X	.	.
			Skin, Scab	Pinna, Left	.	X	.	.	.	.
			Fur, Staining, Red	Dorsal Cervical	.	.	X	X	.	.
		4511	Swollen Firm	Treatment Site No.01	.	.	.	.	2	1
			Swollen Firm	Hindpaw, Right	.	2	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	.
			Skin, Scab	Hindlimb, Left	.	.	X	.	.	.
		4512	Activity Decreased		X	.	.	.	.	.
			Hunched Posture		X	.	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	1
			Swollen Firm	Hindpaw, Right	.	2	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	.
			Skin, Red	Hindpaw, Right	.	X	.	.	.	.
			Fur, Erected		X	.	.	.	.	.
		4513	Swollen Soft	Hindlimb, Right	.	1	.	.	.	.
			Swollen Firm	Treatment Site No.01	.	.	.	.	2	1
		4514	Swollen Firm	Treatment Site No.01	.	.	.	.	3	1
			Swollen Firm	Hindpaw, Right	.	2	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	.
			Skin, Red	Tail	.	.	.	.	.	X
		4515	Swollen Firm	Treatment Site No.01	.	.	.	.	3	1
			Swollen Firm	Hindpaw, Right	.	2	.	.	.	.
			Skin, Red	Treatment Site No.01	.	.	.	.	X	.
			Skin, Red	Hindpaw, Right	.	X	.	.	.	.
			Skin, Red	Forelimb, Right	.	X	.	.	.	.
			Fur, Thin Cover	Forelimb, Right	.	X	X	.	X	X

Severity Codes: X = Present; 1 = Slight; 2 = Moderate; 3 = Severe; Y = Yellow

Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment Explanation Page

Score	Erythema (Redness) Description
0	No erythema
1	Very slight erythema (barely perceptible)
2	Mild erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness to slight eschar formation, injuries in depth)
M	Notable dermal lesions (maximized)

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

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
AVS	Suspected aberrant value	Post Rx	Observation Post dosing
NR	Not recorded	PreRx	Observation predosing
OA	Omitted activity	DE	Detailed examination

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
1	m	1001	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1002	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1003	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1004	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1005	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1006	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1007	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1008	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
1	m	1001	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1002	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1003	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1004	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1005	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1006	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1007	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1008	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
1	m	1009	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1010	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1011	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1012	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1013	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1014	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1015	Erythema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	.	0	0
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
1	m	1009	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1010	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1011	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	0	0	0
		1012	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	1
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	0	1	0
		1013	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	0	0	0
		1014	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	0	0	0
		1015	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
2	m	2001	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	2	.	0	0
			Edema	Treatment Site No.01	.	1	1	0	0	.	.	0
		2002	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	1	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	2	.	0	0
			Edema	Treatment Site No.01	.	2	1	0	0	.	.	0
		2003	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	1	.	0	0
			Edema	Treatment Site No.01	.	0	1	0	0	.	.	0
		2004	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	2	.	0	0
			Edema	Treatment Site No.01	.	3	1	0	0	.	.	0
		2005	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	2	.	0	0
			Edema	Treatment Site No.01	.	3	0	0	0	.	.	0
		2006	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	2	.	0	0
			Edema	Treatment Site No.01	.	3	1	0	0	.	.	0
		2007	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	2	.	0	0
			Edema	Treatment Site No.01	.	2	1	0	0	.	.	0
		2008	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	1	.	0	0
			Edema	Treatment Site No.01	.	2	1	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
2	m	2001	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2002	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2003	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2004	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2005	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		2006	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2007	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2008	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
2	m	2009	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	1	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	1	.	0	0
			Edema	Treatment Site No.01	.	2	1	0	0	.	.	0
		2010	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	2	.	0	0
			Edema	Treatment Site No.01	.	2	1	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
2	m	2009	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2010	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
3	m	3001	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	3	.	0	0
			Edema	Treatment Site No.01	.	3	2	0	0	.	.	0
		3002	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	3	.	0	0
			Edema	Treatment Site No.01	.	3	2	0	0	.	.	0
		3003	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	3	.	0	0
			Edema	Treatment Site No.01	.	3	2	0	0	.	.	0
		3004	Erythema	Treatment Site No.02	.	1	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	2	.	0	0
			Edema	Treatment Site No.01	.	3	2	0	0	.	.	0
		3005	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	3	.	0	0
			Edema	Treatment Site No.01	.	3	2	0	0	.	.	0
		3006	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	2	.	0	0
			Edema	Treatment Site No.01	.	3	2	0	0	.	.	0
		3007	Erythema	Treatment Site No.02	.	1	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	3	.	0	0
			Edema	Treatment Site No.01	.	3	2	0	0	.	.	0
		3008	Erythema	Treatment Site No.02	.	1	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	1	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	3	.	0	0
			Edema	Treatment Site No.01	.	3	2	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
3	m	3001	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		3002	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		3003	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		3004	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		3005	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		3006	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		3007	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		3008	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
3	m	3009	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	3	.	0	0
			Edema	Treatment Site No.01	.	3	1	0	0	.	.	0
		3010	Erythema	Treatment Site No.02	.	1	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	3	.	0	0
			Edema	Treatment Site No.01	.	3	2	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
3	m	3009	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	2	.	.
		3010	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
4	m	4001	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	3	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	3	3	0	0	.	.	0
		4002	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	3	3	0	0	.	.	0
		4003	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	4	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	3	4	0	0	.	.	0
		4004	Erythema	Treatment Site No.02	.	1	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	2	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	3	3	0	0	.	.	0
		4005	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	1	3	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	4	4	0	0	.	.	0
		4006	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	4	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	4	4	0	0	.	.	0
		4007	Erythema	Treatment Site No.02	.	1	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	4	4	0	0	.	.	0
		4008	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	1	1	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	3	.	1	0
			Edema	Treatment Site No.01	.	4	4	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
4	m	4001	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	2	.	.
		4002	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		4003	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	2	.	.
		4004	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	2	.	.
		4005	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	2	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	3	.	.
		4006	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	2	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	2	.	.
		4007	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		4008	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
4	m	4009	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	1	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	3	4	0	0	.	.	0
		4010	Erythema	Treatment Site No.02	.	0	.	0	1	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	4	4	0	0	.	.	0
		4011	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	3	4	0	0	.	.	0
		4012	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	4	4	0	0	.	.	0
		4013	Erythema	Treatment Site No.02	.	1	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	4	4	0	0	.	.	0
		4014	Erythema	Treatment Site No.02	.	0	.	0	0	.	1	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	1	0
			Edema	Treatment Site No.01	.	4	4	0	0	.	.	0
		4015	Erythema	Treatment Site No.02	.	0	.	0	0	.	0	0
			Erythema	Treatment Site No.01	.	0	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	0	.	0	4	.	0	0
			Edema	Treatment Site No.01	.	3	4	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
4	m	4009	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	3	.	.
		4010	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	2	.	.
		4011	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	1	1	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	1	1	0
		4012	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	1	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	1	1	0
		4013	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	2	2	0
			Edema	Treatment Site No.02	0	.	1
			Edema	Treatment Site No.01	3	3	0
		4014	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	1	2	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	2	3	0
		4015	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	1	1	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	2	2	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
1	f	1501	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1502	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1503	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1504	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	1
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Comment Present		.	.	.	.	.	.	.	.
		1505	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1506	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1507	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1508	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
1	f	1501	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1502	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1503	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1504	Erythema	Treatment Site No.02	4	.	.
			Erythema	Treatment Site No.01	4	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
			Comment Present		*	.	.
		1505	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1506	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1507	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1508	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
1	f	1509	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1510	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1511	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1512	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1513	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1514	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	0	.	0	0	0	.	.	0
		1515	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
1	f	1509	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1510	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		1511	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	0	0	0
		1512	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	0	0	0
		1513	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	0	0	0
		1514	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	0	0	0
		1515	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
2	f	2501	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Edema	Treatment Site No.01	2	.	0	0	0	.	.	0
		2502	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Edema	Treatment Site No.01	1	.	1	0	0	.	.	0
		2503	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	2	0	.	0
			Edema	Treatment Site No.01	1	.	1	0	0	.	.	0
		2504	Erythema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Edema	Treatment Site No.01	2	.	0	0	0	.	.	0
		2505	Erythema	Treatment Site No.02	.	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	.	.	.	0	1	0	.	0
			Edema	Treatment Site No.01	2	.	0	0	0	.	.	0
		2506	Erythema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Edema	Treatment Site No.01	2	.	0	0	0	.	.	0
		2507	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Edema	Treatment Site No.01	2	.	0	0	0	.	.	0
		2508	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Edema	Treatment Site No.01	2	.	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
2	f	2501	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2502	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2503	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2504	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	1	.	.
			Edema	Treatment Site No.01	1	.	.
		2505	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2506	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2507	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	1	.	.
			Edema	Treatment Site No.01	1	.	.
		2508	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
2	f	2509	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Edema	Treatment Site No.01	2	.	1	0	0	.	.	0
		2510	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	1	0	.	0
			Edema	Treatment Site No.01	2	.	1	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
2	f	2509	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	1	.	.
		2510	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
3	f	3501	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	2	0	.	0
			Edema	Treatment Site No.01	3	.	2	0	0	.	.	0
		3502	Erythema	Treatment Site No.02	0	.	.	0	0	1	.	0
			Erythema	Treatment Site No.01	1	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	.	0
			Edema	Treatment Site No.01	3	.	3	0	1	.	.	0
		3503	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	1	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	1	.	1
			Edema	Treatment Site No.01	3	.	2	0	0	.	.	0
		3504	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	.	1
			Edema	Treatment Site No.01	4	.	2	0	0	.	.	0
		3505	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	1	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	.	1
			Edema	Treatment Site No.01	3	.	2	0	0	.	.	0
		3506	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	2	2	.	0
			Edema	Treatment Site No.01	3	.	2	0	0	.	.	0
		3507	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	.	0
			Edema	Treatment Site No.01	3	.	2	0	0	.	.	0
		3508	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	1	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	.	0
			Edema	Treatment Site No.01	3	.	2	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
3	f	3501	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	3	.	.
		3502	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	3	.	.
		3503	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	3	.	.
		3504	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	3	.	.
		3505	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	3	.	.
		3506	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	2	.	.
		3507	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	3	.	.
		3508	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
3	f	3509	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	1	.	0
			Edema	Treatment Site No.01	4	.	2	0	0	.	.	0
		3510	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	1	.	0	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	1	.	0
			Edema	Treatment Site No.01	4	.	2	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
3	f	3509	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	3	.	.
		3510	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
4	f	4501	Erythema	Treatment Site No.02	0	.	.	0	0	1	.	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	.	0
			Edema	Treatment Site No.01	4	.	3	0	0	.	.	0
		4502	Erythema	Treatment Site No.02	0	.	.	0	0	1	.	0
			Erythema	Treatment Site No.01	1	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	3	.	0
			Edema	Treatment Site No.01	4	.	3	0	0	.	.	0
		4503	Erythema	Treatment Site No.02	0	.	.	0	0	1	.	0
			Erythema	Treatment Site No.01	2	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	.	0
			Edema	Treatment Site No.01	4	.	3	0	0	.	.	0
		4504	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	1	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	.	0
			Edema	Treatment Site No.01	4	.	4	0	0	.	.	0
		4505	Erythema	Treatment Site No.02	0	.	.	0	0	1	.	0
			Erythema	Treatment Site No.01	1	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	.	0
			Edema	Treatment Site No.01	4	.	3	0	0	.	.	0
		4506	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	.	0
			Edema	Treatment Site No.01	3	.	3	0	0	.	.	0
		4507	Erythema	Treatment Site No.02	0	.	.	0	0	2	.	0
			Erythema	Treatment Site No.01	1	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	.	1
			Edema	Treatment Site No.01	4	.	4	0	0	.	.	0
		4508	Erythema	Treatment Site No.02	0	.	.	0	0	2	.	0
			Erythema	Treatment Site No.01	1	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	.	0
			Edema	Treatment Site No.01	4	.	4	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
4	f	4501	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	4	.	.
		4502	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	4	.	.
		4503	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	4	.	.
		4504	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	4	.	.
		4505	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	4	.	.
		4506	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	4	.	.
		4507	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	4	.	.
		4508	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	0	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	4	.	.

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	2	2 PostRx	4 DE	9	16	18	18 DE	23
4	f	4509	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	.	0
			Edema	Treatment Site No.01	4	.	4	0	0	.	.	0
		4510	Erythema	Treatment Site No.02	0	.	.	0	0	1	.	0
			Erythema	Treatment Site No.01	2	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	4	2	.	1
			Edema	Treatment Site No.01	4	.	3	0	0	.	.	0
		4511	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	1	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	3	.	0
			Edema	Treatment Site No.01	4	.	4	0	0	.	.	0
		4512	Erythema	Treatment Site No.02	0	.	.	0	0	1	.	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	2	.	0
			Edema	Treatment Site No.01	4	.	4	0	0	.	.	0
		4513	Erythema	Treatment Site No.02	0	.	.	0	0	1	.	0
			Erythema	Treatment Site No.01	0	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	4	2	.	1
			Edema	Treatment Site No.01	4	.	4	0	0	.	.	0
		4514	Erythema	Treatment Site No.02	0	.	.	0	0	0	.	0
			Erythema	Treatment Site No.01	1	.	1	0	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	4	3	.	0
			Edema	Treatment Site No.01	4	.	4	0	0	.	.	0
		4515	Erythema	Treatment Site No.02	0	.	.	0	0	2	.	0
			Erythema	Treatment Site No.01	0	.	1	1	0	.	.	0
			Edema	Treatment Site No.02	0	.	.	0	3	3	.	0
			Edema	Treatment Site No.01	4	.	3	0	0	.	.	0

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	32 DE	37
4	f	4509	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	0	.	.
		4510	Erythema	Treatment Site No.02	0	.	.
			Erythema	Treatment Site No.01	1	.	.
			Edema	Treatment Site No.02	0	.	.
			Edema	Treatment Site No.01	4	.	.
		4511	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	1	1	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	4	3	0
		4512	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	1	1	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	4	3	0
		4513	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	0	0	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	3	3	0
		4514	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	1	2	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	4	4	0
		4515	Erythema	Treatment Site No.02	0	.	0
			Erythema	Treatment Site No.01	1	2	0
			Edema	Treatment Site No.02	0	.	0
			Edema	Treatment Site No.01	4	4	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 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 6

Individual Local Irritation Assessment

5002033

Comments

Group	Sex	Animal	Day Number	Time Slot	Comment
1	f	1504	30		skin scab probably due to marking
					skin scab probably due to marking

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)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day -9	-1	7	14	21	28	35	42
1M	1001	228	296	351	395	439	466	--	--
	1002	232	323	406	479	544	585	--	--
	1003	230	299	364	425	480	525	--	--
	1004	221	294	360	421	479	519	--	--
	1005	213	281	346	396	445	481	--	--
	1006	202	274	336	392	434	484	--	--
	1007	218	301	376	442	507	551	--	--
	1008	203	275	337	396	451	485	--	--
	1009	210	286	358	417	480	522	--	--
	1010	209	283	355	422	482	532	--	--
	1011	203	271	332	382	431	465	502	529
	1012	200	261	312	360	407	440	473	497
	1013	227	296	354	402	446	466	495	509
	1014	224	296	357	408	464	496	542	557
	1015	215	279	346	396	459	503	544	583

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day -9	-1	7	14	21	28	35	42
2M	2001	229	299	350	396	439	463	--	--
	2002	225	297	351	395	445	470	--	--
	2003	208	272	320	371	414	446	--	--
	2004	214	278	340	390	445	473	--	--
	2005	211	295	363	436	502	557	--	--
	2006	221	280	324	372	405	439	--	--
	2007	207	281	348	405	454	491	--	--
	2008	223	292	359	416	466	506	--	--
	2009	217	287	352	419	474	517	--	--
	2010	218	294	366	422	475	514	--	--

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day -9	-1	7	14	21	28	35	42
3M	3001	220	307	382	460	531	585	--	--
	3002	210	277	329	390	431	458	--	--
	3003	229	297	350	412	458	513	--	--
	3004	205	265	313	364	410	456	--	--
	3005	226	287	324	370	399	439	--	--
	3006	215	275	321	372	411	447	--	--
	3007	214	295	362	427	466	511	--	--
	3008	219	299	372	444	505	554	--	--
	3009	208	274	340	405	458	502	--	--
	3010	224	295	354	421	468	516	--	--

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day -9	-1	7	14	21	28	35	42
4M	4001	215	278	328	385	425	466	--	--
	4002	211	282	330	396	429	480	--	--
	4003	232	317	372	433	469	506	--	--
	4004	218	284	330	380	409	451	--	--
	4005	213	285	323	376	406	449	--	--
	4006	203	274	322	389	422	468	--	--
	4007	223	284	338	399	427	469	--	--
	4008	228	306	358	414	453	503	--	--
	4009	224	291	334	394	432	471	--	--
	4010	207	278	330	386	423	470	--	--
	4011	201	282	332	388	414	446	464	490
	4012	222	285	333	391	424	471	501	539
	4013	230	304	352	412	447	498	519	560
	4014	208	280	322	383	415	460	482	521
	4015	200	271	310	359	396	428	444	480

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day -10	-1	7	14	21	28	35	42
1F	1501	191	239	270	281	299	313	--	--
	1502	187	228	260	270	283	298	--	--
	1503	190	223	250	269	274	289	--	--
	1504	182	209	238	256	269	278	--	--
	1505	190	231	257	261	285	302	--	--
	1506	198	238	270	283	299	313	--	--
	1507	178	216	248	263	272	284	--	--
	1508	178	209	236	253	272	288	--	--
	1509	194	235	271	285	307	319	--	--
	1510	184	214	249	258	270	292	--	--
	1511	196	232	263	278	292	301	312	327
	1512	172	211	240	255	272	288	297	302
	1513	186	236	268	278	299	305	315	323
	1514	182	225	254	275	289	301	315	329
	1515	195	230	261	277	296	296	296	316

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day -10	-1	7	14	21	28	35	42
2F	2501	193	230	269	286	302	327	--	--
	2502	191	237	255	273	285	299	--	--
	2503	188	240	280	293	314	337	--	--
	2504	188	228	253	266	283	296	--	--
	2505	181	210	228	242	255	269	--	--
	2506	190	208	237	245	265	274	--	--
	2507	182	216	244	254	275	287	--	--
	2508	186	215	235	244	258	265	--	--
	2509	184	216	249	267	284	289	--	--
	2510	182	213	241	257	273	301	--	--

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day -10	-1	7	14	21	28	35	42
3F	3501	182	220	240	256	266	279	--	--
	3502	190	219	237	246	238	246	--	--
	3503	178	222	236	261	278	288	--	--
	3504	188	219	236	243	271	307	--	--
	3505	184	222	244	264	277	286	--	--
	3506	191	232	263	285	300	319	--	--
	3507	186	221	240	249	265	275	--	--
	3508	193	224	245	264	273	292	--	--
	3509	187	220	244	263	287	311	--	--
	3510	182	205	226	243	255	267	--	--

Appendix 7

Individual Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day -10	-1	7	14	21	28	35	42
4F	4501	185	220	232	238	256	264	--	--
	4502	194	226	238	251	259	273	--	--
	4503	189	232	250	258	275	291	--	--
	4504	194	228	250	271	284	299	--	--
	4505	191	234	254	267	269	282	--	--
	4506	187	219	240	255	264	281	--	--
	4507	187	225	256	267	280	298	--	--
	4508	176	211	223	235	250	265	--	--
	4509	200	239	251	262	274	277	--	--
	4510	183	213	239	255	259	277	--	--
	4511	181	214	239	257	262	276	290	298
	4512	196	245	268	272	294	319	330	339
	4513	181	200	214	236	243	249	259	268
	4514	178	223	239	253	261	280	282	307
	4515	193	224	240	243	261	279	278	300

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)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	68	55	44	44	27	--	--
	1002	91	83	73	65	41	--	--
	1003	69	65	61	55	45	--	--
	1004	73	66	61	58	40	--	--
	1005	68	65	50	49	36	--	--
	1006	72	62	56	42	50	--	--
	1007	83	75	66	65	44	--	--
	1008	72	62	59	55	34	--	--
	1009	76	72	59	63	42	--	--
	1010	74	72	67	60	50	--	--
	1011	68	61	50	49	34	37	27
	1012	61	51	48	47	33	33	24
	1013	69	58	48	44	20	29	14
	1014	72	61	51	56	32	46	15
	1015	64	67	50	63	44	41	39

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	70	51	46	43	24	--	--
	2002	72	54	44	50	25	--	--
	2003	64	48	51	43	32	--	--
	2004	64	62	50	55	28	--	--
	2005	84	68	73	66	55	--	--
	2006	59	44	48	33	34	--	--
	2007	74	67	57	49	37	--	--
	2008	69	67	57	50	40	--	--
	2009	70	65	67	55	43	--	--
	2010	76	72	56	53	39	--	--

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	87	75	78	71	54	--	--
	3002	67	52	61	41	27	--	--
	3003	68	53	62	46	55	--	--
	3004	60	48	51	46	46	--	--
	3005	61	37	46	29	40	--	--
	3006	60	46	51	39	36	--	--
	3007	81	67	65	39	45	--	--
	3008	80	73	72	61	49	--	--
	3009	66	66	65	53	44	--	--
	3010	71	59	67	47	48	--	--

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	63	50	57	40	41	--	--
	4002	71	48	66	33	51	--	--
	4003	85	55	61	36	37	--	--
	4004	66	46	50	29	42	--	--
	4005	72	38	53	30	43	--	--
	4006	71	48	67	33	46	--	--
	4007	61	54	61	28	42	--	--
	4008	78	52	56	39	50	--	--
	4009	67	43	60	38	39	--	--
	4010	71	52	56	37	47	--	--
	4011	81	50	56	26	32	18	26
	4012	63	48	58	33	47	30	38
	4013	74	48	60	35	51	21	41
	4014	72	42	61	32	45	22	39
	4015	71	39	49	37	32	16	36

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	48	31	11	18	14	--	--
	1502	41	32	10	13	15	--	--
	1503	33	27	19	5	15	--	--
	1504	27	29	18	13	9	--	--
	1505	41	26	4	24	17	--	--
	1506	40	32	13	16	14	--	--
	1507	38	32	15	9	12	--	--
	1508	31	27	17	19	16	--	--
	1509	41	36	14	22	12	--	--
	1510	30	35	9	12	22	--	--
	1511	36	31	15	14	9	11	15
	1512	39	29	15	17	16	9	5
	1513	50	32	10	21	6	10	8
	1514	43	29	21	14	12	14	14
	1515	35	31	16	19	0	0	20

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	37	39	17	16	25	--	--
	2502	46	18	18	12	14	--	--
	2503	52	40	13	21	23	--	--
	2504	40	25	13	17	13	--	--
	2505	29	18	14	13	14	--	--
	2506	18	29	8	20	9	--	--
	2507	34	28	10	21	12	--	--
	2508	29	20	9	14	7	--	--
	2509	32	33	18	17	5	--	--
	2510	31	28	16	16	28	--	--

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	38	20	16	10	13	--	--
	3502	29	18	9	-8	8	--	--
	3503	44	14	25	17	10	--	--
	3504	31	17	7	28	36	--	--
	3505	38	22	20	13	9	--	--
	3506	41	31	22	15	19	--	--
	3507	35	19	9	16	10	--	--
	3508	31	21	19	9	19	--	--
	3509	33	24	19	24	24	--	--
	3510	23	21	17	12	12	--	--

Appendix 8

Individual Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	35	12	6	18	8	--	--
	4502	32	12	13	8	14	--	--
	4503	43	18	8	17	16	--	--
	4504	34	22	21	13	15	--	--
	4505	43	20	13	2	13	--	--
	4506	32	21	15	9	17	--	--
	4507	38	31	11	13	18	--	--
	4508	35	12	12	15	15	--	--
	4509	39	12	11	12	3	--	--
	4510	30	26	16	4	18	--	--
	4511	33	25	18	5	14	14	8
	4512	49	23	4	22	25	11	9
	4513	19	14	22	7	6	10	9
	4514	45	16	14	8	19	2	25
	4515	31	16	3	18	18	-1	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)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	33.6	36.5	35.8	38.1	38.0	--	--
	1002	33.6	36.5	35.8	38.1	38.0	--	--
	1003	33.6	36.5	35.8	38.1	38.0	--	--
	1004	28.8	30.8	32.9	33.7	35.2	--	--
	1005	28.8	30.8	32.9	33.7	35.2	--	--
	1006	28.8	30.8	32.9	33.7	35.2	--	--
	1007	31.8	35.1	37.1	37.7	38.2	--	--
	1008	31.8	35.1	37.1	37.7	38.2	--	--
	1009	30.3	34.8	35.9	38.7	40.6	--	--
	1010	30.3	34.8	35.9	38.7	40.6	--	--
	1011	30.0	31.5	31.4	32.2	32.6	31.0	31.0
	1012	30.0	31.5	31.4	32.2	32.6	31.0	31.0
	1013	30.0	31.5	31.4	32.2	32.6	31.0	31.0
	1014	31.3	33.5	34.6	35.5	38.6	36.4	34.3
	1015	31.3	33.5	34.6	35.5	38.6	36.4	34.3

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	30.8	31.4	32.6	32.5	34.0	--	--
	2002	30.8	31.4	32.6	32.5	34.0	--	--
	2003	30.8	31.4	32.6	32.5	34.0	--	--
	2004	30.6	32.3	34.1	33.4	37.3	--	--
	2005	30.6	32.3	34.1	33.4	37.3	--	--
	2006	30.6	32.3	34.1	33.4	37.3	--	--
	2007	29.5	31.4	32.9	31.6	34.6	--	--
	2008	29.5	31.4	32.9	31.6	34.6	--	--
	2009	32.1	33.6	36.6	36.6	37.9	--	--
	2010	32.1	33.6	36.6	36.6	37.9	--	--

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	32.3	33.5	37.5	36.5	39.4	--	--
	3002	32.3	33.5	37.5	36.5	39.4	--	--
	3003	32.3	33.5	37.5	36.5	39.4	--	--
	3004	28.4	28.8	31.1	30.7	33.4	--	--
	3005	28.4	28.8	31.1	30.7	33.4	--	--
	3006	28.4	28.8	31.1	30.7	33.4	--	--
	3007	32.4	33.1	37.7	36.9	39.7	--	--
	3008	32.4	33.1	37.7	36.9	39.7	--	--
	3009	30.4	32.2	37.4	34.7	39.3	--	--
	3010	30.4	32.2	37.4	34.7	39.3	--	--

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	31.0	30.4	36.5	32.8	37.0	--	--
	4002	31.0	30.4	36.5	32.8	37.0	--	--
	4003	31.0	30.4	36.5	32.8	37.0	--	--
	4004	29.9	27.9	32.3	30.1	33.7	--	--
	4005	29.9	27.9	32.3	30.1	33.7	--	--
	4006	29.9	27.9	32.3	30.1	33.7	--	--
	4007	29.9	28.9	33.6	29.3	34.9	--	--
	4008	29.9	28.9	33.6	29.3	34.9	--	--
	4009	30.8	30.1	34.8	34.3	35.9	--	--
	4010	30.8	30.1	34.8	34.3	35.9	--	--
	4011	30.7	30.0	34.7	33.0	35.2	31.0	34.3
	4012	30.7	30.0	34.7	33.0	35.2	31.0	34.3
	4013	30.7	30.0	34.7	33.0	35.2	31.0	34.3
	4014	30.6	27.6	33.2	30.1	34.7	30.1	34.0
	4015	30.6	27.6	33.2	30.1	34.7	30.1	34.0

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	22.9	23.9	34.6	23.5	24.2	--	--
	1502	22.9	23.9	34.6	23.5	24.2	--	--
	1503	22.9	23.9	34.6	23.5	24.2	--	--
	1504	21.4	22.1	22.0	21.9	22.6	--	--
	1505	21.4	22.1	22.0	21.9	22.6	--	--
	1506	21.4	22.1	22.0	21.9	22.6	--	--
	1507	19.9	21.3	22.6	22.3	22.3	--	--
	1508	19.9	21.3	22.6	22.3	22.3	--	--
	1509	22.4	25.0	25.2	24.6	26.8	--	--
	1510	22.4	25.0	25.2	24.6	26.8	--	--
	1511	20.9	22.6	23.2	22.5	22.7	22.1	21.9
	1512	20.9	22.6	23.2	22.5	22.7	22.1	21.9
	1513	20.9	22.6	23.2	22.5	22.7	22.1	21.9
	1514	22.1	23.9	23.9	23.7	23.9	23.5	23.2
	1515	22.1	23.9	23.9	23.7	23.9	23.5	23.2

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	22.9	24.0	24.4	24.0	25.4	--	--
	2502	22.9	24.0	24.4	24.0	25.4	--	--
	2503	22.9	24.0	24.4	24.0	25.4	--	--
	2504	18.9	21.2	20.9	21.4	21.0	--	--
	2505	18.9	21.2	20.9	21.4	21.0	--	--
	2506	18.9	21.2	20.9	21.4	21.0	--	--
	2507	21.4	23.1	24.3	24.1	24.5	--	--
	2508	21.4	23.1	24.3	24.1	24.5	--	--
	2509	21.9	22.1	23.9	22.8	24.4	--	--
	2510	21.9	22.1	23.9	22.8	24.4	--	--

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	20.5	20.6	20.4	18.9	18.6	--	--
	3502	20.5	20.6	20.4	18.9	18.6	--	--
	3503	20.5	20.6	20.4	18.9	18.6	--	--
	3504	21.0	21.9	23.3	22.8	24.0	--	--
	3505	21.0	21.9	23.3	22.8	24.0	--	--
	3506	21.0	21.9	23.3	22.8	24.0	--	--
	3507	21.9	22.2	23.4	22.6	24.0	--	--
	3508	21.9	22.2	23.4	22.6	24.0	--	--
	3509	19.9	21.3	21.5	23.0	23.9	--	--
	3510	19.9	21.3	21.5	23.0	23.9	--	--

Appendix 9

Individual Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	22.6	21.1	22.0	21.4	22.9	--	--
	4502	22.6	21.1	22.0	21.4	22.9	--	--
	4503	22.6	21.1	22.0	21.4	22.9	--	--
	4504	22.8	21.5	24.7	20.8	23.2	--	--
	4505	22.8	21.5	24.7	20.8	23.2	--	--
	4506	22.8	21.5	24.7	20.8	23.2	--	--
	4507	21.7	20.5	21.5	20.4	22.3	--	--
	4508	21.7	20.5	21.5	20.4	22.3	--	--
	4509	21.9	20.2	22.6	21.0	22.6	--	--
	4510	21.9	20.2	22.6	21.0	22.6	--	--
	4511	21.6	20.6	23.0	20.9	23.8	23.1	23.1
	4512	21.6	20.6	23.0	20.9	23.8	23.1	23.1
	4513	21.6	20.6	23.0	20.9	23.8	23.1	23.1
	4514	23.2	21.9	24.4	21.7	25.9	23.8	25.9
	4515	23.2	21.9	24.4	21.7	25.9	23.8	25.9

Appendix 10

Individual Body Temperature Values Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed / dead	TERR	Technical error
AVS	Suspected aberrant value	X	Excluded from mean
NR	Not recorded		
pr	Body temperature collected predose	p	Body temperature collected 6h post dose

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 10

Individual Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 29 pr	Day 29 p	Day 30
1M	1001	36.2	37.8	36.2	--	36.5	38.4	36.1
	1002	36.6	37.4	37.0	--	37.0	38.1	36.6
	1003	37.9	37.7	37.1	--	36.8	38.1	36.8
	1004	37.3	37.3	36.9	--	36.4	37.4	36.1
	1005	36.8	37.5	37.3	--	36.8	37.9	36.7
	1006	37.6	37.4	36.6	--	36.2	37.6	35.6
	1007	37.1	38.0	37.3	--	36.6	37.8	36.2
	1008	36.9	38.3	36.9	--	36.4	37.5	36.1
	1009	36.4	37.9	36.5	--	36.2	37.9	36.1
	1010	36.8	37.3	36.5	--	36.4	38.1	36.2
	1011	36.8	37.6	36.8	--	36.4	38.3	36.6
	1012	37.3	37.8	36.5	--	36.4	38.4	36.0
	1013	36.7	38.8	36.8	--	36.4	38.8	36.2
	1014	36.7	37.9	36.7	--	37.0	37.6	36.4
	1015	37.0	36.4	37.0	--	37.8	37.5	36.2

Appendix 10

Individual Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 29 pr	Day 29 p	Day 30
2M	2001	36.3	38.0	36.5	--	36.5	37.7	36.3
	2002	35.7	38.7	37.4	--	36.5	38.1	36.8
	2003	37.6	39.0	37.2	--	36.8	38.1	36.5
	2004	36.9	38.8	37.9	--	36.7	39.0	37.9
	2005	36.8	39.4	37.5	--	36.7	38.0	36.4
	2006	37.2	39.2	37.5	--	37.1	38.8	37.0
	2007	36.8	38.8	37.8	--	36.6	38.2	36.8
	2008	36.2	37.9	37.4	--	36.4	37.6	37.0
	2009	36.8	38.2	37.4	--	36.5	38.4	37.9
	2010	36.9	37.7	36.6	--	36.4	38.3	36.3

Appendix 10

Individual Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 29 pr	Day 29 p	Day 30
3M	3001	37.0	39.3	37.6	--	36.5	38.1	36.6
	3002	36.9	39.4	39.0	37.1	37.1	38.6	37.6
	3003	37.3	38.8	38.4	--	36.8	37.6	37.0
	3004	37.4	39.8	38.2	--	38.0	38.3	37.4
	3005	36.3	39.3	38.5	--	36.9	37.3	37.6
	3006	37.1	39.2	39.3	36.8	36.9	38.7	37.6
	3007	36.4	38.6	38.3	--	36.4	38.3	37.0
	3008	36.9	39.1	38.4	--	36.5	38.5	36.1
	3009	36.7	38.9	37.2	--	36.3	37.9	36.4
	3010	36.6	38.8	38.0	--	36.5	38.0	36.4

Appendix 10

Individual Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 29 pr	Day 29 p	Day 30
4M	4001	37.1	39.7	38.4	--	36.5	38.8	37.1
	4002	36.5	39.1	38.7	--	36.6	38.3	38.6
	4003	37.2	38.7	38.6	--	36.4	38.7	37.4
	4004	37.2	39.4	38.9	--	36.7	39.1	38.5
	4005	36.3	39.2	38.6	--	36.5	38.8	38.0
	4006	37.2	39.3	38.4	--	36.6	39.4	37.3
	4007	36.5	39.2	38.1	--	36.6	38.0	38.0
	4008	37.2	39.5	38.1	--	36.7	38.9	37.8
	4009	37.1	38.6	38.4	--	36.8	38.7	37.3
	4010	37.2	38.7	37.8	--	36.5	38.1	36.6
	4011	37.0	39.2	39.4	36.8	36.6	39.3	38.8
	4012	37.0	39.4	38.8	--	37.1	39.2	38.4
	4013	36.8	38.8	38.0	--	37.3	39.6	38.3
	4014	36.6	39.2	39.4	37.0	36.7	39.8	38.3
	4015	36.6	39.0	38.8	--	36.6	38.5	38.1

Appendix 10

Individual Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 29 pr	Day 29 p	Day 30
1F	1501	37.3	38.6	37.3	--	38.2	37.5	38.2
	1502	37.2	37.6	37.4	--	38.3	38.1	37.8
	1503	36.8	37.3	38.2	--	38.7	39.1	38.4
	1504	36.9	37.9	38.1	--	38.2	38.3	38.4
	1505	38.4	38.4	37.6	--	38.8	38.3	39.1
	1506	36.8	37.3	37.4	--	38.3	38.3	38.9
	1507	36.7	37.5	38.1	--	38.6	38.4	37.6
	1508	36.8	37.5	37.4	--	38.8	38.4	38.2
	1509	37.4	37.3	37.1	--	38.7	38.4	38.4
	1510	36.6	37.9	38.4	--	38.5	38.0	38.7
	1511	37.2	38.3	38.9	--	38.0	39.4	37.9
	1512	37.4	38.1	37.5	--	38.1	38.8	37.9
	1513	37.6	38.4	38.4	--	37.9	38.1	38.1
	1514	36.7	37.9	37.4	--	38.4	38.3	38.5
	1515	37.2	38.3	37.6	--	38.9	38.9	39.4

Appendix 10

Individual Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 29 pr	Day 29 p	Day 30
2F	2501	37.0	38.9	37.8	--	39.0	38.8	38.7
	2502	37.1	38.0	37.2	--	39.0	38.7	38.3
	2503	36.3	37.9	37.4	--	37.7	37.4	37.8
	2504	36.3	38.1	37.9	--	38.5	38.8	38.3
	2505	37.8	38.2	38.5	--	38.9	39.0	38.7
	2506	37.2	37.8	38.6	--	39.2	39.1	39.0
	2507	39.1	38.5	38.3	--	38.9	37.7	39.0
	2508	37.5	36.9	38.3	--	39.5	37.3	39.2
	2509	37.8	37.8	38.4	--	39.1	37.0	39.0
	2510	38.0	37.9	38.1	--	38.7	37.2	38.0

Appendix 10

Individual Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 29 pr	Day 29 p	Day 30
3F	3501	36.8	39.0	38.8	--	38.1	37.8	36.8
	3502	37.5	38.2	38.8	--	37.9	38.9	37.7
	3503	37.1	39.2	38.4	--	38.4	39.5	38.4
	3504	37.6	39.7	38.3	--	38.2	38.8	38.6
	3505	37.2	39.0	38.2	--	38.8	38.0	39.0
	3506	37.3	38.9	38.2	--	38.8	38.6	38.8
	3507	37.2	39.6	38.6	--	39.1	39.5	39.5
	3508	37.8	39.5	38.6	--	39.0	38.9	39.2
	3509	37.4	38.4	37.8	--	38.8	38.9	38.6
	3510	37.9	38.0	38.3	--	38.9	39.1	38.7

Appendix 10

Individual Body Temperature Values (°C)

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	Day 1 pr	Day 1 p	Day 2	Day 3	Day 29 pr	Day 29 p	Day 30
4F	4501	36.8	39.3	39.0	37.0	37.7	38.5	38.8
	4502	36.9	39.3	39.1	36.5	37.8	39.3	39.5
	4503	38.0	39.5	38.3	--	38.3	38.6	38.5
	4504	37.1	38.5	40.0	37.1	38.8	39.1	39.2
	4505	36.6	39.3	39.2	36.7	38.6	40.1	39.0
	4506	37.4	39.6	40.2	37.6	39.3	40.0	39.4
	4507	37.2	39.5	38.3	--	38.7	39.3	38.3
	4508	37.1	39.8	38.8	--	38.2	39.6	39.0
	4509	37.5	39.5	39.8	37.9	38.6	39.0	38.7
	4510	37.0	39.5	39.9	37.0	39.0	38.6	39.3
	4511	37.6	39.5	38.9	--	38.0	38.7	38.8
	4512	37.7	38.9	38.2	--	38.9	39.5	38.8
	4513	37.2	39.3	39.4	38.2	38.7	39.8	38.9
	4514	38.0	39.2	39.2	37.9	39.0	38.7	38.8
	4515	38.3	40.0	38.4	--	38.8	39.9	38.9

Appendix 11

Individual Hematology Values Explanation Page

ADVIA 120 Analyzer
Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Hematocrit	HCT	%	Calculated
Hemoglobin	HGB	g/dL	Colorimetric
Mean Corpuscular Hemoglobin	MCH	pg	Calculated
Mean Corpuscular Hemoglobin Concentration	MCHC	g/dL	Calculated
Mean Corpuscular Volume	MCV	fL(μm^3)	Calculated
Mean Platelet Volume	MPV	fL(μm^3)	Calculated
Platelet Count	PLT	$x10^3/\mu L$	Light scatter
Red Blood Cell Count	RBC	$x10^6/\mu L$	Light scatter
Red Blood Cell Distribution Width	RDW	%	Calculated
Reticulocytes	RETIC	$x10^9/L$	Calculated
Reticulocytes Percent	RETIC	%	Light scatter
White Blood Cell Count	WBC	$x10^3/\mu L$	Light scatter
White Blood Cell Differential Count			
Neutrophils Percent	NEUT	%	Light scatter
Lymphocytes Percent	LYMPH	%	Light scatter
Monocytes Percent	MONO	%	Light scatter
Eosinophils Percent	EOS	%	Light scatter
Basophils Percent	BASO	%	Light scatter
Large Unstained Cells Percent	LUC	%	Light scatter
Neutrophils	NEUT	$x10^3/\mu L$	Calculated
Lymphocytes	LYMPH	$x10^3/\mu L$	Calculated
Monocytes	MONO	$x10^3/\mu L$	Calculated
Eosinophils	EOS	$x10^3/\mu L$	Calculated
Basophils	BASO	$x10^3/\mu L$	Calculated
Large Unstained Cells	LUC	$x10^3/\mu L$	Calculated

Manual and Visual

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Count		% and/or $x10^3/\mu L$	Microscopic enumeration (100 white cells)
- Immature Neutrophils Count	IMM NEUT		
- Immature Neutrophils Percent	IMM NEUT		
- Immature Cells Percent	IMM CELL		
- Immature Cells Count	IMM CELL		
- Large Platelets	LPLT		
- Neutrophils Band Form	NEUT BAND		
- Neutrophils Band Form Percent	NEUT BAND		
- Packed Cell Volume	PCV		
- Neutrophils	NEUT		
- Lymphocytes	LYMPH		

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- Monocytes	MONO		
- Eosinophils	EOS		
- Basophils	BASO		
Others			
- Nucleated Red Blood Cells/100 Leukocytes	RBCNUCLE	#/100 WBC	Microscopic enumeration (100 white cells) Reported as Number but not included in WBC Differential
CELL MORPHOLOGY			
- Cytoplasmic Basophilia Neutrophil	CYTO BASO NEUT	1+ (Minimal) 2+ (Mild)	Microscopic Examination
- Polychromasia	POLY	3+ (Moderate)	
- Anisocytosis	ANISO	4+ (Marked)	
- Hypochromasia	HYPOCHROMIA		
- Reactive Lymphocytes	REACTIVE LYMPH		
- Megakaryocytes	MEGAK		
- Smudge Cells	SMUDGE CELL		
- Microcytes	MICROCYTES		
- Macrocytes	MACROCYTES		
- Poikilocytosis	POIK		
- Rouleaux Formation	ROULEAUX		
- Agglutination	AGGL		
- Red Blood Cell Clumping	RBC Clumping		
- Acanthocytes	ACAN		
- Codocytes	TARGET CELLS		
- Dacryocytes	DACR		
- Platelet Clumps	PLATELET CLUMPS		
- Eccentrocytes	ECCENTCY		
- Schistocytes	SCHZ		
- Spherocytes	SPHR		
- Stomatocytes	STOM		
- Howell Jolly Bodies	HJB		
- Basophilic Stippling	BASO STIP RBC		
- Echinocytes	ECHINO		
- Vacuolated Neutrophils	NEUTVAC		
- Vacuolated Lymphocyted	LYMVAC		
- Döhle Bodies	DOHLE		
- Degenerated Cells	DEG CELL		
- Ovalocytes	OVAL		
- Large Platelets Alpha	LARGE PLATELETS		
- Immature Neutrophils Morphology	IMM NEUT MORPH		
- Heinz Bodies	HEINZ BODY		
- Plasmodium	PLASMOD		
- Kurloff Cell	KURL		
- Burr Cells	BURR		

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- Neutrophils Band Form Morphology	NEUT BAND MORPH		
- Nuclear Swelling	NUC SWELL NEUT		
- Red Blood Cell Morphology	RBC MORPH		
- White Blood Cell Morphology	WBC MORPH		
- Toxic Granulation	TOXG		
- Platelet Morphology	PLT MORPH		
Heinz Bodies Percent	HEINZ BODY	%	Microscopic examination. Methyl violet in physiological saline
Reticulocyte Percent	RETIC	%	Microscopic enumeration, (b) (4)
Bone Marrow Stain		None	Manual, Wright-Giemsa stain
Bone Marrow Slide Fixation		None	Manual, Fixative

Aerospray Automated Slide Stainer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Stain		None	2 parts aqueous stain (Eosin-Thiazin)

Midas III Slide Stainer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Stain		None	Wright-Giemsa stain
Bone Marrow Stain		None	Wright-Giemsa stain
Bone Marrow Slide Fixation		None	Fixative

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
--	Not required for veterinary monitoring / No findings / Not scheduled to be performed/Dead	QNS	Quantity not sufficient
ADQ	Adequate	RSV	Refer to source data
AVS	Suspected aberrant value	SAMU	Large number of smudge cells
CLOT	Sample clotted	SND	Stability not documented
COMM	1+ Hypersegmented neutrophils	SNR	Sample not received
DEC	Decreased	UDPC	Results not confirmed by smear review
INC	Increased	Unsc	Unscheduled bleed
MDIFF	Manual differential	UPTD	Unable to perform due to technical difficulty
NAF	No abnormal findings	UTD	Unable to determine
NRBC	WBC corrected for presence of nucleated RBC	UTDM	Unable to determine, not confirmed by microscopy
NSCH	Not scheduled to be performed	UTDR	Unable to determine, results not reproducible
OA	Omitted activity	Vet	Bleed for veterinary monitoring
OOS	Sample analysed outside of established stability, results for	VNC	Value not calculable

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information only

X Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Note: Additional morphology for flagged samples has been reported for the following animals: 4003, 4009, 4010

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1M	1001	8.69	0.67	7.68	0.17	0.08	0.02	0.08
	1002	11.38	1.18	9.46	0.45	0.11	0.04	0.14
	1003	9.11	1.12	7.56	0.20	0.08	0.02	0.13
	1004	8.64	0.82	7.51	0.15	0.07	0.01	0.08
	1005	9.26	1.29	7.54	0.25	0.10	0.02	0.07
	1006	10.86	0.71	9.76	0.22	0.04	0.02	0.11
	1007	8.70	0.48	7.76	0.23	0.07	0.03	0.13
	1008	4.38	0.45	3.76	0.11	0.04	0.01	0.02
	1009	5.99	0.68	5.04	0.13	0.09	0.01	0.04
	1010	7.99	1.25	6.38	0.22	0.06	0.01	0.07
2M	2001	13.09	6.57	5.91	0.22	0.14	0.02	0.24
	2002	13.51	7.39	5.35	0.28	0.24	0.02	0.23
	2003	11.22	5.62	5.08	0.20	0.18	0.01	0.13
	2004	11.02	4.15	5.82	0.19	0.56	0.02	0.29
	2005	11.15	5.54	4.66	0.35	0.13	0.01	0.45
	2006	15.19	6.11	8.27	0.33	0.12	0.03	0.32
	2007	13.82	4.35	8.55	0.25	0.31	0.02	0.34
	2008	8.42	3.96	4.15	0.11	0.08	0.00	0.11
	2009	10.14	2.40	7.16	0.17	0.22	0.01	0.17
	2010	9.44	3.10	5.79	0.12	0.09	0.02	0.33

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	1001	8.23	14.4	42.6	51.8	17.4	33.7	12.9
	1002	7.52	14.3	42.0	55.9	19.0	33.9	12.5
	1003	7.91	14.4	43.3	54.8	18.3	33.3	12.3
	1004	7.36	14.3	41.4	56.2	19.4	34.6	12.1
	1005	8.06	14.6	44.3	55.0	18.1	33.0	12.1
	1006	7.85	14.6	43.4	55.3	18.5	33.6	12.9
	1007	7.79	14.5	43.9	56.4	18.6	32.9	12.4
	1008	8.30	14.6	42.9	51.6	17.6	34.1	12.4
	1009	7.97	15.0	44.5	55.8	18.8	33.7	12.1
	1010	7.22	13.3	40.6	56.2	18.4	32.6	12.5
2M	2001	7.33	14.5	42.9	58.5	19.8	33.9	11.7
	2002	7.76	14.3	42.9	55.3	18.4	33.3	13.5
	2003	8.15	14.1	42.3	51.9	17.3	33.3	12.8
	2004	7.16	13.8	40.5	56.5	19.3	34.1	13.3
	2005	7.52	13.7	40.4	53.7	18.2	33.8	13.1
	2006	7.29	13.9	41.4	56.8	19.1	33.7	13.3
	2007	7.68	13.6	40.3	52.4	17.7	33.7	13.3
	2008	7.50	13.6	40.4	53.9	18.1	33.7	13.4
	2009	7.45	13.7	41.6	55.9	18.4	33.0	12.8
	2010	7.12	13.2	38.6	54.3	18.6	34.3	13.4

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POLY	POIK	PLT MORPH	WBC MORPH
1M	1001	871	266.4	--	--	--	--	--
	1002	941	240.3	--	--	--	--	--
	1003	1183	264.8	--	--	--	--	--
	1004	1112	249.7	--	--	--	--	--
	1005	1029	273.8	--	--	--	--	--
	1006	1102	270.1	--	--	--	--	--
	1007	1114	246.8	--	--	--	--	--
	1008	1264	235.5	--	--	--	--	--
	1009	1169	267.2	--	--	--	--	--
	1010	1088	265.7	--	--	--	--	--
2M	2001	1275	221.1	--	--	--	--	--
	2002	896	193.1	--	--	--	--	--
	2003	1053	202.5	--	--	--	--	--
	2004	1222	212.5	--	--	--	--	--
	2005	1127	225.4	--	--	--	--	--
	2006	935	230.5	--	--	--	--	--
	2007	1168	222.1	--	--	--	--	--
	2008	1030	189.0	--	--	--	--	--
	2009	1179	210.2	--	--	--	--	--
	2010	1167	223.9	--	--	--	--	--

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	16.13	8.68	6.78	0.28	0.19	0.02	0.18
	3002	15.17	11.12	3.38	0.28	0.14	0.03	0.22
	3003	20.68	15.27	4.62	0.23	0.41	0.02	0.13
	3004	16.51	9.72	6.05	0.26	0.15	0.03	0.30
	3005	12.92	8.49	4.00	0.12	0.23	0.01	0.08
	3006	15.11	9.69	4.83	0.14	0.31	0.02	0.12
	3007	17.20	11.03	5.44	0.20	0.32	0.02	0.20
	3008	9.70	4.44	4.48	0.14	0.30	0.01	0.33
	3009	14.88	7.66	6.42	0.21	0.33	0.02	0.24
	3010	15.85	10.55	4.54	0.30	0.13	0.02	0.30
4M	4001	16.17	11.26	4.18	0.26	0.32	0.02	0.13
	4002	14.92	11.30	2.99	0.17	0.35	0.01	0.10
	4003	12.68	9.82	2.51	0.10	0.19	0.01	0.05
	4004	18.43	12.89	4.96	0.16	0.26	0.03	0.13
	4005	14.68	10.40	3.88	0.13	0.18	0.01	0.07
	4006	18.67	10.91	6.99	0.20	0.40	0.02	0.14
	4007	27.54	18.37	8.22	0.13	0.43	0.06	0.33
	4008	16.85	10.16	6.04	0.12	0.25	0.02	0.26
	4009	17.00	7.82	8.67	0.17	0.34	0.00	--MDIFF
	4010	12.17	6.33	5.23	0.12	0.49	0.00	--MDIFF

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	7.26	13.4	40.6	55.9	18.4	32.9	13.5
	3002	7.48	14.7	43.9	58.7	19.6	33.4	13.3
	3003	7.57	13.9	42.0	55.4	18.4	33.1	13.7
	3004	7.20	14.1	40.8	56.7	19.6	34.5	12.7
	3005	7.58	13.7	40.5	53.4	18.1	33.9	13.0
	3006	8.13	14.9	45.0	55.3	18.4	33.2	12.6
	3007	7.27	13.4	39.7	54.6	18.5	33.8	13.6
	3008	7.76	14.3	43.0	55.5	18.4	33.2	13.0
	3009	7.14	13.4	39.9	55.9	18.8	33.7	13.2
	3010	7.53	13.9	41.3	54.9	18.4	33.6	13.3
4M	4001	7.73	13.8	42.3	54.8	17.8	32.6	14.9
	4002	7.88	14.4	43.2	54.8	18.3	33.3	13.8
	4003	7.96	14.6	43.0	54.0	18.3	34.0	13.5
	4004	7.86	14.6	42.7	54.3	18.6	34.3	13.0
	4005	7.78	13.8	42.0	54.0	17.8	32.9	13.7
	4006	6.89	13.4	39.0	56.6	19.4	34.3	14.0
	4007	8.32	14.2	41.8	50.3	17.0	33.9	14.1
	4008	7.78	14.4	42.2	54.2	18.5	34.0	13.6
	4009	7.67	14.1	41.8	54.5	18.4	33.7	12.9
	4010	7.44	14.2	41.8	56.2	19.1	33.9	13.8

Appendix 11

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POLY	POIK	PLT MORPH	WBC MORPH
3M	3001	1405	221.1	--	--	--	--	--
	3002	1157	182.9	--	--	--	--	--
	3003	1117	203.1	--	--	--	--	--
	3004	1115	217.7	--	--	--	--	--
	3005	1069	206.7	--	--	--	--	--
	3006	1092	212.6	--	--	--	--	--
	3007	1101	130.3	--	--	--	--	--
	3008	1151	206.8	--	--	--	--	--
	3009	1171	174.1	--	--	--	--	--
	3010	1298	191.2	--	--	--	--	--
4M	4001	1031	180.3	--	--	--	--	--
	4002	1151	181.5	--	--	--	--	--
	4003	1070	173.0	1+	--	1+	NAF	--COMM
	4004	1019	158.8	--	--	--	--	--
	4005	1257	156.9	--	--	--	--	--
	4006	1290	175.1	--	--	--	--	--
	4007	1055	181.8	--	--	--	--	--
	4008	1095	152.3	--	--	--	--	--
	4009	952	167.3	1+	--	1+	NAF	--COMM
	4010	790	182.9	1+	1+	1+	NAF	--COMM

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	1501	5.35	0.71	4.31	0.15	0.07	0.01	0.10
	1502	5.28	0.51	4.46	0.15	0.10	0.00	0.07
	1503	5.20	0.50	4.36	0.21	0.06	0.01	0.07
	1504	3.79	0.60	2.87	0.21	0.06	0.00	0.05
	1505	5.83	0.60	4.84	0.17	0.08	0.01	0.12
	1506	8.46	0.34	7.82	0.14	0.06	0.01	0.09
	1507	7.41	0.31	6.76	0.13	0.06	0.01	0.14
	1508	6.64	0.61	5.80	0.11	0.08	0.00	0.05
	1509	5.42	0.21	5.01	0.06	0.07	0.00	0.07
	1510	8.50	0.48	7.70	0.16	0.07	0.01	0.07
2F	2501	12.15	4.73	6.74	0.19	0.29	0.02	0.19
	2502	8.91	4.55	3.89	0.16	0.21	0.01	0.09
	2503	8.29	3.12	4.53	0.18	0.24	0.01	0.21
	2504	7.22	2.36	4.53	0.08	0.16	0.01	0.08
	2505	7.19	1.95	4.96	0.07	0.13	0.01	0.05
	2506	14.40	5.61	7.89	0.22	0.45	0.03	0.21
	2507	12.98	4.91	7.73	0.08	0.16	0.02	0.09
	2508	7.79	2.54	4.81	0.12	0.18	0.01	0.12
	2509	11.68	5.63	5.33	0.19	0.24	0.02	0.27
	2510	7.09	2.82	3.84	0.09	0.22	0.01	0.12

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	7.35	13.8	40.3	54.8	18.8	34.4	11.1
	1502	7.17	13.3	39.5	55.1	18.6	33.8	11.5
	1503	7.70	14.1	41.2	53.6	18.3	34.1	11.2
	1504	7.53	13.9	40.5	53.8	18.5	34.3	11.4
	1505	7.34	13.8	40.7	55.5	18.8	33.9	10.4
	1506	7.47	13.8	40.5	54.3	18.4	33.9	11.8
	1507	6.92	12.6	37.5	54.3	18.3	33.7	10.5
	1508	7.78	14.3	42.3	54.4	18.4	33.9	10.4
	1509	7.23	12.6	38.4	53.2	17.5	32.9	11.4
	1510	7.23	13.4	39.5	54.7	18.5	33.9	11.3
2F	2501	6.68	13.2	39.5	59.2	19.7	33.3	12.3
	2502	7.50	13.1	39.2	52.2	17.5	33.5	11.0
	2503	7.39	13.6	40.1	54.3	18.3	33.8	11.1
	2504	7.88	14.2	41.5	52.7	18.0	34.2	11.0
	2505	7.08	12.9	37.9	53.5	18.2	34.0	11.7
	2506	7.39	13.8	39.4	53.3	18.7	35.1	12.0
	2507	6.59	12.2	36.0	54.6	18.5	33.9	11.6
	2508	7.08	13.1	37.6	53.2	18.4	34.7	11.5
	2509	6.98	12.5	37.4	53.6	17.9	33.3	11.8
	2510	6.54	12.4	36.0	55.0	18.9	34.5	12.5

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Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POLY	POIK	PLT MORPH	WBC MORPH
1F	1501	1295	201.7	--	--	--	--	--
	1502	1536	220.0	--	--	--	--	--
	1503	1226	216.7	--	--	--	--	--
	1504	1243	251.5	--	--	--	--	--
	1505	1143	164.0	--	--	--	--	--
	1506	1211	160.9	--	--	--	--	--
	1507	1246	115.6	--	--	--	--	--
	1508	929	164.9	--	--	--	--	--
	1509	1089	165.1	--	--	--	--	--
	1510	974	152.8	--	--	--	--	--
2F	2501	1085	185.0	--	--	--	--	--
	2502	1254	188.7	--	--	--	--	--
	2503	937	172.4	--	--	--	--	--
	2504	1092	167.6	--	--	--	--	--
	2505	1086	219.4	--	--	--	--	--
	2506	1068	166.9	--	--	--	--	--
	2507	1045	213.1	--	--	--	--	--
	2508	981	197.9	--	--	--	--	--
	2509	1477	184.7	--	--	--	--	--
	2510	1149	225.1	--	--	--	--	--

Appendix 11

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
3F	3501	11.63	7.42	3.68	0.10	0.36	0.00	0.06
	3502	8.85	4.14	3.78	0.07	0.81	0.00	0.04
	3503	11.43	7.94	3.00	0.06	0.34	0.01	0.07
	3504	6.75	3.82	2.62	0.07	0.16	0.00	0.07
	3505	15.39	8.58	6.23	0.10	0.28	0.03	0.17
	3506	9.27	6.17	2.75	0.06	0.20	0.01	0.08
	3507	12.67	7.38	4.46	0.15	0.40	0.01	0.26
	3508	13.14	8.81	3.82	0.19	0.19	0.02	0.11
	3509	10.18	5.54	4.10	0.08	0.34	0.01	0.11
	3510	6.55	3.52	2.66	0.07	0.21	0.00	0.08
4F	4501	9.45	7.42	1.72	0.05	0.16	0.01	0.08
	4502	10.82	8.37	1.95	0.09	0.35	0.00	0.05
	4503	9.35	6.68	2.13	0.04	0.45	0.00	0.07
	4504	8.54	4.89	3.17	0.04	0.36	0.00	0.08
	4505	7.60	4.91	2.38	0.04	0.20	0.00	0.06
	4506	8.27	5.59	2.28	0.08	0.23	0.01	0.08
	4507	9.81	5.75	3.66	0.05	0.25	0.01	0.08
	4508	11.51	6.83	4.23	0.07	0.28	0.01	0.09
	4509	14.42	7.50	6.20	0.36	0.11	0.02	0.23
	4510	11.83	7.92	3.28	0.10	0.37	0.01	0.16

Appendix 11

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
3F	3501	7.36	14.0	40.2	54.6	19.0	34.8	11.8
	3502	7.46	13.5	38.9	52.2	18.2	34.8	11.8
	3503	7.04	13.5	38.8	55.2	19.1	34.6	11.9
	3504	7.20	13.5	39.2	54.4	18.7	34.4	12.9
	3505	7.25	13.7	40.4	55.8	18.9	34.0	12.4
	3506	7.43	14.2	40.3	54.3	19.1	35.2	12.1
	3507	7.54	13.9	40.0	53.1	18.5	34.7	11.4
	3508	7.31	14.1	40.9	56.0	19.3	34.5	12.3
	3509	7.02	13.1	38.2	54.4	18.6	34.2	12.9
	3510	7.30	13.0	38.1	52.2	17.8	34.1	11.7
4F	4501	7.31	14.1	42.1	57.7	19.4	33.6	12.3
	4502	7.50	13.3	38.8	51.7	17.7	34.2	12.5
	4503	7.51	13.3	39.1	52.1	17.7	34.0	12.6
	4504	7.79	14.5	42.2	54.1	18.6	34.5	12.4
	4505	7.77	14.4	43.5	56.1	18.6	33.1	12.0
	4506	7.89	14.0	40.6	51.5	17.8	34.5	12.4
	4507	7.72	14.1	41.5	53.7	18.2	34.0	12.1
	4508	7.48	13.7	40.6	54.3	18.3	33.7	12.4
	4509	7.64	14.0	41.4	54.1	18.3	33.8	12.3
	4510	7.38	13.5	39.1	53.0	18.2	34.4	12.2

Appendix 11

Individual Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POLY	POIK	PLT MORPH	WBC MORPH
3F	3501	888	182.4	--	--	--	--	--
	3502	1102	138.8	--	--	--	--	--
	3503	937	165.6	--	--	--	--	--
	3504	1241	268.4	--	--	--	--	--
	3505	1084	228.9	--	--	--	--	--
	3506	1100	167.2	--	--	--	--	--
	3507	1054	165.3	--	--	--	--	--
	3508	882	185.5	--	--	--	--	--
	3509	1118	179.1	--	--	--	--	--
	3510	939	157.2	--	--	--	--	--
4F	4501	995	241.3	--	--	--	--	--
	4502	975	152.0	--	--	--	--	--
	4503	992	160.8	--	--	--	--	--
	4504	776	176.5	--	--	--	--	--
	4505	908	227.6	--	--	--	--	--
	4506	892	150.9	--	--	--	--	--
	4507	852	177.6	--	--	--	--	--
	4508	887	182.8	--	--	--	--	--
	4509	699	132.0	--	--	--	--	--
	4510	787	132.3	--	--	--	--	--

Appendix 11

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1M	1011	8.77	1.30	7.08	0.19	0.15	0.02	0.03
	1012	6.27	0.86	5.10	0.18	0.10	0.01	0.03
	1013	6.93	0.97	5.67	0.16	0.09	0.01	0.04
	1014	14.36	1.65	12.16	0.31	0.12	0.05	0.08
	1015	5.54	0.78	4.57	0.10	0.06	0.01	0.02
4M	4011	7.80	1.59	5.98	0.13	0.05	0.01	0.04
	4012	11.18	1.13	9.62	0.25	0.11	0.02	0.05
	4013	8.32	1.03	6.90	0.17	0.17	0.01	0.04
	4014	6.63	0.63	5.69	0.17	0.09	0.01	0.05
	4015	7.70	1.76	5.61	0.16	0.12	0.02	0.03

Appendix 11

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	7.65	14.2	41.6	54.4	18.5	34.0	12.4
	1012	7.71	13.9	41.1	53.3	18.0	33.7	13.3
	1013	7.91	14.8	43.0	54.4	18.7	34.4	11.9
	1014	7.87	14.0	41.8	53.1	17.7	33.4	12.4
	1015	8.27	14.4	43.0	52.0	17.4	33.4	12.7
4M	4011	7.44	13.6	40.6	54.6	18.2	33.4	14.4
	4012	7.35	13.9	41.0	55.7	19.0	34.0	14.4
	4013	7.72	14.5	43.1	55.9	18.8	33.7	14.6
	4014	7.06	12.4	37.6	53.3	17.5	32.9	15.2
	4015	7.71	14.2	42.6	55.2	18.4	33.3	14.7

Appendix 11

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POLY	POIK	PLT MORPH	WBC MORPH
1M	1011	1165	192.1	--	--	--	--	--
	1012	1173	269.6	--	--	--	--	--
	1013	1185	201.4	--	--	--	--	--
	1014	1227	209.1	--	--	--	--	--
	1015	1174	221.1	--	--	--	--	--
4M	4011	1352	300.0	--	--	--	--	--
	4012	1018	265.5	--	--	--	--	--
	4013	1165	288.3	--	--	--	--	--
	4014	1262	291.5	--	--	--	--	--
	4015	1205	233.3	--	--	--	--	--

Appendix 11

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	7.12	1.89	4.92	0.18	0.09	0.00	0.04
	1512	9.82	0.64	8.76	0.24	0.05	0.02	0.11
	1513	4.62	0.69	3.71	0.12	0.08	0.00	0.02
	1514	8.94	2.67	5.93	0.22	0.07	0.01	0.04
	1515	5.12	1.64	3.19	0.18	0.04	0.00	0.06
4F	4511	7.99	2.75	4.85	0.26	0.09	0.01	0.03
	4512	6.37	1.90	4.00	0.32	0.09	0.01	0.05
	4513	7.96	2.53	5.03	0.23	0.11	0.01	0.05
	4514	8.24	0.68	7.28	0.10	0.09	0.01	0.07
	4515	4.30	0.80	3.37	0.09	0.01	0.00	0.02

Appendix 11

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	6.76	12.3	36.1	53.4	18.2	34.0	11.9
	1512	6.98	13.4	39.4	56.4	19.2	34.0	10.8
	1513	6.95	13.3	38.1	54.8	19.2	35.0	10.7
	1514	7.02	12.9	36.5	51.9	18.4	35.4	11.1
	1515	7.42	13.2	38.4	51.8	17.8	34.4	11.1
4F	4511	6.69	12.1	36.0	53.9	18.1	33.5	13.3
	4512	6.67	12.5	36.5	54.7	18.8	34.3	12.7
	4513	6.98	11.8	35.1	50.2	16.9	33.7	12.9
	4514	7.27	12.7	36.8	50.7	17.5	34.5	13.0
	4515	7.29	13.4	38.8	53.3	18.3	34.4	13.0

Appendix 11

Individual Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PLT 10^3/uL	RETIC 10^9/L	ANISO	POLY	POIK	PLT MORPH	WBC MORPH
1F	1511	1351	182.9	--	--	--	--	--
	1512	1097	165.6	--	--	--	--	--
	1513	1070	134.0	--	--	--	--	--
	1514	1079	151.6	--	--	--	--	--
	1515	1424	165.5	--	--	--	--	--
4F	4511	1130	171.8	--	--	--	--	--
	4512	1096	142.0	--	--	--	--	--
	4513	1324	117.6	--	--	--	--	--
	4514	1482	202.8	--	--	--	--	--
	4515	1089	197.2	--	--	--	--	--

Appendix 12

Individual Coagulation Values Explanation Page

START 4 Compact Stago Analyzer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Activated Partial Thromboplastin Time	APTT	sec	Viscosity
Fibrinogen	FIB	mg/dL	Viscosity
Prothrombin Time	PT	sec	Viscosity

STA Compact Stago Analyser

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Prothrombin Time	PT	sec	Viscosity
Activated Partial Thromboplastin Time	APTT	sec	Viscosity
Fibrinogen	FIB	mg/dL	Viscosity

Plasma Appearance (Reported as SAMQ PLASMA)

Analyzed Parameter Descriptions

Parameter	Abbreviation	Degree is graded as	Methodology
Normal sample	N	Normal	Manual and visual
Hemolyzed sample	H	+ = slight (pale/light red) ++ = moderate (red) +++ = severe (dark red)	Manual and visual
Lipemic sample	L	+ = slight (cloudy) ++ = moderate (turbid) +++ = severe (lactescent)	Manual and visual
Icterus sample	I	+ = slight (dark yellow) ++ = moderate (very dark yellow) +++ = severe (dark yellow-green)	Manual and visual

Appendix 12

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
--	Not required for veterinary monitoring / Not scheduled to be performed / Dead	RSV	Refer to source data
AVS	Suspected aberrant value	SND	Stability not documented
CLOT	Sample clotted	SNR	Sample not received
COMM	Comment added	Unsc	Unscheduled bleed
NCD	No clot detected	UPTD	Unable to perform due to technical difficulty
NSCH	Not scheduled to be performed	UTD	Unable to determine
OA	Omitted activity	UTDR	Unable to determine, results not reproducible
OOS	Sample analysed outside of established stability, results for information only	Vet	Bleed for veterinary monitoring
QNS	Quantity not sufficient	VNC	Value not calculable
		X	Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 12

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1001	18.5	15.4	300	N
	1002	17.5	17.0	308	N
	1003	17.1	17.5	299	N
	1004	18.6	16.0	284	N
	1005	18.3	15.4	302	N
	1006	17.8	15.6	355	N
	1007	15.8	17.3	284	N
	1008	16.2	15.9	312	N
	1009	17.2	15.5	292	N
	1010	17.5	16.5	292	N
2M	2001	17.7	16.6	613	N
	2002	17.6	17.1	628	N
	2003	16.9	16.7	621	N
	2004	16.6	17.6	559	N
	2005	16.2	17.5	602	N
	2006	17.4	16.3	568	N
	2007	15.7	17.0	574	N
	2008	15.9	16.5	571	N
	2009	16.3	16.6	544	N
	2010	16.1	16.5	856	N

Appendix 12

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3M	3001	18.0	17.6	602	N
	3002	17.8	20.4	606	N
	3003	16.3	18.9	632	N
	3004	17.4	18.7	675	N
	3005	17.0	18.3	689	N
	3006	16.5	18.8	689	N
	3007	17.0	19.2	689	N
	3008	16.2	17.6	588	N
	3009	17.3	17.1	649	N
	3010	16.7	17.1	653	N
4M	4001	17.3	19.0	714	N
	4002	18.0	19.8	632	N
	4003	17.4	19.7	694	N
	4004	17.0	17.9	671	N
	4005	17.6	19.4	709	N
	4006	16.4	18.6	662	N
	4007	15.7	20.4	763	N
	4008	16.2	19.9	821	N
	4009	18.6	19.4	684	N
	4010	15.9	19.6	628	N

Appendix 12

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1501	18.7	15.8	305	N
	1502	18.3	13.2	334	N
	1503	18.0	15.7	230	N
	1504	18.0	15.8	296	N
	1505	17.5	16.8	243	N
	1506	17.7	16.3	308	N
	1507	17.9	15.3	265	N
	1508	17.3	14.4	233	N
	1509	16.2	13.6	299	N
	1510	18.5	16.0	291	N
2F	2501	17.4	14.6	541	N
	2502	18.8	15.9	413	N
	2503	18.7	17.3	456	N
	2504	17.3	17.2	442	N
	2505	17.0	16.1	302	N
	2506	17.4	15.9	333	N
	2507	17.4	18.5	450	N
	2508	17.6	16.0	503	N
	2509	18.1	17.0	521	N
	2510	18.6	15.7	585	N

Appendix 12

Individual Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
3F	3501	18.4	17.9	602	N
	3502	17.1	16.5	222	N
	3503	18.4	18.2	602	N
	3504	17.7	17.5	632	N
	3505	18.5	16.3	632	N
	3506	17.1	17.1	666	N
	3507	17.5	17.5	552	N
	3508	18.5	17.3	699	N
	3509	18.2	16.9	704	N
	3510	17.4	15.9	595	N
4F	4501	18.7	18.2	621	N
	4502	18.3	18.9	585	N
	4503	18.4	20.1	549	N
	4504	17.2	18.5	606	N
	4505	19.2	18.0	625	N
	4506	18.2	20.1	595	N
	4507	18.1	21.6	625	N
	4508	17.4	18.1	699	N
	4509	20.9	19.6	680	N
	4510	17.5	19.2	462	N

Appendix 12

Individual Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1M	1011	17.3	15.3	305	N
	1012	18.5	14.8	293	N
	1013	18.1	15.9	281	N
	1014	18.8	16.0	397	N
	1015	17.1	16.7	340	N
4M	4011	17.5	14.8	346	N
	4012	18.4	16.5	273	N
	4013	18.2	16.5	290	N
	4014	17.6	15.6	289	N
	4015	17.4	15.0	307	N

Appendix 12

Individual Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	PT sec	APTT sec	FIB mg/dL	SAMQ PLASMA
1F	1511	18.5	16.1	195	N
	1512	18.1	17.0	231	N
	1513	17.6	16.0	251	N
	1514	18.0	15.8	231	N
	1515	16.3	12.1	262	N
4F	4511	18.8	16.0	245	N
	4512	17.4	15.6	268	N
	4513	18.4	16.7	276	N
	4514	17.5	18.1	254	N
	4515	17.7	15.0	269	N

Appendix 13

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 13

Serum Appearance
(Reported as SAMQ SERUM)

Analyzed Parameter Descriptions

Parameter	Abbreviation	Key to Results (Code)	Methodology
Normal sample	N	Normal	Manual and visual
Hemolyzed sample	H	+ = slight (pale/light red) ++ = moderate (red) +++ = severe (dark red)	Manual and visual
Lipemic sample	L	+ = slight (cloudy) ++ = moderate (turbid) +++ = severe (lactescent)	Manual and visual
Icterus sample	I	+ = slight (dark yellow) ++ = moderate (very dark yellow) +++ = severe (dark yellow-green)	Manual and visual

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
--	Not evaluated/Not required for veterinary monitoring	SNR	Sample not received
AVS	Suspected aberrant value	TNR	Test not reported
COMM	Comment added	Unsc	Unscheduled bleed
CLOT	Sample clotted	UPTD	Unable to perform due to technical difficulty
LLD	Less than lower limit of detection	UTD	Unable to determine
LLOQ/LLQ	Less than lower limit of quantitation	UTDH	Unable to determine due to marked hemolysis
NSCH	Not scheduled to be performed	UTDL	Unable to determine due to marked lipemia
OA	Omitted activity	UTDR	Unable to determine, results not reproducible
OOS	Sample analysed outside of established stability, results for information only	VARR	Assigned value above reportable range
QNS	Quantity not sufficient	VBRR	Assigned value below reportable range
RSV	Refer to source data	Vet	Bleed for veterinary monitoring
SND	Stability not documented	VNC	Value not calculable
		X	Excluded from mean

Note: This is a comprehensive list of parameters and abbreviations. All of the parameters and abbreviations listed may not be applicable to this report.

Appendix 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-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 13

Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	84	42	176	2VBRR	561	0.10	16
	1002	84	36	124	2VBRR	632	0.08	14
	1003	64	43	136	2VBRR	182	0.08	14
	1004	56	33	155	2VBRR	141	0.08	13
	1005	67	33	125	2VBRR	275	0.10	12
	1006	55	44	175	2VBRR	173	0.09	15
	1007	65	35	139	2VBRR	176	0.08	11
	1008	63	41	154	2VBRR	159	0.08	11
	1009	57	35	134	2VBRR	151	0.07	13
	1010	48	34	165	2VBRR	120	0.07	15
2M	2001	88	45	131	2VBRR	591	0.06	16
	2002	66	42	115	2VBRR	293	0.11	14
	2003	91	38	160	2VBRR	548	0.12	16
	2004	75	35	127	2VBRR	281	0.04	17
	2005	81	46	139	2VBRR	387	0.12	16
	2006	58	43	167	2VBRR	145	0.10	15
	2007	68	33	113	2VBRR	362	0.13	16
	2008	51	28	122	2VBRR	176	0.12	14
	2009	114	35	144	2VBRR	924	0.06	12
	2010	63	31	108	2VBRR	149	0.10	12

Appendix 13

Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	1001	0.4	211	73	41	5.5	3.6	1.9
	1002	0.4	230	79	194	6.1	3.9	2.2
	1003	0.3	205	78	38	5.7	3.8	1.9
	1004	0.3	205	80	61	5.4	3.7	1.7
	1005	0.3	178	63	70	5.7	3.9	1.8
	1006	0.3	208	80	53	5.8	3.9	1.9
	1007	0.4	195	76	28	6.0	3.8	2.2
	1008	0.4	209	72	97	6.0	4.1	1.9
	1009	0.4	168	79	45	5.9	4.0	1.9
	1010	0.4	282	73	76	5.8	3.6	2.2
2M	2001	0.4	144	73	50	6.1	3.3	2.8
	2002	0.4	222	69	78	6.3	3.6	2.7
	2003	0.3	104	61	59	6.4	3.5	2.9
	2004	0.3	161	58	42	5.5	3.2	2.3
	2005	0.4	202	97	58	6.2	3.7	2.5
	2006	0.3	164	59	40	5.8	3.4	2.4
	2007	0.4	126	85	41	6.3	3.4	2.9
	2008	0.3	176	74	42	6.0	3.4	2.6
	2009	0.3	138	70	46	5.9	3.3	2.6
	2010	0.3	189	60	34	5.9	3.3	2.6

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1M	1001	1.9	10.9	8.1	139	5.4	99	N
	1002	1.8	11.2	8.0	139	5.3	98	N
	1003	2.0	11.0	8.0	138	5.1	99	N
	1004	2.2	10.6	7.9	140	5.2	102	N
	1005	2.2	10.6	7.7	139	5.2	99	N
	1006	2.1	11.2	8.2	139	4.7	99	N
	1007	1.7	11.0	8.9	141	5.1	100	N
	1008	2.2	11.0	7.3	141	4.5	103	N
	1009	2.1	10.9	7.1	143	4.7	101	N
	1010	1.6	11.1	8.0	142	5.7	102	N
2M	2001	1.2	11.1	8.7	140	5.6	99	N
	2002	1.3	11.7	8.6	142	5.7	102	N
	2003	1.2	11.3	8.4	140	4.8	98	N
	2004	1.4	11.0	9.0	141	4.9	103	N
	2005	1.5	11.1	8.4	140	5.1	99	N
	2006	1.4	11.2	8.1	142	4.7	104	N
	2007	1.2	10.8	8.5	137	5.2	96	N
	2008	1.3	11.4	8.4	140	5.1	101	N
	2009	1.3	10.9	8.3	138	5.6	100	N
	2010	1.3	11.2	7.9	141	4.7	102	N

Appendix 13

Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	128	37	134	2VBRR	1262	0.09	19
	3002	106	44	152	2VBRR	599	0.07	15
	3003	70	35	164	2VBRR	211	0.14	14
	3004	63	39	167	2VBRR	157	0.06	15
	3005	61	39	145	2VBRR	200	0.11	15
	3006	62	34	149	2VBRR	220	0.13	12
	3007	177	67	123	2VBRR	183	0.10	18
	3008	68	38	132	2VBRR	188	0.11	16
	3009	60	40	177	2VBRR	174	0.11	16
	3010	62	32	132	2VBRR	260	0.13	16
4M	4001	68	45	154	2VBRR	188	0.07	16
	4002	59	33	164	2VBRR	205	0.09	12
	4003	142	40	111	2VBRR	1125	0.08	15
	4004	65	29	139	2VBRR	229	0.10	16
	4005	139	40	199	2VBRR	1134	0.10	14
	4006	69	35	101	2VBRR	333	0.06	16
	4007	70	36	129	2VBRR	324	0.12	12
	4008	70	34	141	2VBRR	383	0.15	13
	4009	81	39	157	2VBRR	408	0.10	10
	4010	61	29	137	2VBRR	270	0.11	12

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	192	95	79	5.9	3.2	2.7
	3002	0.3	142	74	51	6.1	3.5	2.6
	3003	0.4	128	102	51	6.3	3.4	2.9
	3004	0.4	201	73	48	6.3	3.3	3.0
	3005	0.3	173	73	49	5.9	3.3	2.6
	3006	0.3	157	59	44	6.2	3.4	2.8
	3007	0.4	153	63	44	6.2	3.5	2.7
	3008	0.4	148	80	66	6.0	3.4	2.6
	3009	0.4	200	65	37	6.1	3.4	2.7
	3010	0.4	193	54	56	5.8	3.2	2.6
4M	4001	0.4	195	72	67	5.8	3.2	2.6
	4002	0.3	170	77	71	5.9	3.4	2.5
	4003	0.4	135	84	62	6.3	3.4	2.9
	4004	0.5	146	64	47	6.1	3.2	2.9
	4005	0.4	134	68	61	6.0	3.2	2.8
	4006	0.4	191	70	69	5.6	3.1	2.5
	4007	0.4	169	103	62	6.6	3.5	3.1
	4008	0.4	169	65	81	6.3	3.3	3.0
	4009	0.3	164	60	46	5.9	3.2	2.7
	4010	0.4	204	70	60	6.0	3.3	2.7

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
3M	3001	1.2	11.0	8.5	141	5.6	98	N
	3002	1.3	11.1	9.4	142	5.7	103	N
	3003	1.2	11.2	9.8	142	5.3	100	N
	3004	1.1	11.4	8.7	140	5.8	103	H+
	3005	1.3	11.2	9.6	138	5.9	99	N
	3006	1.2	11.2	8.5	141	5.2	99	N
	3007	1.3	10.9	7.4	140	5.2	99	N
	3008	1.3	11.1	8.5	142	5.2	103	N
	3009	1.3	11.1	8.0	138	5.1	99	N
	3010	1.2	11.0	7.9	138	5.7	99	N
4M	4001	1.2	11.0	9.3	140	5.5	101	N
	4002	1.4	11.0	8.8	142	5.2	102	N
	4003	1.2	11.0	8.9	139	6.1	99	N
	4004	1.1	11.1	8.5	142	5.4	101	N
	4005	1.1	11.3	10.6	141	6.3	101	N
	4006	1.2	11.2	8.4	141	5.2	100	N
	4007	1.1	11.6	8.6	137	5.8	96	N
	4008	1.1	11.3	9.4	142	5.9	100	N
	4009	1.2	10.8	10.8	139	5.8	100	N
	4010	1.2	11.2	8.7	140	5.7	100	N

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	59	25	86	2VBRR	148	0.09	11
	1502	87	37	78	2VBRR	409	0.09	16
	1503	82	37	104	2VBRR	285	0.08	12
	1504	194	63	85	2VBRR	423	0.17	17
	1505	53	30	79	2VBRR	94	0.07	14
	1506	52	35	70	2VBRR	102	0.08	15
	1507	94	39	52	2VBRR	193	0.04	15
	1508	79	36	115	2VBRR	359	0.09	16
	1509	97	32	80	2VBRR	154	0.11	14
	1510	64	42	82	2VBRR	156	0.05	16
2F	2501	65	32	59	2VBRR	272	0.05	20
	2502	93	50	94	2VBRR	159	0.04	13
	2503	72	34	93	2VBRR	301	0.05	18
	2504	97	45	102	2VBRR	427	0.10	20
	2505	103	28	48	2VBRR	640	0.05	18
	2506	97	62	69	2VBRR	265	0.05	22
	2507	79	38	97	2VBRR	352	0.00VBRR	15
	2508	81	58	87	2VBRR	338	0.05	14
	2509	51	35	67	2VBRR	149	0.07	19
	2510	51	32	86	2VBRR	124	0.13	15

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	1501	0.4	183	63	34	6.3	4.3	2.0
	1502	0.4	176	88	37	5.8	3.9	1.9
	1503	0.3	164	86	44	6.1	4.2	1.9
	1504	0.5	149	87	44	7.1	4.8	2.3
	1505	0.4	232	74	54	6.3	4.3	2.0
	1506	0.4	210	77	90	6.4	4.3	2.1
	1507	0.3	186	89	47	6.6	4.6	2.0
	1508	0.3	144	57	43	6.2	4.5	1.7
	1509	0.4	234	98	83	6.2	4.2	2.0
	1510	0.4	186	80	63	5.7	4.0	1.7
2F	2501	0.5	198	95	53	6.4	4.2	2.2
	2502	0.3	184	73	36	6.1	4.0	2.1
	2503	0.4	221	70	51	6.3	4.0	2.3
	2504	0.4	125	75	46	6.2	4.3	1.9
	2505	0.3	111	77	43	6.7	4.2	2.5
	2506	0.5	152	96	38	6.3	3.7	2.6
	2507	0.3	179	50	28	6.1	3.9	2.2
	2508	0.4	174	93	49	6.8	4.1	2.7
	2509	0.4	176	76	30	6.2	3.7	2.5
	2510	0.4	168	56	35	6.0	3.6	2.4

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1F	1501	2.2	10.7	6.4	141	4.5	103	N
	1502	2.1	10.7	7.5	142	4.8	103	N
	1503	2.2	10.7	6.5	138	4.6	101	N
	1504	2.1	11.5	7.1	140	4.3	101	N
	1505	2.2	10.9	6.8	139	4.4	100	N
	1506	2.0	11.3	7.4	142	4.8	101	N
	1507	2.3	11.4	8.4	144	5.1	104	N
	1508	2.6	10.9	7.6	141	5.0	101	N
	1509	2.1	11.3	7.1	140	4.6	100	N
	1510	2.4	10.9	8.0	142	4.5	101	N
2F	2501	1.9	11.4	7.7	139	4.6	101	N
	2502	1.9	10.7	7.0	141	4.4	103	N
	2503	1.7	11.0	7.6	139	5.6	101	N
	2504	2.3	11.3	7.2	139	4.8	100	N
	2505	1.7	11.1	7.2	140	5.0	102	N
	2506	1.4	11.2	7.2	141	4.8	101	N
	2507	1.8	10.5	7.3	142	4.9	106	N
	2508	1.5	11.1	6.7	140	4.6	99	N
	2509	1.5	11.2	8.9	139	5.1	100	N
	2510	1.5	11.2	7.1	138	4.9	100	N

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	81	37	92	2VBRR	249	0.10	20
	3502	82	31	91	2VBRR	166	0.04	13
	3503	124	29	53	2VBRR	1065	0.08	17
	3504	124	29	108	2VBRR	1061	0.09	12
	3505	69	34	102	2VBRR	212	0.07	17
	3506	120	42	72	2VBRR	760	0.11	14
	3507	144	34	80	2VBRR	1130	0.04	13
	3508	113	43	103	2VBRR	781	0.05	15
	3509	91	29	121	2VBRR	475	0.10	25
	3510	90	58	76	2VBRR	205	0.09	19
4F	4501	75	32	131	2VBRR	289	0.05	15
	4502	76	37	115	2VBRR	115	0.07	17
	4503	61	29	91	2VBRR	151	0.06	11
	4504	108	79	116	2VBRR	212	0.08	13
	4505	76	32	106	2VBRR	237	0.07	11
	4506	218	161	110	2VBRR	822	0.06	18
	4507	66	38	93	2VBRR	113	0.06	18
	4508	64	30	84	2VBRR	101	0.06	15
	4509	93	30	120	2VBRR	331	0.06	15
	4510	86	46	105	2VBRR	437	0.04	20

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
3F	3501	0.4	116	85	42	6.5	4.1	2.4
	3502	0.4	96	67	36	5.9	3.9	2.0
	3503	0.4	125	51	49	6.2	3.6	2.6
	3504	0.5	173	51	36	6.2	3.9	2.3
	3505	0.4	159	86	48	6.6	4.0	2.6
	3506	0.5	151	103	42	7.0	4.1	2.9
	3507	0.4	165	77	39	5.9	3.7	2.2
	3508	0.5	168	62	50	6.8	4.0	2.8
	3509	0.4	119	68	46	6.0	3.6	2.4
	3510	0.4	137	67	35	6.7	4.5	2.2
4F	4501	0.4	165	91	74	6.3	4.0	2.3
	4502	0.4	156	87	39	6.4	4.0	2.4
	4503	0.3	178	73	52	5.8	3.3	2.5
	4504	0.4	156	80	66	6.4	4.1	2.3
	4505	0.4	103	82	52	6.0	3.5	2.5
	4506	0.4	136	74	61	6.5	4.1	2.4
	4507	0.5	136	66	48	6.1	3.8	2.3
	4508	0.4	137	59	65	6.4	3.7	2.7
	4509	0.4	142	24	44	5.9	3.4	2.5
	4510	0.5	164	66	36	6.8	4.0	2.8

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Individual Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
3F	3501	1.7	10.9	7.9	139	4.8	102	N
	3502	2.0	10.6	7.1	139	4.1	100	N
	3503	1.4	10.7	7.5	138	4.8	100	N
	3504	1.7	11.2	8.3	139	5.0	97	N
	3505	1.5	11.4	7.2	140	4.9	102	N
	3506	1.4	11.4	7.9	139	5.0	97	N
	3507	1.7	10.2	7.4	139	4.9	101	N
	3508	1.4	11.2	7.5	138	5.5	97	N
	3509	1.5	10.9	8.1	139	5.2	100	N
	3510	2.0	11.5	8.0	138	4.5	96	N
4F	4501	1.7	11.4	7.4	141	5.0	104	N
	4502	1.7	11.2	7.0	141	4.3	102	N
	4503	1.3	11.0	7.8	141	4.6	103	N
	4504	1.8	11.3	8.7	138	5.1	98	N
	4505	1.4	10.8	8.6	140	4.8	103	N
	4506	1.7	10.9	7.8	138	5.0	95	N
	4507	1.7	11.1	6.5	141	4.9	103	N
	4508	1.4	11.0	7.3	141	5.2	100	N
	4509	1.4	11.2	9.0	139	5.9	100	N
	4510	1.4	11.1	7.7	138	4.8	96	N

Appendix 13

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	174	46	131	2VBRR	1612	0.05	16
	1012	110	41	96	2VBRR	870	0.07	18
	1013	112	50	140	2VBRR	697	0.06	15
	1014	84	39	119	2VBRR	402	0.06	14
	1015	84	48	137	2VBRR	449	0.11	16
4M	4011	108	45	188	2VBRR	654	0.03	14
	4012	102	44	151	2VBRR	640	0.04	15
	4013	88	53	126	2VBRR	388	0.06	11
	4014	94	42	128	2VBRR	477	0.05	15
	4015	76	54	169	2VBRR	131	0.07	15

Appendix 13

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	159	62	84	5.9	3.8	2.1
	1012	0.3	201	78	104	5.9	3.7	2.2
	1013	0.3	207	61	43	5.9	3.9	2.0
	1014	0.3	134	91	68	5.8	3.6	2.2
	1015	0.3	181	96	122	6.5	4.1	2.4
4M	4011	0.4	232	71	100	6.0	3.8	2.2
	4012	0.3	161	64	65	6.1	3.8	2.3
	4013	0.4	249	66	65	6.3	3.9	2.4
	4014	0.4	201	55	49	6.0	3.7	2.3
	4015	0.3	161	68	42	6.2	3.9	2.3

Appendix 13

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1M	1011	1.8	10.1	7.7	143	5.5	104	N
	1012	1.7	10.4	7.1	140	5.7	100	N
	1013	2.0	10.1	7.6	142	5.3	105	N
	1014	1.6	10.1	9.1	142	5.0	101	N
	1015	1.7	10.2	8.7	141	5.4	101	N
4M	4011	1.7	9.7	6.7	141	5.5	103	N
	4012	1.7	10.3	8.0	141	5.4	104	N
	4013	1.6	10.4	7.5	140	5.4	101	N
	4014	1.6	10.1	8.8	142	5.3	103	N
	4015	1.7	10.4	8.0	142	4.8	101	N

Appendix 13

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	89	34	71	2VBRR	327	0.07	16
	1512	65	42	67	2VBRR	171	0.05	20
	1513	95	28	65	2VBRR	671	0.05	19
	1514	84	37	77	2VBRR	346	0.11	14
	1515	97	34	49	2VBRR	548	0.05	14
4F	4511	124	55	81	2VBRR	723	0.07	18
	4512	97	41	63	2VBRR	202	0.07	17
	4513	158	61	66	2VBRR	781	0.03	24
	4514	79	38	86	2VBRR	343	0.06	15
	4515	62	26	94	2VBRR	116	0.04	11

Appendix 13

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	0.4	222	74	55	6.0	4.4	1.6
	1512	0.4	232	74	90	6.2	4.3	1.9
	1513	0.4	129	67	47	6.3	4.4	1.9
	1514	0.4	177	60	81	6.4	4.5	1.9
	1515	0.4	191	79	65	6.3	4.4	1.9
4F	4511	0.5	198	86	65	6.6	4.5	2.1
	4512	0.4	232	70	77	7.0	4.7	2.3
	4513	0.4	199	63	81	6.4	4.3	2.1
	4514	0.4	210	88	82	7.1	5.0	2.1
	4515	0.3	217	69	51	6.2	4.1	2.1

Appendix 13

Individual Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L	SAMQ SERUM
1F	1511	2.8	10.6	6.7	141	4.8	103	N
	1512	2.3	10.4	7.1	139	4.7	100	N
	1513	2.3	10.6	6.9	139	4.9	102	N
	1514	2.4	11.0	6.9	140	4.7	101	N
	1515	2.3	10.7	6.5	141	4.5	103	N
4F	4511	2.1	10.8	7.0	139	5.1	100	N
	4512	2.0	10.6	6.2	139	4.6	102	N
	4513	2.0	10.3	7.3	139	5.2	100	N
	4514	2.4	10.8	6.7	138	5.1	98	N
	4515	2.0	10.6	6.5	138	4.5	100	N

Appendix 14

FINAL REPORT

Study Phase: Ophthalmology Evaluation

Test Facility Study No. 5002033

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

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1. INTRODUCTION

This report presents the ophthalmology evaluations for the study entitled *A 1-month (3 doses) Study of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat with a 2-Week Recovery Period* (Study No. 5002033).

For the work detailed in this report, the ophthalmology phase start date was 07 Apr 2017, and the ophthalmology phase completion date was 12 May 2017.

2. MATERIALS AND METHODS

Experimental procedures applicable to ophthalmology evaluations are summarized in Text Table 1.

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µl)	Dose Concentration (µg/mL)	No. of Animals			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1653	10	200	50	10	10	-	-
3	mRNA-1653	50	200	250	10	10	-	-
4	mRNA-1653	150	200	750	10	10	5	5

[a] = 10/sex/groups 1 to 4 were necropsied 1 day following the last dose.
[b] = The remaining 5/sex/groups 1 to 4 were necropsied 2 weeks following the last dose.

2.1. Ophthalmic Examinations

Frequency: Examinations were performed once prestudy and again during Week 4 of dosing.

Procedure: All animals were subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used was 1% tropicamide.

2.2. Computerized Systems

The following critical computerized system was used by the Test Facility in the generation of this report (Text Table 2).

Text Table 2
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	8	Ophthalmic evaluations

Appendix 14

3. RESULTS AND DISCUSSION

(Appendix 1)

3.1. Pretreatment Evaluation

Background findings were recorded and recommendations for rejection from study groups were made when appropriate.

3.2. 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. CONCLUSIONS

Administration of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat for 1-month (3 doses) at doses of 10, 50, and 150 µg/dose did not result in any test item-related ophthalmic changes.

Appendix 14

5. REPORT APPROVAL

(b) (6)

(b) (6) Date: 22 Sep 2017

Appendix 14

Appendix 1
Individual Ophthalmic Findings

Appendix 14

Individual Ophthalmic Findings Explanation Page

Abbreviation	Description	Abbreviation	Description
Abs	Absence	Incomp Dil	Incomplete Dilation
Alt Ref	Altered Reflection	Inc	Increased
Ant	Anterior	Irreg	Irregular Reflectivity
Cap	Capsule	Mac	Macula
Ch	Chamber	Multi	Multifocal
Chor	Choroid	Myd	Mydriatic
C-L	Cell-like	Op	Opacity
C/NJ	Cortical/Nuclear Junction	Pers	Persistent
Conj	Conjunctiva	Pers Pup	Persistent Pupillary
Cont	Control	Pig	Pigmented/Pigmentation
Cort	Cortex	Post	Posterior
Depig	Depigmentation	Refl	Reflectivity
Detach	Detachment	Rej	Rejected
Diff	Diffuse	Ret	Retina
Disch	Discharge	Rupt	Rupture
Dru	Drusen	Subcap	Subcapsular
Endo	Endothelium	Subconj	Subconjunctiva
Foll	Follicular	Sut	Suture
Fov	Fovea	TA	Test Article
Hemo	Hemmorhage	Vac	Vacuole
Hyper	HyperPigmentation	Var Rx	Variation from dosing
Hyperpl	Hyperplasia	Vasc	Vascularization
Hypo	HypoPigmentation	V	Visualize
OD	Right Eye	Visu/Visuali	Visualized
OU	Both Eyes	OS	Left Eye

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Only animals with findings are presented in this appendix.

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-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 14
Appendix 1

Individual Ophthalmic Findings

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-13	-12	23	24
1	m	1001	Lens,Op ,Nucleus	Left	.	1	.	1
		1002	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
			Lens,Op ,Nucleus	Right	.	1	.	1
		1003	Cornea, Op, Multi, Pinpoint	Right	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	.	.	1
		1005	Lens Op, Cortex, Ant, Focal	Left	.	.	.	1
		1007	Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		1010	Iris, Pers Pup Membrane	Left	.	X	.	X
		1011	Lens Op, Cortex, Ant, Focal	Left	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	.	.	1
		1012	Iris, Pers Pup Membrane	Right	.	X	.	X
			Cornea, Op, Multi, Pinpoint	Right	.	1	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	2
		1013	Cornea, Op, Multi, Pinpoint	Right	.	2	.	2
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	2
		1015	Cornea, Op, Multi, Pinpoint	Left	.	.	.	1
			Lens,Op ,Nucleus	Right	.	1	.	1

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 14
Appendix 1

Individual Ophthalmic Findings

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-13	-12	23	24
2	m	2002	Lens Op, Cortex, Ant, Focal	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
		2003	Lens Nucleus Prominent	Right	.	X	.	X
			Lens Nucleus Prominent	Left	.	X	.	X
		2004	Vitreous, Hemorrhage	Right	.	.	.	2
			Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		2005	Lens Op, Cortex, Ant, Focal	Right	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		2006	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
			Lens,Op ,Nucleus	Left	.	1	.	1
		2009	Cornea, Loss of Luster	Right	.	.	.	X
		2010	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 - 150 ug/dose

Appendix 14
Appendix 1

Individual Ophthalmic Findings

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-13	-12	23	24
3	m	3002	Lens Op, Cortex, Ant, Focal	Right	.	.	.	1
		3003	Iris, Pers Pup Membrane	Left	.	X	.	X
			Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
			Lens,Op ,Nucleus	Left	.	2	.	2
		3004	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		3007	Cornea, Op, Multi, Pinpoint	Right	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	.	.	1
		3009	Cornea, Op, Multi, Pinpoint	Right	.	.	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	.	.	1
		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 - 150 ug/dose

Appendix 14
Appendix 1

Individual Ophthalmic Findings

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-13	-12	23	24
4	m	4002	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	2	.	1
			Lens,Op ,Nucleus	Right	.	1	.	1
		4004	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4005	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4006	Cornea, Op, Multi, Pinpoint	Right	.	2	.	1
			Lens,Op ,Nucleus	Right	.	1	.	2
		4007	Lens,Op ,Nucleus	Right	.	1	.	1
		4009	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4010	Vitreous, Hemorrhage	Left	.	2	.	1
		4011	Cornea, Op, Multi, Pinpoint	Right	.	1	.	1
			Cornea, Op, Multi, Pinpoint	Left	.	1	.	1
		4012	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 - 150 ug/dose

Appendix 14
Appendix 1

Individual Ophthalmic Findings

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-13	-12	23	24
1	f	1501	Lens Op, Cortex, Ant, Focal	Right Inferior	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	1	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		1502	Lens Op, Cortex, Ant, Multi	Right	.	.	1	.
		1506	Cornea, Op, Multi, Pinpoint	Right	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	.	.	1	.
		1510	Lens,Op ,Nucleus	Right	1	.	2	.
			Lens,Op ,Nucleus	Left	2	.	1	.
		1511	Cornea, Loss of Luster	Left	X	.	.	.
			Cornea, Op, Multi, Pinpoint	Right	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	1	.
			Lens Nucleus Prominent	Right	X	.	X	.
			Lens Nucleus Prominent	Left	X	.	X	.
		1512	Lens,Op ,Nucleus	Right	1	.	2	.
		1513	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 - 150 ug/dose

Appendix 14
Appendix 1

Individual Ophthalmic Findings

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-13	-12	23	24
2	f	2501	Cornea, Op, Multi, Pinpoint	Right	2	.	2	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	2	.
		2502	Lens Op, Cortex, Ant, Focal	Left	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		2505	Lens Op, Cortex, Ant, Focal	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		2506	Lens Nucleus Prominent	Right	X	.	X	.
			Lens Nucleus Prominent	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 - 150 ug/dose

Appendix 14
Appendix 1

Individual Ophthalmic Findings

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-13	-12	23	24
3	f	3502	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3505	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		3507	Cornea, Op, Multi, Pinpoint	Right	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	.	.	1	.
		3508	Cornea, Op, Multi, Pinpoint	Right	2	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	2	.	1	.
		3509	Lens Op, Cortex, Ant, Focal	Right	.	.	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 - 150 ug/dose

Appendix 14
Appendix 1

Individual Ophthalmic Findings

5002033

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-13	-12	23	24
4	f	4504	Cornea, Loss of Luster	Right	X	.	.	.
			Cornea, Op, Multi, Pinpoint	Right	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	.	.	1	.
		4505	Lens Op, Cortex, Ant, Focal	Left Superior	1	.	1	.
			Vitreous, Hemorrhage	Left	.	.	1	.
			Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4506	Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
		4507	Lens,Op ,Nucleus	Right	2	.	2	.
			Lens,Op ,Nucleus	Left	1	.	1	.
		4508	Lens,Op ,Nucleus	Left	1	.	1	.
		4509	Iris, Pers Pup Membrane	Left	X	.	X	.
		4511	Cornea, Loss of Luster	Right	.	.	X	.
			Cornea, Loss of Luster	Left	.	.	X	.
		4512	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.
			Lens,Op ,Nucleus	Left	1	.	1	.
		4514	Cornea, Op, Multi, Pinpoint	Left	.	.	1	.
			Lens,Op ,Nucleus	Right	1	.	1	.
		4515	Cornea, Op, Multi, Pinpoint	Right	1	.	1	.
			Cornea, Op, Multi, Pinpoint	Left	1	.	1	.

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

Group 1 - 0 ug/dose Group 2 - 10 ug/dose Group 3 - 50 ug/dose Group 4 - 150 ug/dose

Appendix 15

NON-GLP FINAL REPORT

Study Phase: Biomarker (Cytokines) Interpretative Report

Test Facility Study No. 5002033

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

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Appendix 15

1. INTRODUCTION

This report describes the biomarker evaluation of Cytokines/Chemokines (IL-1b, IL-6, TNF-α, IP-10, MIP-1α, and MCP-1) in rat plasma (EDTA) samples from Study No. 5002033 entitled "*A 1-month (3 doses) Study of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat with a 2-Week Recovery Period*".

For the work detailed in this report, the Cytokines/Chemokines phase experimental start and end dates were 20 Jun 2017 and 28 Jun 2017, respectively.

2. EXPERIMENTAL PROCEDURES

2.1. Materials and Methods

The methodology and materials used for the biomarker analyses were detailed in the analytical procedure and listed in the table below:

Biomarkers	Analytical Procedure No.	Validation study number(s)
IL-1b, IL-6, TNF-α, IP-10, MIP-1α, and MCP-1α	AP.5002033.CYT.01	Qualified method only

2.2. Computerized Systems

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

Text Table 1
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Bio Plex Manager (Bio-Rad)	Version 6.1	Data collection
Watson LIMS	7.4.2 SP1	Data analysis
Microsoft Excel	2007	Descriptive statistics
Microsoft Word	2007	Reporting of data in the report
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

3. RESULTS AND DISCUSSIONS

The upper limit of the normal range of concentrations was defined as the overall baseline mean (all time points of all Group 1 animals, males and females calculated separately) plus 2 standard deviations. Incidence indicates the number of individual animals per group with Cytokine/Chemokine concentration > upper limit of the normal range of concentrations.
Fold change indicates the ratio of the measured Cytokine/Chemokine concentrations over the upper limit (or below the upper limit) of the normal range of concentration.

Appendix 15

Individual animal data were compared to the upper limit of the normal range for any observed trends (time or dose related changes). For individual animals, if a Cytokine/Chemokine value was above this value, this increase was considered to indicate a potential mRNA-1653 treatment-related effect.

3.1. Cytokines and Chemokines Study Samples

For Cytokines/Chemokines analysis, plasma samples collected from all recovery animals (groups 1 and 4) on Days 1, 15 and 29, 6 hours after dosing, and at scheduled termination on Day 43 were analyzed.

For all Cytokines/Chemokines, study samples were analyzed diluted 2-fold in assay buffer in duplicate using a non-GLP qualified method. As the method was only qualified, no stabilities were proven. Study samples will be discarded prior to report finalization.

3.2. Standards and Quality Control Samples for Cytokines/Chemokines

Standard, Quality control (QC) preparation and acceptance criteria are described in the analytical procedure (Appendix 2). Standard curve and quality control specifications are presented in Text Table 2.

Text Table 2
Cytokines/Chemokines Standard Curve and Quality Controls Specifications

Cytokines	Range of the Curve (pg/mL)	LLOQ (pg/mL)	ULOQ (pg/mL)	QC1 (pg/mL)	QC2 (pg/mL)	QC3 (pg/mL)
IL-1ß, IP-10 and MIP-1α	2.93 to 3000.00*	11.72	1500.00	26.02	150.00	1200.00
TNF-α	2.93 to 3000.00**	2.93	375.00	7.81	37.50	300.00
IL-6	87.89 to 90000.00***	351.56	45000.00	780.47	4500.00	36000.00
MCP-1	35.16 to 36000.00****	140.63	18000.00	312.19	1800.00	14400.00

* Standards 2.93, 5.86 and 3000.00 pg/mL are accessory standards used to define the lower and higher portions of the curve.
** Standards 750.00, 1500.00 and 3000.00 pg/mL are accessory standards used to define the higher portion of the curve.
*** Standards 87.89, 175.78, and 90000.00 pg/mL are accessory standards used to define the lower and higher portions of the curve.
**** Standards 35.16, 70.31, and 36000.00 pg/mL are accessory standards used to define the lower and higher portions of the curve.

A total of 4 assays were performed for Cytokines/Chemokines and all met the method acceptance criteria. All results are reported from the assays that met the acceptance criteria.

3.2.1. Cytokines/Chemokines Results

Acceptance criteria are described in the latest version of the Analytical Procedure (Appendix 2). Results are presented in Appendix 3 and Table 1.

The upper limit of normal range specifications are presented in Text Table 3.

Appendix 15

Text Table 3
Cytokines/Chemokines Upper Limit of Normal Range Specifications (pg/mL)

	IL-1b	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Males	137.26	351.56	156.64	559.53	11.72	2.93
Females	85.94	351.56	104.19	334.69	11.72	2.93

For MCP-1 and IP-10, increases were observed for all animals dosed at 150 µg/dose on Days 1, 15 and 29 (6 hrs post dose). The magnitude of increases observed were higher for IP-10, ranging from 5.2 to 10.4-fold for males, and from 7.0 to 17.5-fold for females, and were apparent for all animals at all dosing timepoints. The increases seen for MCP-1 were observed for all animals at almost all dosing timepoints, but the magnitude of increases was lower, ranging from 1.2 to 3.1-fold for males and from 1.2 to 6.4-fold for females. At recovery Day 43, the level of both MCP-1 and IP-10 were back to the normal range values for all animals. These increases were considered mRNA-1653 related due to the high magnitude and incidence observed for the mRNA-1653 dosed group, as well as the reversibility of mRNA-1653 treatment (Day 43).

For MIP-1α, small increases above the upper limit of normal range were observed on Days 1 and 15 (6 hrs post dose), for some animals, at a similar incidence and magnitude for males and females dosed at 150 µg/dose. Such increases were not observed on Day 29 (6 hrs post dose), and at recovery on Day 43. These increases were considered to be mRNA-1653 related due to similar incidence, magnitude and pattern observed in the mRNA-1653 dosed group.

For IL-1b, slight increases above the upper limit of normal range were noted for 2 females dosed at 150 µg/dose, on Day 15 (1.8-fold) and on Day 29 (1.1-fold) at 6 hrs post dose. Those changes were not considered to be mRNA-1653 related as similar slight increases were also observed in control group animals.

For TNF-α, all concentrations were below the limit of quantitation, except one female dosed at 150 µg/dose on Day 15 (6 hrs post dose), for which an increase of 2.1-fold was observed. Due to the low incidence and magnitude observed, the increase was not considered to be mRNA-1653 treatment-related.

For IL-6, all concentrations were below the limit of quantitation at all timepoints.

Appendix 15

4. CONCLUSION

All samples collected for the Cytokines/Chemokines were analyzed using a qualified immunoassay method. As the method was only qualified, no stabilities were proven. Based on the acceptable performance of the standards and QCs during sample analysis, it is concluded that the values reported for the study samples are valid. The sample results are presented in Appendix 3, and Table 1.

For MCP-1 and IP-10, high incidence and magnitude of change observed for males and females of higher dose group (150 µg/dose) were considered to be mRNA-1653 treatment-related.

Increases observed for MIP-1α were also considered mRNA-1653 related due to the magnitude and incidence observed in the mRNA-1653 dosed groups.

No mRNA-1653 treatment-related results were observed for IL-1β, TNF-α and IL-6.

All the treatment-related increases observed were reversible.

Appendix 15

5. REPORT APPROVAL

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

Date: 11-Oct-2017

Appendix 15

Table 1
Summary of Cytokine Values

Appendix 15
Table 1
Summary of Cytokine Values

IL-1β (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	33.520	11.720	41.868	56.955
	SD	48.746	0.000	67.413	69.694
	N	5	5	5	4
4	Mean	15.348	11.720	18.234	31.920
	SD	8.112	0.000	14.566	45.169
	N	5	5	5	5
	% Diff (G1)	-54	0	-56	-54

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 15
Table 1
Summary of Cytokine Values

IL-6 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	351.560	351.560	351.560	351.560
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	351.560	351.560	351.560	351.560
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
	% Diff (G1)	0	0	0	0

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

Appendix 15
Table 1
Summary of Cytokine Values

IP-10 (pg/mL)
Males

Group 1 - Reference Item Group 4 - mRNA-1653 150 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	100.940	87.850	86.848	96.048
	SD	23.357	29.382	41.068	39.437
	N	5	5	5	5
4	Mean	1336.402 C	1042.548 D	1053.640 C	85.518
	SD	176.918	125.821	142.923	31.168
	N	5	5	5	5
	% Diff (G1)	1224	1087	1113	-11

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

Appendix 15
Table 1
Summary of Cytokine Values

MCP-1 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	319.814	299.612	310.128	215.468
	SD	169.108	167.323	112.655	103.879
	N	5	5	5	5
4	Mean	1060.686 B	897.894 B	940.052 A	172.470
	SD	302.463	279.115	477.052	71.196
	N	5	5	5	5
	% Diff (G1)	232	200	203	-20

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 15
Table 1
Summary of Cytokine Values

MIP-1-α (pg/mL)
Males

Group 1 - Reference Item Group 4 - mRNA-1653 150 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	11.720	11.720	11.720	11.720
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	29.100	22.136	11.720	11.720
	SD	16.513	14.645	0.000	0.000
	N	5	5	5	5
	% Diff (G1)	148	89	0	0

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

Appendix 15
Table 1
Summary of Cytokine Values

TNF-α (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	2.930	2.930	2.930	2.930
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
	% Diff (G1)	0	0	0	0

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

Appendix 15
Table 1
Summary of Cytokine Values

IL-1β (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	23.406	47.226	11.720	19.404
	SD	18.107	53.327	0.000	17.182
	N	5	5	5	5
4	Mean	24.752	39.608	37.564	14.092
	SD	20.616	62.359	37.236	5.304
	N	5	5	5	5
	% Diff (G1)	6	-16	221	-27

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 15
Table 1
Summary of Cytokine Values

IL-6 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	351.560	351.560	351.560	351.560
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	351.560	351.560	351.560	351.560
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
	% Diff (G1)	0	0	0	0

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

Appendix 15
Table 1
Summary of Cytokine Values

IP-10 (pg/mL)
Females

Group 1 - Reference Item Group 4 - mRNA-1653 150 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	63.580	71.542	50.424	53.718
	SD	26.341	32.145	13.307	9.339
	N	5	5	5	5
4	Mean	1447.742 D	1353.880 D	962.920 C	46.626
	SD	370.254	174.064	267.774	12.918
	N	5	5	5	5
	% Diff (G1)	2177	1792	1810	-13

Significantly different from control group (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)

Appendix 15
Table 1
Summary of Cytokine Values

MCP-1 (pg/mL)
Females

Group 1 - Reference Item Group 4 - mRNA-1653 150 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43
1	Mean	179.780	176.052	182.138	176.300
	SD	87.542	79.206	92.815	79.761
	N	5	5	5	5
4	Mean	586.194 C	969.196 E	417.398 B	140.630
	SD	97.076	696.658	97.858	0.000
	N	5	5	5	5
	% Diff (G1)	226	451	129	-20

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 15
Table 1
Summary of Cytokine Values

MIP-1-α (pg/mL)
Females

Group 1 - Reference Item Group 4 - mRNA-1653 150 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	11.720	11.720	11.720	11.720
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	32.154	26.284	11.720	11.720
	SD	25.783	17.405	0.000	0.000
	N	5	5	5	5
	% Diff (G1)	174	124	0	0

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

Appendix 15
Table 1
Summary of Cytokine Values

TNF-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	2.930	2.930	2.930	2.930
	SD	0.000	0.000	0.000	0.000
	N	5	5	5	5
4	Mean	2.930	3.556	2.930	2.930
	SD	0.000	1.400	0.000	0.000
	N	5	5	5	5
	% Diff (G1)	0	21	0	0

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

Appendix 15

Appendix 1
Deviations

Appendix 15

DEVIATIONS

The deviation that occurred during this study phase has been acknowledged by the Study Director, assessed for impact, and documented in the study records. This deviation was not considered to have impacted the overall integrity of this study phase or the interpretation of the study phase results and conclusions.

Appendix 15

Appendix 2
AP.5002033.CYT.01

Appendix 15

charles river | every step of the way.

Title: **LUMINEX METHOD FOR THE QUANTITATIVE DETECTION OF IL-1β, IL-6, IP-10, TNF-α, MCP-1, MIP-1α, IN RAT PLASMA USING THE MAGNETIC BEADS**	AP Number: AP.5002033.CYT.01	Effective Date: Signature of AP
	CR MTL	Supersedes: N/Ap
Prepared by: (b) (6) (b) (6)		Date: 19-Jun-2017
Verified by: (b) (6) (b) (6)		Date: 19 Jun 2017
Management Approval: (b) (6) (b) (6)		Date: 19 Jun 2017

1.0 Purpose

To describe a method to determine the concentration of IL-1β, IL-6, IP-10, TNF-α, MCP-1, MIP-1a in rat plasma by Luminex.

2.0 Scope

This procedure applies to Luminex assays undertaken in the Biomarkers department.

3.0 Responsibilities

All staff performing this assay are responsible for compliance with this analytical procedure.

4.0 Required forms

Appendix 1	Cytokine Multiplex Spiking Sheet (Example of spreadsheet)
Appendix 2	Cytokine Multiplex Assay Sheet (Example of document)
Appendix 3	Daily Solution preparation Sheet (Example of spreadsheet) **Note: Appendix # 2 of CACI-001 can be used as well.**
Appendix 4	Solution preparation Sheet (Example of spreadsheet) **Note: Appendix # 1 of CACI-001 can be used as well.**
Appendix 5	Assay Instructions Sheet (Example of spreadsheet)

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Appendix 15

AP Number: AP. 5002033.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

5.0 **Materials/Equipment/Reagents**

Materials can be substituted provided the same specifications are met.

The procedure may require other general laboratory supplies commonly used in Laboratory Sciences.

5.1 Materials/Equipment

(b) (4)

5.2 Kit Components

(b) (4)

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Appendix 15

AP Number: AP. 5002033.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

Rat cytokine/chemokine magnetic bead panel Kit
(Millipore cat# RECYTMAG-65k-XX, where XX denotes the number of cytokines included in the panel.

(b) (4)

5.3 Other reagents

(b) (4)

6.0 Preparation of Assay Reagents

(b) (4)

6.1

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Appendix 15

AP Number: AP. 5002033.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

6.2 Preparation of the Rat Cytokine Standards and Quality Control (QC) Samples in Assay Buffer

(b) (4)

7.0 Assay procedure

(b) (4)

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Appendix 15

AP Number: AP. 5002033.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

8.0 Plate Washing using Handheld magnetic washer

(b) (4)

9.0 Preparation of the Bio-Plex Suspension Array (Luminex) Protocol

(b) (4)

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Appendix 15

AP Number: AP. 5002033.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

Refer to Appendix 5 and appropriate Study plan for the list of cytokines to be analyzed.

(b) (4)

10.0 Exporting data to Watson LIMS

(b) (4)

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Appendix 15

AP Number: AP. 5002033.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

10.1 Export data to Watson LIMS as follows:

(b) (4)

11.0 Preparation of the Bio-Plex Manager printout

(b) (4)

11.0.3 Calculation

(b) (4)

12.0 Assay Acceptance Criteria

12.1 Standard Curve Acceptance Criteria

(b) (4)

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Appendix 15

AP Number: AP. 5002033.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

12.2 Acceptance Criteria for QC samples prepared in Assay Buffer

(b) (4)

12.3 Run Acceptance Criteria

(b) (4)

(b) (4)

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Appendix 15

AP Number: AP. 5002033.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

12.4 Acceptance criteria for Study samples

(b) (4)

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Appendix 15

AP Number: AP. 5002033.CYT.01	Effective Date: Signature of AP	Supersedes: N/Ap

(b) (4)

12.5 Reporting:

(b) (4)

13.0 Revision History

Version	Date	Reason For Revision
1	Signature of AP	New AP

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Appendix 15

Cytokine Multiplex Spiking Sheet

Study/reference number: 5002033 Assay ID _____
Reference material: Rat Cytokine/Chemokine Standard

Reagent ID:	Lot #	Inventory ID:
Rat cytokine/chemokine standard:		
Assay buffer	refer to appendix # 2	

Standard ID	Stock ID	# of vial(s) used	Volume of UPW added to each vial (µL) Vial inverted several times to mix, and vortex for 10 seconds	Left at ambient RT for at least 5 minutes		Transfer to PP* tube	Pool vials together (if applicable) Performed (√)
				Start:	End:		
STD stock	Rat cytokine /chemokine standard	(b) (4)	( )			( )	( )

Standard/ QC ID	Stock ID	Stock concentration (pg/mL)			Stock		Assay buffer		Total volume (µL)	Final calculated concentration (pg/mL)		
		IL-1β, IP-10, MIP-1α, TNF-α	IL-6	MCP-1	volume	performed (√)	volume	performed (√)		IL-1β, IP-10, MIP-1α, TNF-α	IL-6	MCP-1
STD 11	STD stock	(b) (4)			(b) (4)	( )	(b) (4)	( )	(b) (4)			
STD 10	STD 11					( )		( )				
STD 9	STD 10					( )		( )				
STD 8	STD 9					( )		( )				
STD 7	STD 8					( )		( )				
STD 6	STD 7					( )		( )				
STD 5	STD 6					( )		( )				
STD 4	STD 5					( )		( )				
STD 3	STD 4					( )		( )				
STD 2	STD 3					( )		( )				
STD 1	STD 2					( )		( )				
STD 0	N/A				N/A	( )		( )				
QC3B	**STD 10**				(b) (4)	( )		( )				
QC3A	STD 8					( )		( )				
QC2B	**STD 10**					( )		( )				
QC2A	STD 8					( )		( )				
QC1B	**STD 5**					( )		( )				
QC1A	**STD 5**					( )		( )				

Comments: * PP = Polypropylene

Spiking sheet verified by/ date: _____ Calculations verified by/ date: _____

Spiking performed by/ date: _____ Reviewed by/ date: _____

Appendix 1 (AP.5002033.CYT.01) 1 of 1

Appendix 15

Cytokine Multiplex Assay sheet

Study/Reference No: 5002033 Assay I.D.: _____

Page: 1 of 6

Reagents/ Working Solutions					
Name	*Batch or Lot # (as appropriate)*	*Inventory number* Assay ID:	Assay ID: or ☐ N/Ap	*Expiry Date*	*Entered by /Date*
Rat Cytokine/Chemokine magnetic kit					
Assay Buffer					
Assay Plate					
Bead diluent					
Antibody-Immobilized Beads Working solution	ABWS-	N/Ap	N/Ap		
Streptavidin-Phycoerythrin					
Detection Antibodies		N/Ap	N/Ap		
Wash Buffer Cytokines	rtpCytWB-				
Sheath fluid					
UPW	N/Ap	N/Ap	N/Ap		

PLATE SEQUENCE (Printed from Watson)

In-Process Sample Storage Assay ID: or N/Ap ☐	Performed (√)		Start time	Performed by / Date
Samples transported from Sample Management	Dry Ice	( )	N/Ap	
Samples thawed and diluted	Ambient RT	( )		
Samples placed in temporary storage after use and until returned to Sample Management	Dry Ice	( )		
In-Process Sample Storage **Assay ID:** or N/Ap ☐	**Performed (√)**		**Start time**	**Performed by / Date**
Samples transported from Sample Management	Dry Ice	( )	N/Ap	
Samples thawed and diluted	Ambient RT	( )		
Samples placed in temporary storage after use and until returned to Sample Management	Dry Ice	( )		

Appendix 2 (AP.5002033.CYT.01)

Appendix 15

Cytokine Multiplex Assay sheet

Study/Reference No: 5002033 Assay I.D.: _____

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INSTRUMENTS		
Name	*ID*	*Entered by/ Date*
Day 1		
(b) (4)		
Day 2		
(b) (4)		
	or ( ) N/Ap	

Comments: _____

_____

_____

_____

Appendix 2 (AP.5002033.CYT.01)

Appendix 15

Cytokine Multiplex Assay sheet

Study/Reference No: 5002033 Assay I.D.: _____

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Steps	Incubation times /Performed (√) Assay ID:	Assay ID: or N/Ap ☐	Performed by/ Date
DAY 1			
(b) (4)	( ) ( ) or N/Ap ( )	( ) ( ) or N/Ap ( )	
	( )	( )	
	( )	( )	
	( )	( )	
	( )	( )	
	Start:	Start:	
DAY 2			
(b) (4)	Finish:	Finish:	
	( ) ( ) ( )	( ) ( ) ( )	
	Start:	Start:	
	Finish:	Finish:	
	Start:	Start:	
	Finish:	Finish:	
	( ) ( ) ( )	( ) ( ) ( )	
	Start:	Start:	
	Finish:	Finish:	

Appendix 2 (AP.5002033.CYT.01)

Appendix 15

Cytokine Multiplex Assay sheet

Study/Reference No: 5002033 Assay I.D.: _____

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ASSAY CONT'D					
Steps	Incubation times /Performed (√)				Performed by/ Date
	Assay ID:		Assay ID: or N/Ap ☐		
(b) (4)	Start:		Start:		
	Finish:		Finish:		
	N/Ap ( )		N/Ap ( )		
	Start:		Start:		
	Finish:		Finish:		
	N/Ap ( )		N/Ap ( )		
	Prime ( ) Unclog ( ) or N/Ap( )		Prime ( ) Unclog ( ) or N/Ap ( )		
	Yes ( )	N/Ap ( )	Yes ( )	N/Ap ( )	
	( )		( )		
	( )	N/Ap ( )	( )	N/Ap ( )	
	( )	N/Ap ( )	( )	N/Ap ( )	

Appendix 2 (AP.5002033.CYT.01)

Appendix 15

Cytokine Multiplex Assay sheet

Study/Reference No: 5002033 Assay I.D.:

Page: 5 of 6

SCIENTIFIC DATA REVIEW						
Assay ID:						
	IL-1β or ☐ N/Ap	**IL-6** or ☐ N/Ap	**IP-10** or ☐ N/Ap	**MCP-1** or ☐ N/Ap	**MIP-1a** or ☐ N/Ap	**TNF-a** or ☐ N/Ap
Mean of (FI) Blank < Mean of (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of working standards within ±25% of the theoretical values (±30% for LLOQ and ULOQ):	/	/	/	/	/	/
QC samples						
Number of QC1A within acceptance criteria*:	/	/	/	/	/	/
Number of QC1B within acceptance criteria*:	/	/	/	/	/	/
Number of QC2A within acceptance criteria*:	/	/	/	/	/	/
Number of QC2B within acceptance criteria*:	/	/	/	/	/	/
Number of QC3A within acceptance criteria*:	/	/	/	/	/	/
Number of QC3B within acceptance criteria*:	/	/	/	/	/	/
Number of beads acquired ≥ 30 in all wells:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Samples to repeat:	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap
Performed by / Date:						

*Concentration within 75-125% of theoretical, %CV ≤ 25% between duplicates.

Appendix 2 (AP.5002033.CYT.01)

Appendix 15

Cytokine Multiplex Assay sheet

Study/Reference No: 5002033 Assay I.D.: _____

Page: 6 of 6

SCIENTIFIC DATA REVIEW						
Assay ID: *or N/Ap* ☐						
	IL-1β or ☐ N/Ap	**IL-6** or ☐ N/Ap	**IP-10** or ☐ N/Ap	**MCP-1** or ☐ N/Ap	**MIP-1a** or ☐ N/Ap	**TNF-a** or ☐ N/Ap
Mean of (FI) Blank < Mean of (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of working standards within ±25% of the theoretical values (±30% for LLOQ and ULOQ):	/	/	/	/	/	/
QC samples						
Number of QC1A within acceptance criteria*:	/	/	/	/	/	/
Number of QC1B within acceptance criteria*:	/	/	/	/	/	/
Number of QC2A within acceptance criteria*:	/	/	/	/	/	/
Number of QC2B within acceptance criteria*:	/	/	/	/	/	/
Number of QC3A within acceptance criteria*:	/	/	/	/	/	/
Number of QC3B within acceptance criteria*:	/	/	/	/	/	/
Number of beads acquired ≥ 30 in all wells:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Assay is acceptable:	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Samples to repeat:	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap	Yes or No or N/Ap
Performed by / Date:						

*Concentration within 75-125% of theoretical, %CV ≤ 25% between duplicates.

Appendix #2 Reviewed by/date: _____

Appendix 2 (AP.5002033.CYT.01)

Appendix 15

Daily Solution Preparation Sheet

Study/Reference no: 5002033 Assay ID: _____

Preparation of: **Antibody-Immobilized Beads Working Solution (code: ABWS)**

Note: If not all cytokines are needed to be analyzed, Bead Diluent should be used to replace the missing antibody-bead volume. The total volume of the solution needs to be 3.000 mL. (Dilution 1/50)

Batch #	Reagents	Supplier	Lot/Batch no	Inventory Number	*Calculated Volume units (µL)	Actual Volume units (µL)	Performed by & Date	*Calculations verified by/date:
	Bead Diluent	Millipore						
	Anti-IL-1β beads	Millipore						
	Anti-IL-6 beads	Millipore						
	Anti-IP-10 beads	Millipore						
	Anti-MCP-1 beads	Millipore						
	Anti-MIP-1α beads	Millipore						
	Anti-TNF-α beads	Millipore						
					Total volume:			

* Applicable only when the volumes are scaled up or down.

Reviewed by/date: _____

Appendix 3 (AP.5002033.CYT.01)

Appendix 15

Solution Preparation Sheet

Study/Reference no: 5002033

Preparation **Wash Buffer Cytokines (Code: rtpCyt(WB)**

Storage: Location / Expiration: _____ or discarded after use ☐

Batch no	Reagents	Supplier	Lot no	Expiry date	Inventory Number	*Calculated Volume units	Actual Volume units	Prepared by & Date	*Calculations verified by/date:
rtpCyt WB/	(b) (4)								
			N/Ap		N/Ap				
					Total volume:				

*Applicable only when the volumes are scaled up or down

Comments _____

Reviewed by/Date: _____

Appendix 4 (AP.5002033.CYT.01)

Appendix 15

Assay instruction sheet

Study/reference number: 5002033

Assay ID: _____

ID	lot# to be used *
Rat cytokine/chemokine magnetic bead panel kit	
Rat cytokine standard	

* Lots qualified in assay(s): _____

Cytokines to be analyzed:

IL-1β	√
IL-6	√
IP-10	√
MCP-1	√
MIP-1α	√
TNF-α	√

• Study samples to be diluted as per dilution sheet.

Standard and QC concentrations:

Standards ID	Concentration (pg/mL)					
	IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Standard stock	(b) (4)					
STD 11						
STD 10						
STD 9						
STD 8						
STD 7						
STD 6						
STD 5						
STD 4						
STD 3						
STD 2						
STD 1						
STD 0						
QC ID	**Concentration (pg/mL)**					
	IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
QC3B	(b) (4)					N/A
QC3A	N/Ap	N/Ap	N/Ap	N/Ap	N/Ap	(b)
QC2B	(b) (4)					N/Ap
QC2A	N/Ap	N/Ap	N/Ap	N/Ap	N/Ap	(b) (4)
QC1B	(b) (4)					N/Ap
QC1A	N/Ap	N/Ap	N/Ap	N/Ap	N/Ap	(b) (4)

Bold concentrations reflect the appropriate levels for each cytokine (LLOQ, ULOQ and QCs)

Threshold value

The threshold value for a replicate to reach a limit of % CV acceptance criteria from LLOQ (pg/mL)*	Concentration (pg/mL)					
	IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Threshold value:	(b) (4)					

*Fold dilution not taken into account.

_____

_____

Verified by/date: _____ Reviewed by/date: _____

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Appendix 15

Appendix 3
Individual Cytokines Values

Appendix 15

Individual Cytokine Values Explanation Page

Abbreviation	Description	Abbreviation	Description
--	No findings / Dead	QNS	Quantity not sufficient
CLOT	Sample clotted	SNR	Sample not received
NA	Not applicable	TNR	Test not reported
NC	Not calculable	X	Excluded from mean
NR	Not reported	SNC	Sample not collected
PD	Post Dose		
a	% CV between singlicate values > acceptance criteria. Mean of original and repeat values reported for information purposes only		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note:

For IL-1β, MIP-1-α

Lower Limit of Quantitation (LLOQ) = 11.72 pg/mL (23.44 pg/mL when taking the dilution factor into account), <23.44 was assigned as 23.44/2 (11.72 pg/mL) for statistical analysis purposes

For IL-6

Lower Limit of Quantitation (LLOQ) = 351.56 pg/mL (703.12 pg/mL when taking the dilution factor into account), <703.12 was assigned as 703.12/2 (351.56 pg/mL) for statistical analysis purposes

For MCP-1

Lower Limit of Quantitation (LLOQ) = 140.63 pg/mL (281.26 pg/mL when taking the dilution factor into account), <281.26 was assigned as 281.26/2 (140.63 pg/mL) for statistical analysis purposes

For TNF-α

Lower Limit of Quantitation (LLOQ) = 2.93 pg/mL (5.86 pg/mL when taking the dilution factor into account), <5.86 was assigned as 5.86/2 (2.93 pg/mL) for statistical analysis purposes

Appendix 15

The upper limit of the normal range of concentration was defined as:
The overall baseline mean (predose/pretreatment values for all animals* in all groups) ** + 2 standard deviations

Incidence of Cytokine elevations was reported as:
The number of individual animals* per group with Cytokine concentrations > upper limit of the normal range of concentrations

Fold Change was reported as:
The ratio of the measured Cytokine concentration / upper limit of the normal range of concentrations

The fold change was calculated for each sample

*Calculations were done separately for females and males

** If predose values were not available, values from all animals of the non-treated group(s) were used to generate the overall baseline mean

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 15
Appendix 3
Individual Cytokine Values

Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1011	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	102.35	0	0.7
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	95.75	0	0.6
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	86.10	0	0.5
		43	45.68	0	0.3	< 703.12	0	1.0	90.25	0	0.6
	1012	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	88.79	0	0.6
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	84.13	0	0.5
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	54.64	0	0.3
		43	< 23.44	0	0.1	< 703.12	0	1.0	40.22	0	0.3
	1013	1 - 6 h PD	120.72	0	0.9	< 703.12	0	1.0	140.94	0	0.9
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	131.87	0	0.8
		29 - 6 h PD	162.46	1	1.2	< 703.12	0	1.0	157.01	1	1.0
		43	158.70	1	1.2	< 703.12	0	1.0	140.08	0	0.9
	1014	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	84.80	0	0.5
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	75.53	0	0.5
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	75.08	0	0.5
		43	< 23.44	0	0.1	< 703.12	0	1.0	82.74	0	0.5

Appendix 15
Appendix 3
Individual Cytokine Values

Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	MCP-1 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1011	1 - 6 h PD	369.29	0	0.7	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	320.12	0	0.6	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0
	1012	1 - 6 h PD	471.02	0	0.8	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	539.33	0	1.0	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	448.80	0	0.8	< 23.44	0	1.0	< 5.86	0	1.0
		43	351.79	0	0.6	< 23.44	0	1.0	< 5.86	0	1.0
	1013	1 - 6 h PD	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	360.08	0	0.6	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0
	1014	1 - 6 h PD	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	285.27	0	0.5	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0

Appendix 15
Appendix 3
Individual Cytokine Values

Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1015	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	87.82	0	0.6
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	51.97	0	0.3
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	61.41	0	0.4
		43	115.48 a	1	NC	< 703.12	0	1.0	126.95	0	0.8

Appendix 15
Appendix 3
Individual Cytokine Values

Males

Group 1 - Reference Item						Group 4 - mRNA-1653 150 µg/dose					
Group	Animal Number	Day	MCP-1 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1015	1 - 6 h PD	477.50	0	0.9	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	317.39	0	0.6	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	355.82	0	0.6	< 23.44	0	1.0	< 5.86	0	1.0
		43	303.66	0	0.5	< 23.44	0	1.0	< 5.86	0	1.0

Appendix 15
Appendix 3
Individual Cytokine Values

Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4011	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1316.44	1	8.4
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	954.11	1	6.1
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1190.15	1	7.6
		43	< 23.44	0	0.1	< 703.12	0	1.0	42.86	0	0.3
	4012	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1263.06	1	8.1
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	915.02	1	5.8
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	821.33	1	5.2
		43	< 23.44	0	0.1	< 703.12	0	1.0	77.73	0	0.5
	4013	1 - 6 h PD	29.86	0	0.2	< 703.12	0	1.0	1621.42	1	10.4
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1219.60	1	7.8
		29 - 6 h PD	44.29	0	0.3	< 703.12	0	1.0	1115.32	1	7.1
		43	112.72	0	0.8	< 703.12	0	1.0	111.73	0	0.7
	4014	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1340.07	1	8.6
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1002.28	1	6.4
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1119.27	1	7.1
		43	< 23.44	0	0.1	< 703.12	0	1.0	75.00	0	0.5

Appendix 15
Appendix 3
Individual Cytokine Values

Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	MCP-1 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4011	1 - 6 h PD	755.69	1	1.4	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	536.21	0	1.0	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	1005.95	1	1.8	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0
	4012	1 - 6 h PD	744.57	1	1.3	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	710.65	1	1.3	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	541.31	0	1.0	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0
	4013	1 - 6 h PD	1214.61	1	2.2	40.27	1	3.4	< 5.86	0	1.0
		15 - 6 h PD	953.97	1	1.7	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	1738.84	1	3.1	< 23.44	0	1.0	< 5.86	0	1.0
		43	299.83	0	0.5	< 23.44	0	1.0	< 5.86	0	1.0
	4014	1 - 6 h PD	1435.98	1	2.6	47.36	1	4.0	< 5.86	0	1.0
		15 - 6 h PD	1041.49	1	1.9	42.46	1	3.6	< 5.86	0	1.0
		29 - 6 h PD	720.55	1	1.3	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0

Appendix 15
Appendix 3
Individual Cytokine Values

Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4015	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1141.02	1	7.3
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1121.73	1	7.2
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1022.13	1	6.5
		43	< 23.44	0	0.1	< 703.12	0	1.0	120.27	0	0.8

Appendix 15
Appendix 3
Individual Cytokine Values

Males

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	MCP-1 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4015	1 - 6 h PD	1152.58	1	2.1	34.43	1	2.9	< 5.86	0	1.0
		15 - 6 h PD	1247.15	1	2.2	33.06	1	2.8	< 5.86	0	1.0
		29 - 6 h PD	693.61	1	1.2	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.3	< 23.44	0	1.0	< 5.86	0	1.0

Appendix 15
Appendix 3
Individual Cytokine Values

Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1511	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	74.28	0	0.7
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	62.15	0	0.6
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	51.35	0	0.5
		43	< 23.44	0	0.1	< 703.12	0	1.0	60.13	0	0.6
	1512	1 - 6 h PD	28.95	0	0.3	< 703.12	0	1.0	84.80	0	0.8
		15 - 6 h PD	69.50	0	0.8	< 703.12	0	1.0	108.41	1	1.0
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	52.07	0	0.5
		43	< 23.44	0	0.1	< 703.12	0	1.0	50.57	0	0.5
	1513	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	30.60	0	0.3
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	45.49	0	0.4
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	34.58	0	0.3
		43	< 23.44	0	0.1	< 703.12	0	1.0	51.30	0	0.5
	1514	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	40.42	0	0.4
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	39.16	0	0.4
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	43.54	0	0.4
		43	< 23.44	0	0.1	< 703.12	0	1.0	41.22	0	0.4

Appendix 15
Appendix 3
Individual Cytokine Values

Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	MCP-1 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1511	1 - 6 h PD	336.38	1	1.0	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	317.74	0	0.9	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	348.17	1	1.0	< 23.44	0	1.0	< 5.86	0	1.0
		43	318.98	0	1.0	< 23.44	0	1.0	< 5.86	0	1.0
	1512	1 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
	1513	1 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
	1514	1 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0

Appendix 15
Appendix 3
Individual Cytokine Values

Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1515	1 - 6 h PD	52.92	0	0.6	< 703.12	0	1.0	87.80	0	0.8
		15 - 6 h PD	131.47	1	1.5	< 703.12	0	1.0	102.50	0	1.0
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	70.58	0	0.7
		43	50.14	0	0.6	< 703.12	0	1.0	65.37	0	0.6

Appendix 15
Appendix 3
Individual Cytokine Values

Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	MCP-1 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1515	1 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0

Appendix 15
Appendix 3
Individual Cytokine Values

Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4511	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1825.58	1	17.5
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1503.21	1	14.4
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	880.16	1	8.4
		43	< 23.44	0	0.1	< 703.12	0	1.0	25.35	0	0.2
	4512	1 - 6 h PD	29.70	0	0.3	< 703.12	0	1.0	1349.83	1	13.0
		15 - 6 h PD	151.16	1	1.8	< 703.12	0	1.0	1369.22	1	13.1
		29 - 6 h PD	59.95	0	0.7	< 703.12	0	1.0	832.30	1	8.0
		43	23.58	0	0.3	< 703.12	0	1.0	47.54	0	0.5
	4513	1 - 6 h PD	58.90	0	0.7	< 703.12	0	1.0	1383.83	1	13.3
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1190.98	1	11.4
		29 - 6 h PD	92.71	1	1.1	< 703.12	0	1.0	1418.39	1	13.6
		43	< 23.44	0	0.1	< 703.12	0	1.0	58.45	0	0.6
	4514	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	910.44	1	8.7
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1542.89	1	14.8
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	956.21	1	9.2
		43	< 23.44	0	0.1	< 703.12	0	1.0	46.55	0	0.4

Appendix 15
Appendix 3
Individual Cytokine Values

Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	MCP-1 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4511	1 - 6 h PD	481.69	1	1.4	29.77	1	2.5	< 5.86	0	1.0
		15 - 6 h PD	456.95	1	1.4	29.24	1	2.5	< 5.86	0	1.0
		29 - 6 h PD	336.38	1	1.0	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
	4512	1 - 6 h PD	547.71	1	1.6	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	492.42	1	1.5	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	310.26	0	0.9	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
	4513	1 - 6 h PD	596.27	1	1.8	< 23.44	0	1.0	< 5.86	0	1.0
		15 - 6 h PD	1086.71	1	3.2	< 23.44	0	1.0	< 5.86	0	1.0
		29 - 6 h PD	512.58	1	1.5	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0
	4514	1 - 6 h PD	562.21	1	1.7	32.77	1	2.8	< 5.86	0	1.0
		15 - 6 h PD	677.61	1	2.0	24.60	1	2.1	< 5.86	0	1.0
		29 - 6 h PD	522.54	1	1.6	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0

Appendix 15
Appendix 3
Individual Cytokine Values

Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4515	1 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1769.03	1	17.0
		15 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	1163.10	1	11.2
		29 - 6 h PD	< 23.44	0	0.1	< 703.12	0	1.0	727.54	1	7.0
		43	< 23.44	0	0.1	< 703.12	0	1.0	55.24	0	0.5

Appendix 15
Appendix 3
Individual Cytokine Values

Females

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group	Animal Number	Day	MCP-1 pg/mL	Incidence	Fold Change	MIP-1-α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4515	1 - 6 h PD	743.09	1	2.2	74.79	1	6.4	< 5.86	0	1.0
		15 - 6 h PD	2132.29	1	6.4	54.14	1	4.6	6.06	1	2.1
		29 - 6 h PD	405.23	1	1.2	< 23.44	0	1.0	< 5.86	0	1.0
		43	< 281.26	0	0.4	< 23.44	0	1.0	< 5.86	0	1.0

Appendix 16

FINAL REPORT

Study Phase: Molecular Biology – Purity Analysis

Test Facility Study No. 5002033

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

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Appendix 16

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Appendix 16

1. SUMMARY

The bulk test item was analyzed using the (b) (4) System for the determination of mRNA-1653 purity.

The bulk test item was collected at the end of the dosing period of Study No. 5002033 entitled "*A 1-Month (3 Doses) Study of mRNA-1653 by Intramuscular Injection in Sprague-Dawley Rats With a 2-Week Recovery Period.*"

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

2. INTRODUCTION

This report describes the analytical evaluation of mRNA-1653 purity in the bulk test item from Study No. 5002033.

For the work detailed in this report, the analytical experimental phase start date was 13 Jun 2017 and end date was 19 June 2017.

3. EXPERIMENTAL DESIGN

3.1. Bulk Test Item End of Use Analysis

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

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

4. MATERIALS AND METHODS

4.1. Materials

4.1.1. Reference Standard

Identification:	CX-001049 mRNA
Physical Description:	Clear, colorless solution, essentially free of visible particulates
Batch/Lot No.:	MTDS16003
Concentration:	2.05 mg/mL
Retest Date:	Jul 2017
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

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4.1.2. Bulk Test Item

Identification:	mRNA-1653 (in lipid nanoparticles)
Physical Description:	0.5 mL per vial, white to off-white lipid nanoparticle dispersion
Batch/Lot No.:	MTDP17038
Concentration:	2.2 mg/mL
Expiry Date:	The end of use bulk Test Item analysis demonstrated that the Test Item was suitable for use during the study period.
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

4.1.3. Characterization of Reference Standard and Bulk Test Item Sample

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

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

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

4.2. Methods

(b) (4)

4.3. Computerized Systems

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

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Text Table 1
Computerized Systems

	Version No.	Description of Data Collected and/or Analyzed
(b) (4)	1.1.0.11	Data acquisition
Empower 3 (Waters Corporation)	Build 3471 SR1	Data regression analysis and measurement of purity
Excel	2007	Data analysis and tabulation
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

5. DEVIATIONS

Deviations from the analytical procedure did not occur during this phase of the study. No study plan deviation occurred during this phase of the study.

(b) (4)

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

Appendix 16

7. REPORT APPROVAL

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

(b) (6)

Appendix 16

Table 1 End of Dosing Period Sample Purity Results

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

Appendix 16

Appendix 1

(b) (4)

Appendix 16

charles river

ANALYTICAL PROCEDURE

(b) (4)

	AP No: AP.5002033.RNA.01	Effective Date: Signature of AP
	Page 1 of 2 pages	Supersedes Date: N/Ap
Prepared by: (b) (6)	(b) (6)	Date: 09 Jun 2017
Reviewed by: (b) (6)	(b) (6)	Date: 09 Jun 2017
Approved by: (b) (6)	(b) (6)	Date: 09 Jun 2017

(b) (4)

3.0 RESPONSIBILITY

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

(b) (4)

5.0 MATERIALS

(b) (4)

Appendix 16

AP No: AP.5002033.RNA.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 2 of 2 pages

5.3 (b) (4)

6.0 GENERAL GUIDELINES

(b) (4)

7.0 (b) (4)

8.0 REVISION HISTORY

Version	Date	Reason for revision
01	Signature of AP	New AP

Appendix 16

(b) (4)

Study/Reference No: 5002033 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.5002033.RNA.01)

Appendix 16

(b) (4)

Study/Reference No: 5002033

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.5002033.RNA.01)

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(b) (4)

Study/Reference No: 5002033 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.5002033.RNA.01)

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Appendix 2

(b) (4)

Appendix 16

charles river

ANALYTICAL PROCEDURE

(b) (4)	AP No: AP.5002033.RQF.01	Effective Date: Signature of AP
	Page 1 of 4 pages	Supersedes Date: N/Ap
Prepared by: (b) (6)	(b) (6)	Date: 09 Jun 2017
Reviewed by: (b) (6)	(b) (6)	Date: 09 Jun 2017
Approved by: (b) (6)	(b) (6)	Date: 09 Jun 2017

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 16

AP No: AP.5002033.RQF.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 2 of 4 pages

5.2 (b) (4)

5.3 (b) (4)

5.4 **Reagents**

(b) (4)

6.0 PREPARATION OF REAGENTS

(b) (4)

Appendix 16

AP No: AP.5002033.RQF.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 3 of 4 pages

6.1 (b) (4)

6.2

6.3

6.4

7.0 (b) (4)

8.0 **ACCEPTANCE CRITERIA**

(b) (4)

Appendix 16

AP No: AP.5002033.RQF.01	Effective date: Signature of AP	Supersedes: N/Ap	Page 4 of 4 pages

8.2 (b) (4)

8.3

8.4 (b) (4)

9.0 **REVISION HISTORY**

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

Appendix 16

(b) (4)

Study/Reference No: 5002033 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.5002033.RQF.01)

Appendix 16

(b) (4)

Study/Reference No: 5002033 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.5002033.RQF.01)

Appendix 16

(b) (4)

Study/Reference No: 5002033 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.5002033.RQF.01)

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(b) (4)

Study/Reference No: 5002033 Assay I.D.: Pro-xx

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(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.5002033.RQF.01)

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(b) (4)

Study/Reference No: 5002033 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.5002033.RQF.01)

Appendix 16

(b) (4)

Study/Reference No: 5002033 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.5002033.RQF.01)

Appendix 16

(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.5002033.RQF.01) Page 01 of 01

Appendix 16

Appendix 3
Certificates of Analysis

Appendix 16

moderna
messenger therapeutics

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

Summary of Analysis

Document number	mRNA 1653 TA COT
Date of Document Generation	14 Apr 2017
Revision	001
Product name	**mRNA 1653 test article**
Product description	mRNA 1653 LNP in 100mM Tris, 7% PG, 1mM DTPA, pH 7.4
Lot No.	**MTDP 17038**
Drug Substance (API)	MTDS 16003 and MTDS 16015
Date of Manufacture	30-Mar-2017
Time Point	T = Initial

Test	Method	Testing Reference	Acceptance Criteria (mg/mL)	Results
RNA Content	(b) (4)	NoteBook: 2017_04_14- (b) (6)	(b) (4)	
Endotoxin	USP 85 (b) (4)	Report 0417-024		
Bioburden (TAMC)	USP 61	# 957262		

Data Approved: (b) (6) (b) (6) Date: 4-14-201

Doc: mRNA1653 TA COT *Page 1 of 1*

Appendix 16

Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

eurofins | Advantar

Summary of Analysis ***DATE: 14 July 2017***

[2]Part II Release Testing for mRNA-1653 LNP Drug Product Lot # MTDP17038

Protocol Number: MRA-C0020-RTP0003.00 **Document Number:** MRA-C0020-RTR0006.00 (CPR15057)	**Date Received at Eurofins Advantar:** April 7, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1653 in a white to off-white lipid nanoparticle dispersion (100mM Tris Buffer, 7% PG, and 1mM DTPA, pH 7.4)
Time point: Release **Storage Condition:** -20°C	**Product Lot #:** MTDP17038	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Appearance (MRA-C0000-GTM0016.00)	White to off-white dispersion, no visible particulates	04/27/2017	Conforms (CPR15052, Page 10)
Purity (MRA-C0000-GTM0019.01)	(b) (4)	04/26/2017	(b) (4)
Related Impurities (MRA-C0000-GTM0019.01)		04/26/2017	
Encapsulated RNA (MRA-C0000-GTM0014.00)		04/27/2017	
Osmolality (mOsm/Kg) (USP <785>) USP39NF34 Supplement 2		05/08/2017	
Lipid Identification		05/22/2017	
SM102	Matches retention time of standard		Conforms
PEG2000-DMG	Matches retention time of standard		Conforms
Cholesterol	Matches retention time of standard		Conforms
DSPC	Matches retention time of standard		Conforms
(UHPLC-CAD)			(CPR15052, ADR D1)
Lipid Content	Lipid (mg/mL)	05/22/2017	(b) (4)
SM102	Report results		
PEG2000-DMG	Report results		
Cholesterol	Report results		
DSPC	Report results		
(UHPLC-CAD)			

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Eurofins Advantar Laboratories, Inc.
5451 Oberlin Drive, Suite 100
San Diego, CA 92121
Phone: (858) 228-778

eurofins | Advantar

Summary of Analysis ***DATE: 14 July 2017***

[2]Part II Release Testing for mRNA-1653 LNP Drug Product Lot # MTDP17038

Protocol Number: MRA-C0020-RTP0003.00 **Document Number:** MRA-C0020-RTR0006.00 (CPR15057)	**Date Received at Eurofins Advantar:** April 7, 2017	**Product Description:** 0.5 mL of approximately 2 mg/mL mRNA-1653 in a white to off-white lipid nanoparticle dispersion (100mM Tris Buffer, 7% PG, and 1mM DTPA, pH 7.4)
Time point: Release **Storage Condition**: -20°C	**Product Lot #:** MTDP17038	**Container/Closure:** **Vial:** 2 mL, 13 mm, Type I, S-L FNT W/BB NV WOS Serum/Lyophilization **Stopper:** 13 mm, Serum, Novapure RP-S2-F451, Gray, FluroTec Coated Plug **Seal:** 13 mm, Flip-Off, TruEdge TE (6-B)3767, Blue Button

ASSAY (TEST METHOD)	DRAFT SPECIFICATIONS (per protocol)	TEST DATE	RESULTS
Lipid Impurities (UHPLC-CAD)	(b) (4)	05/22/2017	(b) (4)
Mean Particle Size (nm) (MRA-C0000-GTM0015.02)		04/26/2017	
Polydispersity (MRA-C0000-GTM0015.02)		04/26/2017	
pH (MRA-C0000-GTM0017.01)		04/27/2017	
Particulate matter [1] (USP <788> Method 2)		04/13/2017	
Residual Solvents, ethanol (MRA-C0000-GTM0018.01) (USP <467>)		05/04/2017	

[1] Testing performed at Nelson Laboratories.
[2] Part I included AEX, Bacterial Endotoxins, and Bioburden.

The data generated at Advantar and described within this Summary of Analysis were reviewed by the Project Director for accuracy and compliance with Good Scientific Practices. Advantar has archived the raw data.

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

14 JUL 2017
Date

Appendix 16

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200 Technology Square • Cambridge, MA 02139
Phone 617.714.6500 • Fax 617.583.1998

SUMMARY OF ANALYSIS

Sample Description:	**CX-001049** (former name MDPC-0010) (mRNA API)
mRNA length:	(b)
Plasmid ID:	PL-006165
SSC:	33.09 µg/mL
Lot or Batch No:	**MTDS16003**
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics
Date of Manufacture:	February 2016
Date of Analysis:	July 2016
Storage:	Shipping Temperature: ≤ -15°C Storage Temperature: - 20°C ± 5°C
Retest Date:	July 2017

TEST	TEST METHOD	SPECIFICATION	RESULT	REFERENCE
Appearance	MRA-C0000-GTM0008.00	Clear, colorless solution, essentially free of visible particulates	Clear, colorless solution, essentially free of visible particulates	CPR11146 ADR C1
Identity by Sanger Sequencing	TSOP134.00	(b) (4)		209-TSOP134-076.00
Total RNA content	DSAD-TM-0019*	(b) (4)		2017_04_10-046-(b) (6)
Purity	MRA-C0000-GTM0001.02			CPR11147 ADR C16
Product related impurities	MRA-C0000-GTM0001.02			CPR11147 ADR C16
pH	USP<791>			CPR11146 ADR B1
Residual DNA template	qPCR TSOP344.01			209-TSOP344-072.00

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Residual solvents TEA	MRA-C0000-GTM0005.02	(b) (4)	CPR11150 ADR P9
IPA	MRA-C0000-GTM0007.02		CPR11151 ADR B28
Ethanol	MRA-C0000-GTM0007.02		CPR11151 ADR B28
Hexylene glycol	MRA-C0000-GTM0007.02		CPR11152 P11
% Poly A tailed RNA (% Tailless RNA)	MRA-C0000-GTM0003.02		CPR11148 ADR A20
% 5′ Capped	MRA-C0000-GTM0002.01		CPR11149 ADR B6
Bioburden	USP<61>		16-02274
Bacterial Endotoxins	USP<85>		PD Batch Record MTDS16003

(b) (4)

Signatures:

(b) (6)

Generated by: (b) (6)

11 Apr 17
Date:

(b) (6)

Reviewed

11 APR 2017
Date:

CX-001049 Page 2 of 2 version 01

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(b) (4)

--Final Study Report--

(b) (4) **in vitro Protocol #: TC 7.2.1 hMPV/PIV3**

Sponsor study #: 5002033

Title: Measurement of Sprague Dawley (SD) rat serum for neutralizing antibody titers against human metapneumovirus (hMPV/A2) and human parainfluenza virus type 3 (PIV/3) by manual 60% plaque reduction assay.

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

Study monitor: (b) (6)
Moderna Therapeutics, Inc.
200 Technology Square, Third Floor
Cambridge, MA 02139, USA

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

(b) (4)

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(b) (4)

Title: Measurement of Sprague Dawley (SD) rat serum for neutralizing antibody titers against human metapneumovirus (hMPV/A2) and human parainfluenza virus type 3 (PIV/3) by manual 60% plaque reduction assay.

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6 Appendix 8

Date of Report: 07. Sep. 2017

1 Approval

(b) (4), (b) (6)

Report prepared by:

(b) (4)

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2 Objective

The objective of this study was to measure 60% serum neutralizing antibody titers (PRNT60) from Sprague Dawley rats intramuscularly immunized on day 1with test vaccine mRNA-1653 at escalating doses of 10, 50, and 150ug per dose with a booster on days 15 and 29. Serum samples were collected on days 0, 30, and 43 for analysis.

3 Study Deviation(s)

During the *in vitro* assay, no deviations were recorded.

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(b) (4)

4 Executive Summary

Sprague Dawley serum samples obtained before (day 0) and after (days 30 and 43) immunization with different doses of mRNA-1653 vaccine preparation were used to determine neutralizing activity against hMPV/A2 and PIV/3. No neutralizing antibodies against hMPV/A2 were detected in serum samples obtained prior to immunization. However, low to moderate levels of neutralizing antibodies against PIV/3 were detected in the serum samples prior to immunization with titers in the range of 20.82 to 222.58. Therefore analysis of vaccine immunogenicity on these samples were performed using the basal detection levels on day 30 or 43 of the negative control group 1 serum samples and not the standard limit of detection (4.32 Log_2) for the PIV/3 PRNT.

hMPV/A2 PRNT60

Sprague Dawley serum samples on day 30 immunized with all dose different doses of mRNA-1653 (10, 50, and 150ug) all showed significant rise in serum neutralizing antibody titers (NT) against hMPV/A2 strain of virus after three intramuscular vaccinations of the test material on days 1, 15, and 29. There were no dose responses to the level of NT in the vaccine groups (5.0, 4.7, and 4.9 Log2 for escalating vaccine groups). This could be due to plateau effect of the immunogen as the lowest dose of the vaccine had already achieve maximal level of immunogenicity. Rat serum samples analyzed on day 43 consisted of two groups, the negative control group 1 and the highest dose group 4 at 150ug of the test vaccine. By day 43, the highest dosed group 4 had 10.3 Log2 NT, 6.0 Log 2 rise compared to the negative control group 1. Additionally, there was a 1.1 Log2 NT rise in group 4 when compared to day 30 and day 43 samples, indicative of the booster effect on day 29.

hMPV/A2	Day 0			Day 30			Day 43		
Groups	Log2	SD	SE	Log2	SD	SE	Log2	SD	SE
1	4.321928095	0	0	4.32192809	0	0	4.32192809	0	0
2	4.321928095	0	0	9.34510442	1.0844	0.386			
3	4.321928095	0	0	9.03195791	0.7915	0.2595			
4	4.321928095	0	0	9.20840797	0.8529	0.2793	10.3469815	0.3398	0.1077

(b) (4)

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(b) (4)

PIV/3 PRNT60

Sprague Dawley serum samples on day 30 immunized with all dose different doses of mRNA-1653 (10, 50, and 150ug) all showed moderate rise in serum NT against PIV/3 strain of virus after three intramuscular vaccinations of the test material on days 1, 15, and 29. There were no dose responses to the level of NT in the vaccine groups (3.8, 2.8, and 3.1 Log2 for escalating vaccine groups). This again could be due to plateau effect of the immunogen as the lowest dose of the vaccine had already achieve maximal level of immunogenicity. Rat serum samples analyzed on day 43 consisted of two groups, the negative control group 1 and the highest dose group 4 at 150ug of the test vaccine. By day 43, the highest dosed group 4 had 10.1 Log2 NT, 3.8 Log 2 rise compared to the negative control group 1. Additionally, there was a 0.8 Log2 NT rise in group 4 when compared to day 30 and day 43 samples, indicative of the booster effect on day 29.

PIV3	Day 0			Day 30			Day 43		
Groups	Log2	SD	SE	Log2	SD	SE	Log2	SD	SE
1	4.463114795	0.3517	0.1692	6.14455777	1.356	0.5697	6.2867719	1.1948	0.5207
2	4.442326308	0.413	0.1987	9.97667311	0.5171	0.1597			
3	4.385988211	0.3307	0.159	9.01389519	0.792	0.2632			
4	4.645495461	0.8532	0.4104	9.26123399	0.7795	0.2421	10.09877	0.6285	0.1951

(b) (4)

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5 Materials and Methods

hMPV/A2 Virus:

Human Metapneumovirus was propagated in MK2 cells. A pool of virus, designated as hMPV Lot# 092315 and containing approximately 4 x 10^6 pfu/ml in sucrose stabilizing media, was used. This stock of virus was stored under -80ºC conditions and has been characterized for hMPV/A2 neutralization assay with the appropriate cotton rat sera as reference standards.

hMPV/A2 neutralizing antibody assay (60% plaque reduction)

Heat inactivated sera samples are diluted 1:10 with OptiMEM and serially diluted further 1:4. Diluted serum samples are incubated with hMPV/A2 (25-50 PFU) for 1 hour at room temperature and inoculated in duplicates onto confluent MK-2 monolayers in 24-well plates. After one hour incubation at 37°C in a 5% CO_2 incubator, the wells are overlaid with 0.75% Methylcellulose medium. After 7 days of incubation, the overlays are removed and washed once in PBS. The cells are fixed in cold acetone/methanol solution for one hour and air dried for immuno-staining. The wells are permeabilized in 0.4% Triton-X solution and incubated in blocking solution (10% BSA). Mouse anti-hMPV N protein at a 1:1,000 dilution is added to each well, followed by HRP conjugated rabbit anti-mouse IgG diluted at 1:5,000. AEC chromogen detection solution is used for coloration after two hours of incubation or until red plaques are visible. Plaques are counted and virus titers are expressed as plaque forming units. The corresponding reciprocal neutralizing antibody titers are determined at the 60% reduction end-point of the virus control using the statistics program "**plqrd.manual.entry**". The geometric means ± standard error for all animals in a group at a given time are calculated.

PIV/3 Virus:

Human Parainfluenza Virus type 3 was propagated in MA-104 cells. A pool of virus, designated as PIV3 Lot# 030917 and containing approximately 2 x 10^7 pfu/ml in sucrose stabilizing media, was used. This stock of virus was stored under -80ºC conditions and has been characterized for PIV/3 neutralization assay with the appropriate cotton rat sera as reference standards.

PIV3 neutralizing antibody assay (60% plaque reduction)

Heat inactivated sera samples are diluted 1:10 with EMEM and serially diluted further 1:4. Diluted serum samples are incubated with PIV3 (25-50 PFU) for 1 hour at room temperature and inoculated in duplicates onto confluent MA-104 monolayers in 24 well plates. After two hour incubation at 37°C in a 5% CO_2 incubator, the wells are overlaid with 0.75% Methylcellulose medium. After 4 days of incubation, the overlays are removed and the cells are fixed and stained with 0.1% crystal violet for one hour and then rinsed and air dried. The corresponding reciprocal neutralizing antibody titers are determined at the 60% reduction end-point of the virus control using the statistics program "**plqrd.manual.entry**". The geometric means ± standard error for all animals in a group at a given time are calculated.

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(b) (4)

Test Samples:

The Sprague Dawley serum samples pertaining to this study were received in good condition and were stored according to the sponsor's instructions until the start of this study on June 22nd, 2017. All retention samples were re-frozen on dry ice and stored at -80C for archiving.

Shipment Delivery Form charles river

To Be Completed By Submitter:

TO: (b) (4), (b) (6)

Date of Shipment: 12-Jun-2017
CRL Study Number (If Applicable): 5002033
Sponsor Reference (If Applicable):

Shipping Conditions	Storage conditions
Dry Ice	-80°C

Total Amount of dry ice (if applicable) 11.0 Kg

Study Director: (b) (6)
Sponsor: Moderna Therapeutics, Inc.
Notes:

Test Material/Dose Formulation Only (if applicable)

TM/DF Identification # / Name:
Therapeutic Action / Clinical application
Manufacturer & Country of origin:

Description of Items Shipped

	Item 1	Item 2 (if applicable)	Item 3 (if applicable)	Item 4 (if applicable)
Species:	Rats			
Matrix:	Serum			
Sample Type:	ATA			
Quantity:	210 Plastic Vial			
Unit of Measure:	—			

Number of Boxes: 1

Box No.		
	1	12.8 Kg
	2	Kg
	3	Kg
	4	Kg
	5	Kg
	6	Kg
	7	Kg
	8	Kg
	9	Kg
	10	Kg

Total Weight: 12.8 Kg

Documents included in the shipment

- ☐ Treatment (dosing) Worksheets
- ☐ Blood Collection sheets
- ☐ Plasma or Serum Collection sheets
- ☑ Itemized Sample Inventory
- ☐ Sample Processing Sheet

Performed by/Date: (b) (6), (b) (4) 12 Jun 2017

To Be Completed By Recipient:

After Completing Section, Please Email back to MTL-SampleShipments@crl.com (if any discrepancies are noted, please add the annotated inventory to the e-mail).

Date Received: 13 June 2017
Received By (print name): (b) (6), (b) (4)
Received By (signature):
Condition Upon Receipt: (Check One) ☑ Good ☐ Damaged

Appendix 1 (ST04-01-01), Issue Date: 14-Dec-2015; Supersedes: 12-May-2014

(b) (4)

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(b) (4)

6 Appendix

Raw Data hMPV/A2 60% PRNT

Day	ID#	1/20		1/80		1/320		1/1280		Recip. Unit	Log2			
										60% PRNT		GeoMean Log2	SD	SE
day 0	1001	37	48							20	4.322	4.321928095	0	0
day 0	1002	45	46							20	4.322			
day 0	1003	52	44							20	4.322			
day 0	1004	35	31							20	4.322			
day 0	1005	28	30							20	4.322			
day 0	1006	37	40							20	4.322			
day 0	1007	41	43							20	4.322			
day 0	1008	46	53							20	4.322			
day 0	1009	47	36							20	4.322			
day 0	1010	43	50							20	4.322			
day 0	1011	39	50							20	4.322			
day 0	1012	54	44							20	4.322			
day 0	1013	32	29							20	4.322			
day 0	1014	45	42							20	4.322			
day 0	1015	35	46							20	4.322			
day 0	1501	53	39							20	4.322			
day 0	1502	49	50							20	4.322			
day 0	1503	50	53							20	4.322			
day 0	1504	40	36							20	4.322			
day 0	1505	38	47							20	4.322			
day 0	1506	43	38							20	4.322			
day 0	1507	46	35							20	4.322			
day 0	1508	41	53							20	4.322			
day 0	1509	58	56							20	4.322			
day 0	1510	54	53							20	4.322			
day 0	1511	46	47							20	4.322			
day 0	1512	44	47							20	4.322			
day 0	1513	43	38							20	4.322			
day 0	1514	42	35							20	4.322			
day 0	1515	37	44							20	4.322			
day 0	2001	34	43							20	4.322	4.321928095	0	0
day 0	2002	31	38							20	4.322			
day 0	2003	50	47							20	4.322			
day 0	2004	34	36							20	4.322			
day 0	2005	49	59							20	4.322			
day 0	2006	61	58							20	4.322			
day 0	2007	42	47							20	4.322			
day 0	2008	53	63							20	4.322			
day 0	2009	59	64							20	4.322			
day 0	2010	48	41							20	4.322			
day 0	2501	39	53							20	4.322			
day 0	2502	40	54							20	4.322			
day 0	2503	52	40							20	4.322			
day 0	2504	57	48							20	4.322			
day 0	2505	38	42							20	4.322			
day 0	2506	58	53							20	4.322			
day 0	2507	62	58							20	4.322			
day 0	2508	66	53							20	4.322			
day 0	2509	57	42							20	4.322			
day 0	2510	50	41							20	4.322			

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(b) (4)

day 0	3001	56	57							20	4.322	4.321928095	0	0
day 0	3002	56	54							20	4.322			
day 0	3003	41	39							20	4.322			
day 0	3004	53	56							20	4.322			
day 0	3005	55	45							20	4.322			
day 0	3006	36	49							20	4.322			
day 0	3007	46	51							20	4.322			
day 0	3008	58	60							20	4.322			
day 0	3009	35	41							20	4.322			
day 0	3010	53	61							20	4.322			
day 0	3501	64	63							20	4.322			
day 0	3502	52	56							20	4.322			
day 0	3503	40	42							20	4.322			
day 0	3504	58	58							20	4.322			
day 0	3505	38	40							20	4.322			
day 0	3506	51	56							20	4.322			
day 0	3507	57	52							20	4.322			
day 0	3508	53	41							20	4.322			
day 0	3509	61	68							20	4.322			
day 0	3510	69	58							20	4.322			
day 0	4001	45	46							20	4.322	4.321928095	0	0
day 0	4002	53	54							20	4.322			
day 0	4003	44	44							20	4.322			
day 0	4004	48	53							20	4.322			
day 0	4005	51	49							20	4.322			
day 0	4006	39	35							20	4.322			
day 0	4007	39	46							20	4.322			
day 0	4008	38	42							20	4.322			
day 0	4009	44	37							20	4.322			
day 0	4010	36	30							20	4.322			
day 0	4011	40	34							20	4.322			
day 0	4012	40	39							20	4.322			
day 0	4013	22	25							20	4.322			
day 0	4014	37	39							20	4.322			
day 0	4015	39	35							20	4.322			
day 0	4501	65	52							20	4.322			
day 0	4502	65	62							20	4.322			
day 0	4503	60	59							20	4.322			
day 0	4504	69	60							20	4.322			
day 0	4505	58	69							20	4.322			
day 0	4506	74	67							20	4.322			
day 0	4507	69	65							20	4.322			
day 0	4508	56	55							20	4.322			
day 0	4509	66	69							20	4.322			
day 0	4510	57	50							20	4.322			
day 0	4511	60	64							20	4.322			
day 0	4512	57	58							20	4.322			
day 0	4513	68	59							20	4.322			
day 0	4514	62	66							20	4.322			
day 0	4515	54	43							20	4.322			

(b) (4)

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(b) (4)

day 30	1001	58	45							20	4.322	4.321928095	0	0
day 30	1002	41	46							20	4.322			
day 30	1003	48	52							20	4.322			
day 30	1004	53	55							20	4.322			
day 30	1005	45	54							20	4.322			
day 30	1006	48	53							20	4.322			
day 30	1007	36	38							20	4.322			
day 30	1008	39	44							20	4.322			
day 30	1009	41	44							20	4.322			
day 30	1010	46	34							20	4.322			
day 30	1501	44	48							20	4.322			
day 30	1502	55	59							20	4.322			
day 30	1503	54	55							20	4.322			
day 30	1504	39	46							20	4.322			
day 30	1505	52	54							20	4.322			
day 30	1506	54	46							20	4.322			
day 30	1507	54	55							20	4.322			
day 30	1508	58	53							20	4.322			
day 30	1509	58	50							20	4.322			
day 30	1510	53	54							20	4.322			
day 30	2001	0	0	3	5	20	21			237.78	7.893	9.345104424	1.084	0.386
day 30	2002	0	0	6	4	20	20			233.2	7.865			
day 30	2003	0	0	1	1	13	12	16	14	787.06	9.62			
day 30	2004	0	0	0	1	2	2	5	13	1511.1	10.56			
day 30	2005	0	0	1	2	14	14	31	25	398.89	8.64			
day 30	2006	0	0	4	8	18	21			228.23	7.834			
day 30	2007	0	0	0	1	5	10	22	14	914.25	9.836			
day 30	2008	0	0	12	4	25	26			155.25	7.278			
day 30	2009	0	0	0	2	12	11	25	27	495.6	8.953			
day 30	2010	0	0	1	2	13	16	31	28	371.94	8.539			
day 30	2501	0	0	0	0	9	4	18	17	1117.83	10.13			
day 30	2502	0	0	0	0	6	2	16	13	1366.76	10.42			
day 30	2503	0	0	4	3	11	12	21	26	587.48	9.198			
day 30	2504	0	0	0	0	2	4	14	14	1385.14	10.44			
day 30	2505	0	0	0	0	1	0	11	13	1410.26	10.46			
day 30	2506	0	0	0	0	1	0	11	13	1410.26	10.46			
day 30	2507	0	0	0	2	6	7	15	12	1410.92	10.46			
day 30	2508	0	0	0	1	5	9	17	13	1303.75	10.35			
day 30	2509	0	0	0	0	6	6	14	21	1146.57	10.16			
day 30	2510	0	0	0	3	11	13	28	25	531.67	9.054			

(b) (4)

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(b) (4)

day 30	3001	0	0	0	0	10	13	21	26	631.28	9.302	9.031957914	0.791	0.26
day 30	3002	0	0	0	0	6	2	11	16	1409.46	10.46			
day 30	3003	0	0	2	4	20	7	30	30	425.3	8.732			
day 30	3004	0	0	1	1	6	7	19	21	958.57	9.905			
day 30	3005	0	0	1	3	16	9	32	27	464.65	8.86			
day 30	3006	0	0	0	0	12	9	19	23	745.92	9.543			
day 30	3007	0	0	0	1	7	10	26	27	647.01	9.338			
day 30	3008	0	0	2	0	11	12	27	27	541.08	9.08			
day 30	3009	0	0	4	3	24	21			241.92	7.918			
day 30	3010	0	0	1	0	12	10	21	29	603.96	9.238			
day 30	3501	0	0	2	1	9	11	25	23	652.22	9.349			
day 30	3502	0	0	0	1	12	3	27	26	679.74	9.409			
day 30	3503	0	0	2	3	11	24	37	35	309.39	8.273			
day 30	3504	0	0	2	3	14	17	24	22	489.2	8.934			
day 30	3505	0	0	0	3	12	7	19	21	809.29	9.661			
day 30	3506	0	0	0	0	18	16	30	29	383.27	8.582			
day 30	3507	0	0	1	1	28	17	37	36	251.21	7.973			
day 30	3508	0	0	0	0	1	2	3	10	1583.5	10.63			
day 30	3509	0	0	1	7	25	27			205.13	7.68			
day 30	3510	0	0	4	9	11	18	30	35	344.45	8.428			
day 30	4001	0	0	1	0	8	14	19	28	642.49	9.328	9.20840797	0.853	0.279
day 30	4002	0	0	1	0	9	6	27	30	632.28	9.304			
day 30	4003	0	0	1	3	11	26	34	39	295.94	8.209			
day 30	4004	0	0	0	0	11	3	18	16	1137.74	10.15			
day 30	4005	0	0	5	4	11	16	26	24	479.99	8.907			
day 30	4006	0	0	2	3	13	17	20	33	442.12	8.788			
day 30	4007	0	0	1	0	9	8	26	27	581.47	9.184			
day 30	4008	0	0	0	3	25	22			235.63	7.88			
day 30	4009	0	0	9	4	22	19			211.65	7.726			
day 30	4010	0	0	2	2	11	12	29	33	421.77	8.72			
day 30	4501	0	0	3	2	23	22			232.7	7.862			
day 30	4502	0	0	0	0	2	5	12	16	1340.3	10.39			
day 30	4503	0	0	2	0	8	3	16	17	1124.53	10.14			
day 30	4504	0	0	1	2	15	13	18	19	584.42	9.191			
day 30	4505	0	0	0	1	5	3	19	21	977.04	9.932			
day 30	4506	0	0	0	0	7	8	20	20	824.33	9.687			
day 30	4507	0	0	2	3	12	10	24	20	581.83	9.184			
day 30	4508	0	0	0	0	3	4	8	18	1387.88	10.44			
day 30	4509	0	0	1	0	7	9	19	15	951.08	9.893			
day 30	4510	0	0	1	0	2	4	14	25	1043.33	10.03			

day 43	1011	38	35							20	4.322	4.321928095	0	0
day 43	1012	48	46							20	4.322			
day 43	1013	39	43							20	4.322			
day 43	1014	52	44							20	4.322			
day 43	1015	39	46							20	4.322			
day 43	1511	43	53							20	4.322			
day 43	1512	59	57							20	4.322			
day 43	1513	55	58							20	4.322			
day 43	1514	54	63							20	4.322			
day 43	1515	58	52							20	4.322			
day 43	4011	0	0	1	0	7	5	23	13	997.86	9.963	10.34698152	0.34	0.108
day 43	4012	0	0	0	0	3	5	11	11	1473.53	10.53			
day 43	4013	0	0	0	0	2	3	9	11	1490.54	10.54			
day 43	4014	0	0	0	1	7	8	13	21	980.38	9.937			
day 43	4015	0	0	0	0	0	1	5	14	1456.15	10.51			
day 43	4511	0	0	0	0	3	1	7	7	1570.6	10.62			
day 43	4512	0	0	0	0	8	5	13	28	846.65	9.726			
day 43	4513	0	0	0	0	2	2	8	10	1512.76	10.56			
day 43	4514	0	0	0	0	0	1	3	5	1637.46	10.68			
day 43	4515	0	0	0	0	5	3	14	11	1412	10.46			

(b) (4)

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Raw Data PIV/3 60% PRNT

Day	ID#	1/20		1/80		1/320		1/1280		Recip. Unit	Log2			
										60% PRNT		GeoMean Log2	SD	SE
day 0	1001	30	25							20	4.32193	4.463114795	0.352	0.169
day 0	1002	36	35							20	4.32193			
day 0	1003	28	32							20	4.32193			
day 0	1004	41	42							20	4.32193			
day 0	1005	36	32							20	4.32193			
day 0	1006	35	28							20	4.32193			
day 0	1007	43	40							20	4.32193			
day 0	1008	35	43							20	4.32193			
day 0	1009	11	7	32	35					29.48	4.88166			
day 0	1010	40	38							20	4.32193			
day 0	1011	39	39							20	4.32193			
day 0	1012	35	32							20	4.32193			
day 0	1013	13	9	35	33					26.38	4.72137			
day 0	1014	4	6	33	27					39.93	5.3194			
day 0	1015	39	45							20	4.32193			
day 0	1501	12	12	33	28					26.23	4.71315			
day 0	1502	23	22							20	4.32193			
day 0	1503	16	19	27	35					20	4.32193			
day 0	1504	1	4	25	23					55.15	5.78529			
day 0	1505	31	33							20	4.32193			
day 0	1506	19	12	33	26					20.82	4.3799			
day 0	1507	40	35							20	4.32193			
day 0	1508	11	13	27	19					33.04	5.04614			
day 0	1509	14	22	35	30					20	4.32193			
day 0	1510	34	43							20	4.32193			
day 0	1511	32	35							20	4.32193			
day 0	1512	32	18							20	4.32193			
day 0	1513	33	29							20	4.32193			
day 0	1514	22	29							20	4.32193			
day 0	1515	30	34							20	4.32193			
day 0	2001	46	38							20	4.32193	4.442326308	0.413	0.199
day 0	2002	35	37							20	4.32193			
day 0	2003	27	19							20	4.32193			
day 0	2004	26	27							20	4.32193			
day 0	2005	0	0	29	27					65.93	6.04286			
day 0	2006	30	35							20	4.32193			
day 0	2007	41	39							20	4.32193			
day 0	2008	21	20							20	4.32193			
day 0	2009	40	48							20	4.32193			
day 0	2010	27	29							20	4.32193			
day 0	2501	36	35							20	4.32193			
day 0	2502	34	24							20	4.32193			
day 0	2503	34	38							20	4.32193			
day 0	2504	28	27							20	4.32193			
day 0	2505	4	11	30	24					34.6	5.1127			
day 0	2506	26	24							20	4.32193			
day 0	2507	22	17							20	4.32193			
day 0	2508	12	17	32	22					21.04	4.39506			
day 0	2509	26	24							20	4.32193			
day 0	2510	11	14	36	34					21.88	4.45154			

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day 0	3001	41	34							20	4.32193	4.385988211	0.331	0.159
day 0	3002	36	33							20	4.32193			
day 0	3003	34	35							20	4.32193			
day 0	3004	34	35							20	4.32193			
day 0	3005	25	26							20	4.32193			
day 0	3006	29	31							20	4.32193			
day 0	3007	38	49							20	4.32193			
day 0	3008	25	22							20	4.32193			
day 0	3009	18	24							20	4.32193			
day 0	3010	26	25							20	4.32193			
day 0	3501	31	35							20	4.32193			
day 0	3502	33	28							20	4.32193			
day 0	3503	36	26							20	4.32193			
day 0	3504	26	27							20	4.32193			
day 0	3505	33	29							20	4.32193			
day 0	3506	31	33							20	4.32193			
day 0	3507	1	4	21	23					55.74	5.80064			
day 0	3508	16	19							20	4.32193			
day 0	3509	26	23							20	4.32193			
day 0	3510	26	20							20	4.32193			
day 0	4001	39	34							20	4.32193	4.645495461	0.853	0.41
day 0	4002	36	35							20	4.32193			
day 0	4003	38	43							20	4.32193			
day 0	4004	29	20							20	4.32193			
day 0	4005	35	32							20	4.32193			
day 0	4006	20	18							20	4.32193			
day 0	4007	32	20							20	4.32193			
day 0	4008	33	25							20	4.32193			
day 0	4009	38	32							20	4.32193			
day 0	4010	27	16	31	36					20	4.32193			
day 0	4011	9	4	29	33					35.12	5.13422			
day 0	4012	37	39							20	4.32193			
day 0	4013	30	40							20	4.32193			
day 0	4014	35	23							20	4.32193			
day 0	4015	36	32							20	4.32193			
day 0	4501	1	0	2	3	18	26			222.58	7.79818			
day 0	4502	14	20	33	29					20	4.32193			
day 0	4503	16	12	31	31					20.94	4.38819			
day 0	4504	31	28							20	4.32193			
day 0	4505	4	5	31	25					39.67	5.30998			
day 0	4506	29	29							20	4.32193			
day 0	4507	8	11	32	25					29.33	4.87431			
day 0	4508	23	18							20	4.32193			
day 0	4509	25	25							20	4.32193			
day 0	4510	30	31							20	4.32193			
day 0	4511	35	31							20	4.32193			
day 0	4512	3	2	6	7	34	28			127.85	6.99831			
day 0	4513	28	25							20	4.32193			
day 0	4514	1	2	24	17					62.52	5.96625			
day 0	4515	5	3	26	21					48.25	5.59246			

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day 30	1001	2	1	25	28					50.75	5.66534	6.144557767	1.356	0.57
day 30	1002	2	5	32	26					40.97	5.3565			
day 30	1003	14	12	24	23					26.72	4.73985			
day 30	1004	37	35							20	4.32193			
day 30	1005	0	0	5	4	24	30			165.82	7.37347			
day 30	1006	33	33							20	4.32193			
day 30	1007	15	18	30	38					20	4.32193			
day 30	1008	0	0	16	14	30	27			88.27	6.46385			
day 30	1009	0	0	7	5	21	26			175.13	7.45228			
day 30	1010	3	5	23	27					45.81	5.51759			
day 30	1501	0	1	18	14	34	35			75.63	6.24089			
day 30	1502	0	0	5	5	31	28			148.16	7.21101			
day 30	1503	2	1	9	13	23	28			118.57	6.8896			
day 30	1504	0	0	1	1	19	26			240.4	7.90929			
day 30	1505	0	1	16	21					71.14	6.15259			
day 30	1506	0	0	0	6	20	18			252.91	7.98248			
day 30	1507	13	5	31	24					31.41	4.97315			
day 30	1508	0	1	6	7	24	31			145.52	7.18507			
day 30	1509	0	1	17	11	21	28			105.15	6.71631			
day 30	1510	0	0	0	0	7	4	34	34	494	8.94837			
day 30	2001	0	0	1	1	5	3	14	9	1429.58	10.4814	9.976673113	0.517	0.16
day 30	2002	0	0	1	1	3	6	22	20	844.85	9.72255			
day 30	2003	0	0	1	0	1	1	5	7	1573.59	10.6198			
day 30	2004	0	0	0	1	1	3	6	9	1546.96	10.5952			
day 30	2005	0	0	0	0	1	0	6	10	1485.31	10.5365			
day 30	2006	0	0	0	0	1	2	12	14	1349.29	10.398			
day 30	2007	0	0	1	2	5	6	13	18	1117.64	10.1262			
day 30	2008	0	1	1	0	2	4	21	21	914.39	9.83667			
day 30	2009	2	0	2	1	15	2	28	23	549.55	9.10211			
day 30	2010	0	0	0	0	3	4	13	9	1447.85	10.4997			
day 30	2501	0	0	1	0	4	4	21	16	1030.85	10.0096			
day 30	2502	0	0	3	1	7	5	19	23	802.71	9.64874			
day 30	2503	0	0	0	1	5	11	23	34	651.15	9.34685			
day 30	2504	0	0	0	0	2	1	14	7	1449.96	10.5018			
day 30	2505	0	0	0	0	1	0	10	7	1474.49	10.526			
day 30	2506	0	0	2	1	4	8	18	20	899.94	9.81369			
day 30	2507	0	0	0	0	12	6	19	22	713.34	9.47845			
day 30	2508	0	0	2	0	4	5	22	14	1036.01	10.0168			
day 30	2509	0	0	3	3	6	10	30	22	568.56	9.15117			
day 30	2510	0	0	1	2	13	4	31	13	665.96	9.37929			

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day 30	3001	0	0	1	0	6	10	31	27	531.79	9.05471	9.013895187	0.792	0.263
day 30	3002	0	0	3	3	10	10	23	29	503.44	8.97568			
day 30	3003	0	0	3	2	14	11	24	26	453.31	8.82435			
day 30	3004	0	0	1	0	2	1	15	20	1169.49	10.1917			
day 30	3005	1	1	7	8	22	23			173.71	7.44054			
day 30	3006	0	0	0	0	8	6	12	15	1291.27	10.3346			
day 30	3007	2	0	0	0	11	8	22	30	545.11	9.0904			
day 30	3008	0	0	7	5	12	12	35	32	353.44	8.46532			
day 30	3009	0	0	5	4	27	14	31	24	246.44	7.94509			
day 30	3010	0	1	1	3	8	18	25	24	452.39	8.82142			
day 30	3501	0	0	5	2	11	15	27	27	400.58	8.64595			
day 30	3502	0	0	0	2	4	4	11	13	1422.22	10.4739			
day 30	3503	0	0	0	1	3	13	23	23	665.51	9.37832			
day 30	3504	0	1	5	3	14	16	31	30	320	8.32193			
day 30	3505	0	1	6	5	19	15	35	24	274.35	8.09987			
day 30	3506	0	0	2	1	9	5	24	25	651.64	9.34793			
day 30	3507	2	0	2	6	9	10	30	31	449.19	8.81118			
day 30	3508	0	0	0	1	13	11	27	24	780.1	9.60752			
day 30	3509	0	0	0	1	3	8	24	22	761.94	9.57353			
day 30	3510	0	0	0	0	6	7	21	24	743.17	9.53755			
day 30	4001	0	0	0	1	4	3	14	14	1323.2	10.3698	9.261233994	0.779	0.242
day 30	4002	0	1	4	2	16	24			445.93	8.80067			
day 30	4003	0	0	0	0	4	3	12	19	1236.42	10.272			
day 30	4004	0	0	0	1	6	6	27	25	656.2	9.35799			
day 30	4005	0	0	0	0	6	8	24	17	797.99	9.64023			
day 30	4006	0	0	4	6	13	19	32	33	284.38	8.15168			
day 30	4007	0	0	0	0	6	6	19	30	671.85	9.392			
day 30	4008	0	0	4	6	8	20	31	31	313.2	8.29094			
day 30	4009	0	0	3	0	16	20			279.81	8.1283			
day 30	4010	0	0	0	0	4	2	15	13	1303.33	10.348			
day 30	4501	1	0	0	1	8	7	18	30	627.09	9.29253			
day 30	4502	1	0	2	3	20	17			264.15	8.04521			
day 30	4503	0	0	1	1	4	6	27	36	553.11	9.11142			
day 30	4504	0	0	1	2	9	19	24	26	403.91	8.65789			
day 30	4505	0	0	0	1	7	12	21	28	548.74	9.09998			
day 30	4506	1	0	0	0	7	5	15	17	1060.54	10.0506			
day 30	4507	0	0	1	2	5	6	15	16	1117.64	10.1262			
day 30	4508	0	0	1	2	11	7	26	26	525.56	9.03771			
day 30	4509	0	0	0	1	10	12	21	14	697.49	9.44603			
day 30	4510	0	0	0	0	1	6	15	16	1204.32	10.234			

day 43	1011	7	4	24	31					38.47	5.26566	6.286771898	1.195	0.521
day 43	1012	1	1	22	24					59.09	5.88484			
day 43	1013	1	1	8	8	24	20			165.11	7.36728			
day 43	1014	1	0	4	12	31	35			113.54	6.82706			
day 43	1015	1	0	8	7	29	34			121.69	6.92707			
day 43	1511	1	1	24	25					56.28	5.81455			
day 43	1512	1	1	20	34					52.14	5.70432			
day 43	1513	0	0	3	0	31	27			187.68	7.55213			
day 43	1514	1	1	1	1	18	14	30	34	304.75	8.25148			
day 43	1515	26	27							20	4.32193			
day 43	4011	0	0	2	1	2	4	14	13	1329.52	10.3767	10.09877	0.628	0.195
day 43	4012	0	0	0	0	2	4	27	8	1095.06	10.0968			
day 43	4013	0	0	0	0	0	2	18	7	1362.93	10.4125			
day 43	4014	0	0	0	1	3	2	15	16	1225.3	10.2589			
day 43	4015	0	0	0	0	1	1	22	18	1052.6	10.0397			
day 43	4511	0	0	0	0	0	1	0	3	1812.36	10.8237			
day 43	4512	0	0	1	2	12	18	26	26	368.04	8.52372			
day 43	4513	0	0	1	0	2	2	18	16	1154.04	10.1725			
day 43	4514	0	0	0	0	7	2	24	15	920.33	9.84601			
day 43	4515	0	0	0	0	1	2	7	5	1580.42	10.6261			

(b) (4)

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Contact Information

Regarding study report:

(b) (4), (b) (6)

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Appendix 18

FINAL REPORT

Study Phase: Pathology

Test Facility Study No. 5002033

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

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Appendix 18

1. SUMMARY

This report presents the pathology findings in rats assigned to Study No. 5002033. The objectives of this study were to determine the potential toxicity of mRNA-1653, when given by intramuscular injection for 1 month (3 doses) to Sprague Dawley rat and to evaluate the potential reversibility of any findings. The experimental design was as specified in the study plan. A complete gross pathological examination was performed on all animals and organ weights were recorded, as specified in the Study Plan. A detailed microscopic evaluation of all study plan-defined tissues was conducted on main study animals from Groups 1 and 4 with only potential drug target tissues and gross lesions from main study animals in Groups 2 and 3 and recovery animals in groups 1 and 4.

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

At the end of the main study, the microscopic changes related to administration of mRNA-1653 were seen in both sexes at the injection site, liver, bone marrow, spleen, lymph nodes (popliteal, inguinal and iliac) and sciatic nerve. A mixed cell inflammation was considered related to mRNA-1653 at the injection site (graded minimal to marked) at ≥ 10 µg/dose, in the popliteal, inguinal and/or iliac lymph nodes (graded minimal to moderate) at ≥ 10 µg/dose and in the sciatic nerve (graded minimal to mild) at ≥ 10 µg/dose. The mixed cell inflammation correlated macroscopically with firm abnormal consistency, swelling and/or thick at the injection site and with enlargement in the lymph nodes. The lymph nodes and sciatic nerve inflammatory changes were regarded as secondary to the injection site inflammation.

In the liver, minimal to mild hepatocellular vacuolation was considered related to mRNA-1653 at 150 µg/dose. In the bone marrow, minimal to mild increased hematopoiesis of the myeloid lineage occurred in both sexes at ≥ 10 µg/dose. This bone marrow change was likely a reactive response to the inflammation observed at the injection site. In the spleen, there was minimal to mild decreased cellularity of the periarteriolar lymphoid sheath often associated with an increase in macrophages in both sexes at 10, 50 and/or 150 µg/dose of mRNA-1653.

The remaining changes related to mRNA-1653 in the main study were higher liver weights in females at 150 µg/dose that had no microscopic correlations, and higher spleen weights in males at ≥ 50 µg/dose and females at ≥ 10 µg/dose that had no microscopic correlations.

After 2 weeks of recovery, the remaining RNA-1653-related microscopic changes were mixed cell inflammation around the popliteal lymph node and mononuclear cell infiltration around the sciatic nerve and at injection site. The popliteal lymph node mixed cell inflammation occurred with a decreased incidence and/or severity indicating partial recovery. The sciatic nerve and injection site mononuclear cell infiltration had a lower number of cells compared to the mixed cell inflammation observed in the main study indicating partial recovery. Other mRNA-1653-related microscopic findings observed during the main study in the liver (hepatocellular vacuolation), inguinal and iliac lymph nodes (mixed cell inflammation), bone marrow (increased hematopoiesis, myeloid) and spleen (decreased cellularity and increased macrophages in the periarteriolar lymphoid sheath) were not present in the recovery study indicating reversibility.

Appendix 18

2. INTRODUCTION

This report presents the pathology findings in rats assigned to Study No. 5002033. The objectives of this study were to determine the potential toxicity of mRNA-1653, when given by intramuscular injection for 1 month (3 doses) to Sprague Dawley rat and to evaluate the potential reversibility of any findings.

3. MATERIALS AND METHODS

Experimental procedures applicable to pathology investigations are summarized in Text Table 1.

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µl)	Dose Concentration (µg/mL)	No. of Animals			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1653	10	200	50	10	10	-	-
3	mRNA-1653	50	200	250	10	10	-	-
4	mRNA-1653	150	200	750	10	10	5	5

[a] = 10/sex/groups 1 to 4 necropsied 1 day following the last dose
[b] = The remaining 5/sex/groups 1 to 4 necropsied 2 weeks following the last dose.

A complete gross pathological examination was performed on all animals and organ weights were recorded, as specified in the Study Plan. A detailed microscopic evaluation of all study plan-defined tissues was conducted on main study animals from Groups 1 and 4 with only potential drug target tissues (injection site, liver, bone marrow, spleen, lymph nodes (popliteal, inguinal and other lymph node collected when gross lesions were present) and sciatic nerve) and gross lesions from main study animals in Groups 2 and 3 and recovery animals in Groups 1 and 4. Additional details along with deviations from these procedures may be found in the main study report.

3.1. Computerized Systems

Critical computerized systems used in this study phase are listed in Text Table 2.

Text Table 2
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	8	Terminal body weight, Organ weight data, gross pathology and histopathology.
Nevis	2	Statistical analyses of numerical terminal data.

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4. RESULTS AND DISCUSSIONS

4.1. Mortality

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

4.2. Gross Pathology

4.2.1. Terminal Euthanasia Animals (Day 30)

(Table 1 and Appendix 4)

Gross pathology findings related to mRNA-1653 were seen in the injection site and the popliteal lymph node and are summarized in Text Table 3.

Text Table 3
Summary of Gross Pathology Findings – Scheduled Euthanasia (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**150**	**0**	**10**	**50**	**150**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Injection Site (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency; firm	0	8	10	9	0	6	10	10
Swelling	0	4	6	10	0	1	6	9
Thick	0	0	0	3	0	0	1	1
Popliteal Lymph Node (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	4	1	0	0	1	3
Lymph Node, Inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	1	1	3	0	0	0	3
Lymph Node[a] (No. Examined)	0	1	1	3	0	0	2	4
Enlargement	0	1	1	3	0	0	2	4

a: Iliac lymph node

At the injection site, firm abnormal consistency, swelling and/or thick was observed in both sexes at 10, 50 and/or 150 µg/dose of mRNA-1653. The injection site swelling occurred with a dose-related increased incidence at 10, 50 and 150 µg/dose. These changes correlated microscopically with mixed cell inflammation.

In the lymph nodes (popliteal, inguinal and iliac), enlargement occurred in both sexes at 10, 50 and/or 150 µg/dose of mRNA-1653. Enlargement correlated microscopically with perinodal mixed cell inflammation.

Other gross findings observed were considered incidental, of the nature observed in this stain and age of rats, and/or were of similar incidence in control and treated animals and therefore, were considered unrelated to administration of mRNA-1653.

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4.2.2. Recovery Euthanasia Animals (Day 43)

(Table 1 and Appendix 4)

After 2 weeks of recovery, the mRNA-1653-related popliteal lymph node enlargement observed during the main study was still present in females administered 150 µg/dose of mRNA-1653 and are summarized in Text Table 4. Other mRNA-1653-related gross findings observed during the main study at the injection site (firm abnormal consistency, swelling and thick) and in the inguinal and iliac lymph nodes (enlargement) were not present in the recovery study.

Text Table 4
Summary of Gross Pathology Findings – Scheduled Euthanasia (Day 43)

	Males		Females	
Group	**1**	**4**	**1**	**4**
Dose (µg/dose)	**0**	**150**	**0**	**150**
No. Animals Examined	**5**	**5**	**5**	**5**
Popliteal Lymph Node (No. Examined)	5	5	5	5
Enlargement	0	0	0	2

Other gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in control and treated animals and, therefore, were considered unrelated to administration of mRNA-1653.

4.3. Organ Weights

4.3.1. Terminal Euthanasia Animals (Day 30)

(Table 2, Table 3, Table 4, Appendix 1, Appendix 2, and Appendix 3)

The organ weight changes related to mRNA-1653 were increases in liver and spleen weights, and are summarized in Text Table 5.

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Text Table 5
Summary of Organ Weight Data – Scheduled Euthanasia (Day 30)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**10**	**50**	**150**	**10**	**50**	**150**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Terminal Body Weight	-6.0	-5.2	**-10.4**	-1.0	-4.2	-6.0
Liver (No. Weighed)[a]	10	10	10	10	10	10
Absolute value	-	-	-	0.47	-1.69	2.72
% of body weight	-	-	-	1.71	2.40	**9.34**
% of brain weight	-	-	-	-2.08	-0.97	2.68
Spleen (No. Weighed)	10	10	10	10	10	10
Absolute value	3.65	15.17	14.79	**24.86**	**31.14**	**21.37**
% of body weight	10.27	**21.80**	**27.58**	**26.40**	**37.21**	**28.66**
% of brain weight	1.96	15.35	15.47	**21.44**	**32.18**	**21.17**

[a] All values expressed as percent difference of control group means.
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – $P \leq 0.05$; refer to data tables for actual significance levels and tests used.
- = Not test item-related

Liver weights (relative to body weights) were higher in a statistically significant manner in females administered 150 µg/dose and were considered to be related to mRNA-1653. Higher liver weights had no microscopic correlations.

Statistically significant higher (absolute and/or relative to body and/or brain weights) spleen weights occurred in males at ≥ 50 µg/dose and females at ≥ 10 µg/dose. These spleen weight changes were considered to be related to mRNA-1653 and had no microscopic correlations.

There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or secondary to the lower terminal body weight, and therefore, unrelated to administration of mRNA-1653.

4.3.2. Recovery Euthanasia Animals (Day 43)

(Table 2, Table 3, Table 4, Appendix 1, Appendix 2, and Appendix 3)

After 2 weeks of recovery, the mRNA-1653-related higher liver weight changes observed during the main study were still present in females administered 150 µg/dose of mRNA-1653 and had no microscopic correlations. These liver weight changes are summarized in Text Table 6. The higher spleen changes observed during the main study were not present in the recovery study.

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Text Table 6
Summary of Organ Weight Data – Scheduled Euthanasia (Day 43)

	Males	Females
Group	**4**	**4**
Dose (µg/dose)	**150**	**150**
No. Animals per Group	**5**	**5**
Terminal Body Weight	-2.0	-4.4
Liver (No. Weighed)[a]	5	5
Absolute value	-	8.62
% of body weight	-	**13.45**
% of brain weight	-	6.93

[a] All values expressed as percent difference of control group means.
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – $P \leq 0.05$; refer to data tables for actual significance levels and tests used.
- = Not test item-related

There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or secondary to the lower terminal body weight, and therefore, unrelated to administration of mRNA-1653.

4.4. Histopathology

4.4.1. Terminal Euthanasia Animals (Day 30)

(Table 5 and Appendix 4)

Microscopic changes related to administration of mRNA-1653 were seen at the injection site, liver, bone marrow, spleen, lymph nodes (popliteal, inguinal and iliac) and sciatic nerve which are summarized in Text Table 7.

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Text Table 7
Summary of Microscopic Findings – Scheduled Euthanasia (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**50**	**150**	**0**	**10**	**50**	**150**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Injection Site (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(1)[a]	(10)	(10)	(10)	(3)	(9)	(10)	(10)
Minimal	1	1	-	-	2	1	-	-
Mild	-	1	1	-	1	4	-	-
Moderate	-	8	5	5	-	4	6	5
Marked	-	-	4	5	-	-	4	5
Liver (No. Examined)	10	10	10	10	10	10	10	10
Vacuolation, hepatocellular	(1)	(1)	(2)	(7)	(2)	(1)	(2)	(9)
Minimal	1	1	2	3	2	1	2	5
Mild	-	-	-	4	-	-	-	4
Bone Marrow (No. Examined)	10	10	10	10	10	10	10	10
Increased hematopoiesis: myeloid	0	10	10	10	0	10	10	10
Minimal	-	10	7	3	-	10	8	5
Mild	-	-	3	7	-	-	2	5
Popliteal Lymph Node (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(0)	(9)	(8)	(10)	(0)	(10)	(9)	(9)
Minimal	-	1	3	2	-	3	1	4
Mild	-	8	5	7	-	7	6	3
Moderate	-	-	-	1	-	-	2	2
Inguinal Lymph Node (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(0)	(2)	(1)	(4)	(0)	(0)	(0)	(6)
Minimal	-	2	1	3	-	-	-	2
Mild	-	-	-	1	-	-	-	4
Lymph Node[b] (No. Examined)	0	1	1	3	0	0	2	4
Inflammation, mixed cell	(0)	(1)	(1)	(2)	(0)	(0)	(2)	(4)
Minimal	-	1	1	1	-	-	1	-
Mild	-	-	-	1	-	-	1	4
Sciatic Nerve (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(0)	(9)	(10)	(10)	(0)	(10)	(10)	(7)
Minimal	-	8	9	9	-	9	9	6
Mild	-	1	1	1	-	1	1	1
Spleen (No. Examined)	10	10	10	10	10	10	10	10
Decreased cellularity; periarteriolar lymphoid sheath	(0)	(2)	(4)	(7)	(0)	(1)	(2)	(7)
Minimal	-	2	4	3	-	1	2	6
Mild	-	-	-	4	-	-	-	1
Increased macrophages; periarteriolar lymphoid sheath	(0)	(0)	(3)	(5)	(0)	(0)	(2)	(7)
Minimal	-	-	3	5	-	-	2	7

[a] Numbers in parentheses represent the number of animals with the finding.
[b] Iliac lymph node

At the injection site, there was a minimal to marked mixed cell inflammation in both sexes administered reference and test items. The exacerbation of the mixed cell inflammation was

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considered to be related to mRNA-1653 at ≥ 10 µg/dose based on the increased incidence and severity compared to controls. The change occurred with an apparent dose-related increase in severity and was characterized by an infiltration of mostly neutrophils but also macrophages and lymphocytes in the intramuscular connective tissue and subcutis; edema, necrotic debris, hemorrhage and/or rare degenerated myofibers were also present. The injection site mixed cell inflammation correlated macroscopically with firm abnormal consistency, swelling and/or thick.

In the lymph node (popliteal, inguinal and/or iliac), minimal to moderate perinodal mixed cell inflammation was seen in both sexes at ≥ 10 µg/dose. Mixed cell inflammation occurred generally with an increased incidence and severity in the popliteal lymph node. The lymph node inflammation correlated macroscopically with enlargement. Minimal to mild mixed cell inflammation was also noted in the sciatic nerve of animals at ≥ 10 µg/dose in connective tissue surrounding the nerve. The lymph nodes and sciatic nerve inflammatory changes were regarded as secondary to the injection site inflammation.

In the liver, there was minimal to mild hepatocellular vacuolation in both sexes administered the reference item and mRNA-1653. The increased incidence and severity observed at 150 µg/dose was considered related to the administration of m-RNA-1653. It consisted of the presence of intracytoplasmic microvesicles with enlarged hepatocytes.

In the bone marrow, there was minimal to mild increased hematopoiesis of the myeloid lineage in both sexes at ≥ 10 µg/dose; this change was likely a reactive response to the inflammation observed at the injection site.

In the spleen, there was minimal to mild decreased cellularity of the periarteriolar lymphoid sheath often associated with an increase in macrophages in both sexes at 10, 50 and/or 150 µg/dose of mRNA-1653.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered unrelated to administration of mRNA-1653.

4.4.2. Recovery Euthanasia Animals (Day 43)

(Table 5 and Appendix 4)

After 2 weeks of recovery, the remaining RNA-1653-related microscopic changes were mixed cell inflammation around the popliteal lymph node and mononuclear cell infiltration around the sciatic nerve and at the injection site. The popliteal lymph node mixed cell inflammation occurred with a decreased incidence and/or severity indicating partial recovery. The sciatic nerve and injection site mononuclear cell infiltration had a low number of cells compared to the mixed cell inflammation observed in the main study indicating partial recovery. The incidence of these microscopic findings is presented in Text Table 8. Other mRNA-1653-related microscopic findings observed during the main study in the liver (hepatocellular vacuolation), inguinal and iliac lymph nodes (mixed cell inflammation), bone marrow (increased hematopoiesis, myeloid) and spleen (decreased cellularity and increased macrophages in the periarteriolar lymphoid sheath) were not present in the recovery study indicating reversibility.

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Text Table 8
Summary of Microscopic Findings – Scheduled Euthanasia (Day 43)

	Males		Females	
Group	**1**	**4**	**1**	**4**
Dose (µg/dose)	**0**	**150**	**0**	**150**
No. Animals Examined	**5**	**5**	**5**	**5**
Injection Site (No. Examined)	5	5	5	5
Infiltration, mononuclear cell	(0)[a]	(5)	(0)	(5)
Minimal	-	4	-	5
Mild	-	1	-	-
Popliteal Lymph Node (No. Examined)	5	5	5	5
Inflammation, mixed cell	(0)	(3)	(0)	(5)
Minimal	-	3	-	5
Nerve, sciatic (No. Examined)	5	5	5	5
Infiltration, mononuclear cell	(0)	(5)	(0)	(4)
Minimal	-	5	-	4

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

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered unrelated to administration of mRNA-1653.

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5. CONCLUSIONS

At the end of the main study, the microscopic changes related to administration of mRNA-1653 were seen in both sexes at the injection site, liver, bone marrow, spleen, lymph nodes (popliteal, inguinal and iliac) and sciatic nerve. A mixed cell inflammation was considered related to mRNA-1653 at the injection site (graded minimal to marked) at ≥ 10 µg/dose, in the popliteal, inguinal and/or iliac lymph nodes (graded minimal to moderate) at ≥ 10 µg/dose and in the sciatic nerve (graded minimal to mild) at ≥ 10 µg/dose. The mixed cell inflammation correlated macroscopically with firm abnormal consistency, swelling and/or thick at the injection site and with enlargement in the lymph nodes. The lymph nodes and sciatic nerve inflammatory changes were regarded as secondary to the injection site inflammation.

In the liver, minimal to mild hepatocellular vacuolation was considered related to mRNA-1653 at 150 µg/dose. In the bone marrow, minimal to mild increased hematopoiesis of the myeloid lineage occurred in both sexes at ≥ 10 µg/dose. This bone marrow change was likely a reactive response to the inflammation observed at the injection site. In the spleen, there was minimal to mild decreased cellularity of the periarteriolar lymphoid sheath often associated with an increase in macrophages in both sexes at 10, 50 and/or 150 µg/dose of mRNA-1653.

The remaining changes related to mRNA-1653 in the main study were higher liver weights in females at 150 µg/dose that had no microscopic correlations, and higher spleen weights in males at ≥ 50 µg/dose and females at ≥ 10 µg/dose that had no microscopic correlations.

After 2 weeks of recovery, the remaining RNA-1653-related microscopic changes were mixed cell inflammation around the popliteal lymph node and mononuclear cell infiltration around the sciatic nerve and at injection site. The popliteal lymph node mixed cell inflammation occurred with a decreased incidence and/or severity indicating partial recovery. The sciatic nerve and injection site mononuclear cell infiltration had a lower number of cells compared to the mixed cell inflammation observed in the main study indicating partial recovery. Other mRNA-1653-related microscopic findings observed during the main study in the liver (hepatocellular vacuolation), inguinal and iliac lymph nodes (mixed cell inflammation), bone marrow (increased hematopoiesis, myeloid) and spleen (decreased cellularity and increased macrophages in the periarteriolar lymphoid sheath) were not present in the recovery study indicating reversibility.

Appendix 18

6. REPORT APPROVAL

(b) (6) Date: 10 OcT 2017

(b) (6)

Appendix 18

Table 1
Incidence of Necropsy Findings by Organ/Group/Sex

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Incidence of Necropsy Findings by Organ/Group/Sex Explanation Page

Abbreviation	Description
GALT	Gut Associated Lymphoid Tissue

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BODY CAVITY, NASAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE MARROW								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE, FEMUR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE, STERNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
Abnormal appearance; bent	0	0	0	0	0	0	0	0
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	10	10	10	10	10
EYE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GALT								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

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Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, ADRENAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
Focus; dark	0	0	0	0	0	0	0	0
GLAND, HARDERIAN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, MAMMARY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PARATHYROID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PITUITARY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PROSTATE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, SEMINAL VESICLE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, THYROID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
HEART								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
KIDNEY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	8	10	10	9	10	10	8	10

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Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
KIDNEY (Continued...)								
Dilatation; pelvis	1	0	0	0	0	0	0	0
Focus; dark	0	0	0	1	0	0	0	0
Focus; depressed	1	0	0	1	0	0	0	0
Focus; pale	0	0	0	1	0	0	0	0
Cyst; pale	0	0	0	0	0	0	1	0
Discoloration; dark	0	0	0	0	0	0	1	0
LARGE INTESTINE, CECUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, COLON								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, RECTUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	9	10	10
Parasite	0	0	0	0	0	1	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	4	6	9	9	7	8	5
Focus; dark	0	0	1	0	0	0	0	0
Focus; depressed	0	0	1	0	0	0	0	0
Focus; pale	2	6	4	1	1	3	2	5
LUNG								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	7	6	5	8	9	10	10	8
Focus; dark	3	3	4	1	1	0	0	2
Focus; pale	0	1	1	2	0	0	0	0
Discoloration; pale	0	0	1	0	0	0	0	0
LYMPH NODE								

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE (Continued...)								
Submitted	0	1	1	3	0	0	2	4
Enlargement	.	1	1	3	.	.	2	4
LYMPH NODE, INGUINAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	9	7	10	10	10	7
Enlargement	0	1	1	3	0	0	0	3
LYMPH NODE, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	10	10	9	8	9	9	9
Enlargement	1	0	0	1	2	1	1	1
Focus; dark	0	0	0	0	0	0	0	0
LYMPH NODE, MESENTERIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LYMPH NODE, POPLITEAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	7	6	9	9	10	8	7
Focus; dark	1	0	1	0	0	0	1	0
Enlargement	0	3	4	1	0	0	1	3
Discoloration; dark	0	0	0	0	1	0	0	0
MUSCLE, SKELETAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, OPTIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, SCIATIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
OVARY								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	9	10	10	10
Cyst; pale	.	.	.	.	1	0	0	0

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
PANCREAS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SITE, INJECTION								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	1	0	0	9	4	0	0
Abnormal consistency; firm	0	8	10	9	0	6	10	10
Swelling	0	4	6	10	0	1	6	9
Thick	0	0	0	3	0	0	1	1
Focus; dark	0	0	0	0	1	0	0	0
Material accumulation; clot	0	0	0	0	0	0	1	0
SKIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	9	10	10	10
Scab; pale	0	0	0	0	1	0	0	0
SMALL INTESTINE, DUODENUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, ILEUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, JEJUNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
Focus; dark	0	0	0	0	0	0	0	0
SPINAL CORD, CERVICAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, LUMBAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, THORACIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SPLEEN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	10	10	10	10	9	10
Nodule	0	1	0	0	0	0	0	0
Focus; pale	0	0	0	0	0	0	1	0
Adhesion	0	0	0	0	0	0	1	0
STOMACH								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	8	10	10
Focus; dark	0	0	0	0	0	1	0	0
Focus; pale	0	0	0	0	0	1	0	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	8	8	7	8	10	8	10	7
Focus; dark	2	2	3	2	0	2	0	3
TONGUE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
TRACHEA								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
URINARY BLADDER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
UTERUS								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
VAGINA								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
ARTERY, AORTA				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BODY CAVITY, NASAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE MARROW				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, FEMUR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, STERNUM				
Submitted	5	5	5	5
No Visible Lesions	5	4	5	5
Abnormal appearance; bent	0	1	0	0
BRAIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
CERVIX				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
EPIDIDYMIS				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
ESOPHAGUS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
EYE				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GALT				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, ADRENAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	4	5
Focus; dark	0	0	1	0
GLAND, HARDERIAN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, MAMMARY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PARATHYROID				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PITUITARY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PROSTATE				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, SALIVARY, MANDIBULAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, SEMINAL VESICLE				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, THYROID				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
HEART				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
KIDNEY				
Submitted	5	5	5	5
No Visible Lesions	5	4	4	4

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
KIDNEY (Continued...)				
Dilatation; pelvis	0	1	0	1
Focus; dark	0	0	0	0
Focus; depressed	0	0	1	0
Focus; pale	0	0	0	0
Cyst; pale	0	0	0	0
Discoloration; dark	0	0	0	0
LARGE INTESTINE, CECUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, COLON				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, RECTUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Parasite	0	0	0	0
LARYNX				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LIVER				
Submitted	5	5	5	5
No Visible Lesions	3	5	4	5
Focus; dark	0	0	0	0
Focus; depressed	0	0	0	0
Focus; pale	2	0	1	0
LUNG				
Submitted	5	5	5	5
No Visible Lesions	5	3	5	5
Focus; dark	0	0	0	0
Focus; pale	0	2	0	0
Discoloration; pale	0	0	0	0
LYMPH NODE				

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE (Continued...)				
Submitted	0	0	0	0
LYMPH NODE, INGUINAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Enlargement	0	0	0	0
LYMPH NODE, MANDIBULAR				
Submitted	5	5	5	5
No Visible Lesions	5	4	0	0
Enlargement	0	0	0	0
Focus; dark	0	1	5	5
LYMPH NODE, MESENTERIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LYMPH NODE, POPLITEAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	3
Focus; dark	0	0	0	0
Enlargement	0	0	0	2
Discoloration; dark	0	0	0	0
MUSCLE, SKELETAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, OPTIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, SCIATIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
OVARY				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
Cyst; pale	.	.	0	0

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	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
Abnormal consistency; firm	0	0	0	0
Swelling	0	0	0	0
Thick	0	0	0	0
Focus; dark	0	0	0	0
Material accumulation; clot	0	0	0	0
SKIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Scab; pale	0	0	0	0
SMALL INTESTINE, DUODENUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, ILEUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, JEJUNUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	4	5
Focus; dark	0	0	1	0
SPINAL CORD, CERVICAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, LUMBAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, THORACIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
SPLEEN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Nodule	0	0	0	0
Focus; pale	0	0	0	0
Adhesion	0	0	0	0
STOMACH				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Focus; dark	0	0	0	0
Focus; pale	0	0	0	0
TESTIS				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
THYMUS				
Submitted	5	5	5	5
No Visible Lesions	4	5	1	1
Focus; dark	1	0	4	4
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 18
Table 1

Incidence of Necropsy Findings by Organ/Group/Sex
5002033

Key Page

Measurement/Statistics

Measurement	Descriptive	Comparative	Arithmetic/Adjusted	Transformation
Pathology Observation	Count Positives			

Group Information

Short Name	Long Name	Report Headings		
1	1	0	ug/dose	Group 1
2	2	10	ug/dose	Group 2
3	3	50	ug/dose	Group 3
4	4	150	ug/dose	Group 4

Removal Reason Grouping

Grouping Name	Abbreviation	Removal Reasons
TERMINAL EUTHANASIA	TERM	TERMINAL EUTHANASIA
RECOVERY EUTHANASIA	REC	RECOVERY EUTHANASIA

Appendix 18

Table 2
Summary of Absolute Organ Weights

Appendix 18
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	509.2	2.1829	1.1342	0.06651	0.01537	1.2266	0.02308
	SD	37.7	0.0540	0.0774	0.00528	0.00090	0.1969	0.00577
	N	10	10	10	10	10	10	10
2M	Mean	478.9	2.2204	1.1345	0.06227	0.01412	1.2568	0.02190
	SD	37.1	0.0591	0.0973	0.01041	0.00155	0.2297	0.00379
	N	10	10	10	10	10	10	10
	%Diff G1	-6.0	1.7179	0.0265	-6.37498	-8.13273	2.4621	-5.11265
3M	Mean	482.6	2.1868	1.1029	0.06348	0.01287c	1.1674	0.02302
	SD	46.8	0.0888	0.0488	0.00890	0.00132	0.1793	0.00274
	N	10	10	10	10	10	10	10
	%Diff G1	-5.2	0.1787	-2.7597	-4.55571	-16.26545	-4.8263	-0.25997
4M	Mean	456.0b	2.1714	1.0853	0.07283	0.01326b	1.1638	0.02090
	SD	18.9	0.0659	0.0572	0.01106	0.00168	0.1961	0.00489
	N	10	10	10	10	10	10	10
	%Diff G1	-10.4	-0.5268	-4.3114	9.50233	-13.72804	-5.1198	-9.44541

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

Appendix 18
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	Mean	1.7243	3.0488	15.0571	1.7365	--	0.9533	3.7928
	SD	0.1207	0.3630	2.9466	0.1586	--	0.1408	0.2124
	N	10	10	10	10	--	10	10
2M	Mean	1.6182	2.9075	13.8250	1.7170	--	0.9881	3.7446
	SD	0.0875	0.1859	1.8288	0.1069	--	0.1542	0.2964
	N	10	10	10	10	--	10	10
	%Diff G1	-6.1532	-4.6346	-8.1829	-1.1229	--	3.6505	-1.2708
3M	Mean	1.5756a	3.0435	14.7776	1.7188	--	1.0979	3.5984
	SD	0.1360	0.2607	1.8828	0.0771	--	0.1444	0.2953
	N	10	10	10	10	--	10	10
	%Diff G1	-8.6238	-0.1738	-1.8563	-1.0193	--	15.1684	-5.1255
4M	Mean	1.5719a	3.0316	14.4609	1.6902	--	1.0943	3.5640
	SD	0.1269	0.1945	1.4740	0.0717	--	0.1357	0.3330
	N	10	10	10	10	--	10	10
	%Diff G1	-8.8384	-0.5642	-3.9596	-2.6663	--	14.7907	-6.0325

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

Appendix 18
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		THYMUS g	UTERUS g
1M	Mean	0.5287	--
	SD	0.1486	--
	N	10	--
2M	Mean	0.5611	--
	SD	0.1019	--
	N	10	--
	%Diff G1	6.1282	--
3M	Mean	0.5132	--
	SD	0.0766	--
	N	10	--
	%Diff G1	-2.9317	--
4M	Mean	0.5013	--
	SD	0.1193	--
	N	10	--
	%Diff G1	-5.1825	--

Appendix 18
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		Body Weight g	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1F	Mean	290.7	1.9886	--	0.06839	0.01587	--	0.01690
	SD	11.5	0.0775	--	0.00775	0.00256	--	0.00307
	N	10	10	--	10	10	--	10
2F	Mean	287.8	2.0468	--	0.06691	0.01674	--	0.01813
	SD	21.9	0.1076	--	0.00985	0.00307	--	0.00197
	N	10	10	--	10	10	--	10
	%Diff G1	-1.0	2.9267	--	-2.16406	5.48204	--	7.27811
3F	Mean	278.5	1.9764	--	0.06584	0.01424	--	0.01692
	SD	19.4	0.0689	--	0.00737	0.00156	--	0.00271
	N	10	10	--	10	10	--	10
	%Diff G1	-4.2	-0.6135	--	-3.72862	-10.27095	--	0.11834
4F	Mean	273.3	1.9903	--	0.07276	0.01462	--	0.01698
	SD	13.0	0.0476	--	0.01329	0.00154	--	0.00427
	N	10	10	--	10	10	--	10
	%Diff G1	-6.0	0.0855	--	6.38982	-7.87650	--	0.47337

Appendix 18
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	Mean	1.0869	1.8123	8.3382	1.2758	0.1210	0.5710	--
	SD	0.0993	0.1697	0.7287	0.0560	0.0632	0.0563	--
	N	10	10	10	10	10	10	--
2F	Mean	1.0280	1.8450	8.3771	1.2853	0.1093	0.7130b	--
	SD	0.0699	0.2048	0.6818	0.1079	0.0143	0.0757	--
	N	10	10	10	10	10	10	--
	%Diff G1	-5.4191	1.8043	0.4665	0.7446	-9.6694	24.8687	--
3F	Mean	1.0064	1.8466	8.1972	1.2424	0.1029	0.7488c	--
	SD	0.0632	0.1107	1.0659	0.0633	0.0205	0.1031	--
	N	10	10	10	10	10	10	--
	%Diff G1	-7.4064	1.8926	-1.6910	-2.6180	-14.9587	31.1384	--
4F	Mean	0.9893	1.8543	8.5647	1.2643	0.0990	0.6930b	--
	SD	0.1059	0.1176	0.5545	0.0928	0.0259	0.0954	--
	N	10	10	10	10	10	10	--
	%Diff G1	-8.9797	2.3175	2.7164	-0.9014	-18.1818	21.3660	--

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

Appendix 18
Table 2
Summary of Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		THYMUS g	UTERUS g
1F	Mean	0.4712	0.5035
	SD	0.0714	0.0612
	N	10	10
2F	Mean	0.4521	0.7324
	SD	0.0864	0.3520
	N	10	10
	%Diff G1	-4.0535	45.4618
3F	Mean	0.4614	0.6299
	SD	0.1276	0.3269
	N	10	10
	%Diff G1	-2.0798	25.1043
4F	Mean	0.4440	0.8358
	SD	0.0953	0.3293
	N	10	10
	%Diff G1	-5.7725	65.9980

Appendix 18
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	519.6	2.1974	1.2276	0.06362	0.01456	1.3190	0.02408
	SD	32.1	0.0548	0.0524	0.00483	0.00121	0.1908	0.00310
	N	5	5	5	5	5	5	5
4M	Mean	509.2	2.2234	1.1614	0.06442	0.01358	1.3372	0.01986
	SD	32.9	0.1300	0.0398	0.01008	0.00183	0.0932	0.00340
	N	5	5	5	5	5	5	5
	%Diff G1	-2.0	1.1832	-5.3926	1.25747	-6.73077	1.3798	-17.52492

Appendix 18
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	Mean	1.6908	3.2134	14.4982	1.7580	--	0.8970	3.8370
	SD	0.1455	0.2972	1.6774	0.0732	--	0.1596	0.0938
	N	5	5	5	5	--	5	5
4M	Mean	1.5918	2.9214	13.8620	1.6556	--	0.9924	3.5642a
	SD	0.1442	0.2891	1.2007	0.1680	--	0.1201	0.1776
	N	5	5	5	5	--	5	5
	%Diff G1	-5.8552	-9.0869	-4.3881	-5.8248	--	10.6355	-7.1097

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

Appendix 18
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		THYMUS g	UTERUS g
1M	Mean	0.4736	--
	SD	0.1014	--
	N	5	--
4M	Mean	0.4592	--
	SD	0.0501	--
	N	5	--
	%Diff G1	-3.0405	--

Appendix 18
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 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	307.0	1.9772	--	0.06694	0.01580	--	0.01584
	SD	8.3	0.0438	--	0.00422	0.00212	--	0.00196
	N	5	5	--	5	5	--	5
4F	Mean	293.6	2.0176	--	0.06652	0.01494	--	0.01412
	SD	26.7	0.1483	--	0.00830	0.00197	--	0.00338
	N	5	5	--	5	5	--	5
	%Diff G1	-4.4	2.0433	--	-0.62743	-5.44304	--	-10.85859

Appendix 18
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	Mean	1.2172	1.9330	8.0992	1.3258	0.0878	0.6414	--
	SD	0.0643	0.2052	0.3850	0.0406	0.0195	0.1031	--
	N	5	5	5	5	5	5	--
4F	Mean	1.1294	1.8994	8.7976	1.3524	0.0890	0.5390	--
	SD	0.0933	0.1877	1.1764	0.0370	0.0195	0.0884	--
	N	5	5	5	5	5	5	--
	%Diff G1	-7.2133	-1.7382	8.6231	2.0063	1.3667	-15.9651	--

Appendix 18
Table 2
Summary of Absolute Organ Weights: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		THYMUS g	UTERUS g
1F	Mean	0.4534	0.8344
	SD	0.1152	0.3727
	N	5	5
4F	Mean	0.3160a	0.4740
	SD	0.0238	0.0707
	N	5	5
	%Diff G1	-30.3044	-43.1927

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

Appendix 18

Table 3
Summary of Organ Weights Relative to Body Weight

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.43036	0.22358	0.01314	0.00303	0.24233	0.00451	0.33908
	SD	0.02651	0.01907	0.00161	0.00026	0.04588	0.00101	0.01648
	N	10	10	10	10	10	10	10
2M	Mean	0.46624	0.23744	0.01309	0.00295	0.26158	0.00456	0.33910
	SD	0.03873	0.01972	0.00245	0.00029	0.03639	0.00062	0.02356
	N	10	10	10	10	10	10	10
	%Diff G1	8.33847	6.20007	-0.38311	-2.59516	7.94318	1.16574	0.00395
3M	Mean	0.45656	0.23064	0.01325	0.00268	0.24205	0.00478	0.32779
	SD	0.04194	0.02590	0.00204	0.00034	0.03185	0.00049	0.02752
	N	10	10	10	10	10	10	10
	%Diff G1	6.08786	3.16138	0.82649	-11.44009	-0.11494	5.98167	-3.32972
4M	Mean	0.47681a	0.23861	0.01599a	0.00290	0.25599	0.00459	0.34462
	SD	0.02237	0.01969	0.00250	0.00032	0.04733	0.00107	0.02250
	N	10	10	10	10	10	10	10
	%Diff G1	10.79486	6.72507	21.67497	-4.16814	5.63659	1.84044	1.63391

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

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.59820	2.93967	0.34158	--	0.18797	0.74878	0.10304
	SD	0.04935	0.36303	0.02602	--	0.03078	0.07360	0.02304
	N	10	10	10	--	10	10	10
2M	Mean	0.60918	2.88217	0.35918	--	0.20728	0.78378	0.11778
	SD	0.04504	0.25197	0.01602	--	0.03443	0.05915	0.02177
	N	10	10	10	--	10	10	10
	%Diff G1	1.83492	-1.95607	5.15410	--	10.27292	4.67468	14.30374
3M	Mean	0.63411	3.05804	0.35872	--	0.22896a	0.74942	0.10718
	SD	0.06541	0.19042	0.03334	--	0.03337	0.06936	0.01998
	N	10	10	10	--	10	10	10
	%Diff G1	6.00213	4.02650	5.01862	--	21.80424	0.08580	4.01648
4M	Mean	0.66495a	3.16937	0.37105	--	0.23982b	0.78269	0.11027
	SD	0.03536	0.27609	0.01825	--	0.02623	0.07594	0.02747
	N	10	10	10	--	10	10	10
	%Diff G1	11.15870	7.81367	8.62931	--	27.58013	4.52913	7.02133

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

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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 18
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	Mean	0.68493	--	0.02349	0.00545	--	0.00581	0.37411
	SD	0.03607	--	0.00199	0.00080	--	0.00105	0.03373
	N	10	--	10	10	--	10	10
2F	Mean	0.71529	--	0.02333	0.00588	--	0.00630	0.35809
	SD	0.06974	--	0.00353	0.00142	--	0.00049	0.02401
	N	10	--	10	10	--	10	10
	%Diff G1	4.43191	--	-0.68327	7.89223	--	8.41455	-4.28048
3F	Mean	0.71326	--	0.02370	0.00513	--	0.00607	0.36215
	SD	0.06254	--	0.00279	0.00056	--	0.00084	0.02278
	N	10	--	10	10	--	10	10
	%Diff G1	4.13545	--	0.91887	-6.00373	--	4.52608	-3.19471
4F	Mean	0.73013	--	0.02656	0.00535	--	0.00622	0.36175
	SD	0.04610	--	0.00420	0.00048	--	0.00157	0.03164
	N	10	--	10	10	--	10	10
	%Diff G1	6.59979	--	13.08100	-1.99488	--	7.01466	-3.30214

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	Mean	0.62296	2.86516	0.43966	0.04126	0.19685	--	0.16262
	SD	0.04626	0.16610	0.02904	0.01981	0.02231	--	0.02796
	N	10	10	10	10	10	--	10
2F	Mean	0.64089	2.91426	0.44741	0.03825	0.24881b	--	0.15733
	SD	0.04760	0.17097	0.03207	0.00621	0.03183	--	0.02908
	N	10	10	10	10	10	--	10
	%Diff G1	2.87695	1.71376	1.76351	-7.30408	26.39718	--	-3.25092
3F	Mean	0.66485	2.93405	0.44734	0.03707	0.27009c	--	0.16528
	SD	0.04557	0.22861	0.02779	0.00762	0.04383	--	0.04367
	N	10	10	10	10	10	--	10
	%Diff G1	6.72426	2.40457	1.74767	-10.16334	37.20510	--	1.63829
4F	Mean	0.67897a	3.13279b	0.46283	0.03607	0.25328b	--	0.16331
	SD	0.03964	0.10935	0.03096	0.00854	0.02920	--	0.03881
	N	10	10	10	10	10	--	10
	%Diff G1	8.99008	9.34092	5.26905	-12.58273	28.66458	--	0.42447

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

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		UTERUS %
1F	Mean	0.17350
	SD	0.02267
	N	10
2F	Mean	0.25835
	SD	0.13369
	N	10
	%Diff G1	48.90489
3F	Mean	0.22721
	SD	0.12008
	N	10
	%Diff G1	30.95963
4F	Mean	0.30921
	SD	0.13087
	N	10
	%Diff G1	78.22227

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.42384	0.23656	0.01229	0.00280	0.25310	0.00465	0.32533
	SD	0.02065	0.00831	0.00133	0.00020	0.02595	0.00067	0.01759
	N	5	5	5	5	5	5	5
4M	Mean	0.43767	0.22888	0.01267	0.00266	0.26350	0.00389	0.31258
	SD	0.03146	0.01731	0.00200	0.00024	0.02536	0.00056	0.01951
	N	5	5	5	5	5	5	5
	%Diff G1	3.26413	-3.24709	3.10657	-5.13465	4.11111	-16.22595	-3.91919

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.61956	2.78476	0.33891	--	0.17253	0.74006	0.09139
	SD	0.05989	0.17497	0.01595	--	0.02846	0.03519	0.02063
	N	5	5	5	--	5	5	5
4M	Mean	0.57313	2.72181	0.32466	--	0.19598	0.70183	0.08999
	SD	0.03246	0.14838	0.01748	--	0.03048	0.04950	0.00464
	N	5	5	5	--	5	5	5
	%Diff G1	-7.49395	-2.26077	-4.20552	--	13.59037	-5.16534	-1.53454

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		UTERUS %
1M	Mean	--
	SD	--
	N	--
4M	Mean	--
	SD	--
	N	--
	%Diff G1	--

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	Mean	0.64435	--	0.02183	0.00516	--	0.00517	0.39670
	SD	0.01998	--	0.00168	0.00077	--	0.00073	0.02346
	N	5	--	5	5	--	5	5
4F	Mean	0.68957	--	0.02262	0.00512	--	0.00479	0.38624
	SD	0.05344	--	0.00133	0.00079	--	0.00085	0.03648
	N	5	--	5	5	--	5	5
	%Diff G1	7.01748	--	3.63316	-0.74731	--	-7.46510	-2.63619

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	Mean	0.63002	2.63975	0.43204	0.02851	0.20871	--	0.14799
	SD	0.06880	0.14485	0.01545	0.00573	0.03109	--	0.03847
	N	5	5	5	5	5	--	5
4F	Mean	0.64822	2.99491a	0.46387	0.03055	0.18325	--	0.10848
	SD	0.05243	0.30545	0.04719	0.00719	0.02301	--	0.01348
	N	5	5	5	5	5	--	5
	%Diff G1	2.88872	13.45437	7.36709	7.15326	-12.19857	--	-26.69970

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

Appendix 18
Table 3
Summary of Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		UTERUS %
1F	Mean	0.27111
	SD	0.11990
	N	5
4F	Mean	0.16220
	SD	0.02623
	N	5
	%Diff G1	-40.17277

Appendix 18

Table 4
Summary of Organ Weights Relative to Brain Weight

Appendix 18
Table 4
Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	51.95851	3.04915	0.70497	56.14193	1.05543	78.96855	139.46490
	SD	3.29219	0.25943	0.05239	8.65488	0.25708	4.71157	14.28206
	N	10	10	10	10	10	10	10
2M	Mean	51.12308	2.80467	0.63618	56.68506	0.98629	72.94975	131.04493
	SD	4.48331	0.46810	0.07035	11.05841	0.16704	4.83018	9.22151
	N	10	10	10	10	10	10	10
	%Diff G1	-1.60789	-8.01784	-9.75695	0.96742	-6.55134	-7.62177	-6.03734
3M	Mean	50.49508	2.90133	0.58951b	53.31933	1.05200	72.15224a	139.27980
	SD	2.77763	0.37463	0.06636	7.56868	0.11358	6.85297	12.11703
	N	10	10	10	10	10	10	10
	%Diff G1	-2.81655	-4.84775	-16.37704	-5.02761	-0.32555	-8.63167	-0.13272
4M	Mean	50.00461	3.34685	0.61114a	53.63243	0.96053	72.39489a	139.74413
	SD	2.64283	0.43830	0.07949	9.15261	0.21236	5.58155	10.06981
	N	10	10	10	10	10	10	10
	%Diff G1	-3.76050	9.76367	-13.30978	-4.46991	-8.99234	-8.32440	0.20022

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

Appendix 18
Table 4
Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	Mean	688.91370	79.52588	--	43.63288	173.81589	24.16539	--
	SD	127.65861	6.61343	--	6.11008	10.11568	6.47023	--
	N	10	10	--	10	10	10	--
2M	Mean	624.04749	77.38221	--	44.48643	168.78999	25.23355	--
	SD	93.88268	5.34446	--	6.75893	14.56423	4.24479	--
	N	10	10	--	10	10	10	--
	%Diff G1	-9.41572	-2.69556	--	1.95620	-2.89150	4.42023	--
3M	Mean	676.90400	78.68745	--	50.33207	164.94528	23.53776	--
	SD	94.26734	4.25389	--	7.06076	16.75121	3.96102	--
	N	10	10	--	10	10	10	--
	%Diff G1	-1.74328	-1.05428	--	15.35354	-5.10345	-2.59722	--
4M	Mean	666.82511	77.87834	--	50.38452	164.31760	23.09465	--
	SD	74.34558	3.50588	--	5.92408	16.28695	5.50819	--
	N	10	10	--	10	10	10	--
	%Diff G1	-3.20629	-2.07170	--	15.47374	-5.46457	-4.43087	--

Appendix 18
Table 4
Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	Mean	--	3.44509	0.80011	--	0.85368	54.71653	91.32104
	SD	--	0.41866	0.14006	--	0.17158	5.18820	9.86953
	N	--	10	10	--	10	10	10
2F	Mean	--	3.27863	0.81985	--	0.89027	50.29414	90.39129
	SD	--	0.53050	0.15215	--	0.12856	3.58712	11.31987
	N	--	10	10	--	10	10	10
	%Diff G1	--	-4.83189	2.46772	--	4.28645	-8.08236	-1.01811
3F	Mean	--	3.32759	0.72203	--	0.85559	51.02233	93.47398
	SD	--	0.31208	0.09125	--	0.13122	4.34201	5.54899
	N	--	10	10	--	10	10	10
	%Diff G1	--	-3.41063	-9.75818	--	0.22459	-6.75151	2.35756
4F	Mean	--	3.65664	0.73492	--	0.85185	49.78404	93.19786
	SD	--	0.67356	0.07919	--	0.20237	5.96262	5.98852
	N	--	10	10	--	10	10	10
	%Diff G1	--	6.14052	-8.14753	--	-0.21432	-9.01462	2.05519

Appendix 18
Table 4
Summary of Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	Mean	419.70333	64.27184	6.03921	28.75383	--	23.63518	25.35901
	SD	38.51260	4.28157	2.94375	3.03348	--	2.94543	3.26919
	N	10	10	10	10	--	10	10
2F	Mean	410.96467	62.90735	5.34826	34.92000a	--	22.09060	35.66189
	SD	45.96752	5.73269	0.70577	4.14173	--	4.08065	16.69502
	N	10	10	10	10	--	10	10
	%Diff G1	-2.08211	-2.12300	-11.44108	21.44471	--	-6.53510	40.62809
3F	Mean	415.62405	62.96786	5.20976	38.00626c	--	23.42855	31.58064
	SD	59.11624	4.52765	1.05026	5.91302	--	6.66167	15.36798
	N	10	10	10	10	--	10	10
	%Diff G1	-0.97194	-2.02885	-13.73452	32.17808	--	-0.87428	24.53421
4F	Mean	430.94601	63.55001	4.98632	34.84122a	--	22.27550	41.85829
	SD	35.69728	4.82184	1.35395	4.95481	--	4.57921	16.13954
	N	10	10	10	10	--	10	10
	%Diff G1	2.67872	-1.12309	-17.43429	21.17073	--	-5.75279	65.06279

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

Appendix 18
Table 4
Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	55.86180	2.89834	0.66295	59.89430	1.09491	76.89573	146.12276
	SD	1.78648	0.25664	0.05844	7.38229	0.12757	5.50922	11.37055
	N	5	5	5	5	5	5	5
4M	Mean	52.44329	2.89521	0.61195	60.45905	0.89034a	71.74599	131.44025
	SD	4.55940	0.39525	0.08306	7.38423	0.11377	7.08522	11.16420
	N	5	5	5	5	5	5	5
	%Diff G1	-6.11958	-0.10779	-7.69286	0.94290	-18.68371	-6.69703	-10.04806

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

Appendix 18
Table 4
Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	Mean	659.15779	79.98066	--	40.74511	174.66207	21.58082	--
	SD	66.10586	1.59877	--	6.67162	4.36759	4.85346	--
	N	5	5	--	5	5	5	--
4M	Mean	626.05511	74.54598	--	44.92236	160.71381a	20.66958	--
	SD	75.82381	7.51119	--	7.48740	11.51969	2.09149	--
	N	5	5	--	5	5	5	--
	%Diff G1	-5.02197	-6.79500	--	10.25217	-7.98585	-4.22245	--

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

Appendix 18
Table 4
Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	Mean	--	3.38595	0.79804	--	0.80105	61.61303	97.71425
	SD	--	0.20967	0.09514	--	0.09754	4.08438	9.36720
	N	--	5	5	--	5	5	5
4F	Mean	--	3.30401	0.74370	--	0.69726	56.32757	94.46934
	SD	--	0.40325	0.11659	--	0.13991	7.44176	10.37993
	N	--	5	5	--	5	5	5
	%Diff G1	--	-2.42011	-6.81004	--	-12.95631	-8.57846	-3.32081

Appendix 18
Table 4
Summary of Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item

Group 4 - mRNA-1653 150 µg/dose

Group / Sex		LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	Mean	409.67189	67.06893	4.44944	32.45869	--	22.88168	41.90513
	SD	18.59824	2.10912	1.02928	5.31383	--	5.53254	18.03551
	N	5	5	5	5	--	5	5
4F	Mean	438.06363	67.27778	4.43878	26.87745	--	15.75907a	23.60777
	SD	69.98035	4.53741	1.04273	5.23576	--	1.94582	4.15352
	N	5	5	5	5	--	5	5
	%Diff G1	6.93036	0.31139	-0.23955	-17.19491	--	-31.12801	-43.66377

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

Appendix 18

Table 5
Summary of Microscopic Gradings by Organ/Group/Sex

Appendix 18

Summary of Microscopic Gradings by Organ/Group/Sex Explanation Page

Abbreviation	Description
GALT	Gut Associated Lymphoid Tissue

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE MARROW								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	0	0	0	10	0	0	0
Increased hematopoiesis; myeloid	0	10	10	10	0	10	10	10
.... minimal	0	10	7	3	0	10	8	5
.... mild	0	0	3	7	0	0	2	5
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

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
CERVIX (Continued...)								
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	.	.	10	10	.	.	10
EYE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GALT								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, ADRENAL								
Examined	10	0	0	10	10	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

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	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	10	0	0	10	10	0	0	9
No Visible Lesions	10	.	.	10	10	.	.	9
Not Examined: Not Present In Section.	0	0	0	0	0	0	0	1
GLAND, PITUITARY								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, PROSTATE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, SEMINAL VESICLE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
GLAND, THYROID								

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, THYROID (Continued...)								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
HEART								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
KIDNEY								
Examined	10	0	0	10	10	0	2	10
No Visible Lesions	3	.	.	6	8	.	0	10
Amphophilic vacuolar tubular carcinoma	0	.	.	0	0	.	1	0
Cyst	2	.	.	1	0	.	1	0
.... minimal	1	.	.	0	0	.	1	0
.... mild	1	.	.	0	0	.	0	0
.... moderate	0	.	.	1	0	.	0	0
Inflammation; interstitial	4	.	.	1	0	.	0	0
.... minimal	3	.	.	0	0	.	0	0
.... mild	1	.	.	1	0	.	0	0
Basophilia; tubular	1	.	.	3	2	.	1	0
.... minimal	1	.	.	3	2	.	1	0
Dilatation; pelvis	1	.	.	0	0	.	0	0

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
KIDNEY (Continued...)								
.... mild	1	.	.	0	0	.	0	0
LARGE INTESTINE, CECUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
LARGE INTESTINE, COLON								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
LARGE INTESTINE, RECTUM								
Examined	10	0	0	10	10	1	0	10
No Visible Lesions	10	.	.	10	10	1	.	10
LIVER								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	8	5	5	3	7	6	5	1
Necrosis	0	0	1	1	1	0	1	1
.... minimal	0	0	0	1	0	0	1	0
.... mild	0	0	0	0	1	0	0	1
.... moderate	0	0	1	0	0	0	0	0
Infiltration, mononuclear cell	1	1	0	0	1	0	1	1
.... minimal	1	1	0	0	1	0	1	1

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LIVER (Continued...)								
Tension lipidosis	0	3	2	0	1	3	2	0
.... minimal	0	3	2	0	1	3	2	0
Vacuolation, hepatocellular	1	1	2	7	2	1	2	9
.... minimal	1	1	2	3	2	1	2	5
.... mild	0	0	0	4	0	0	0	4
LUNG								
Examined	10	4	5	10	10	0	0	10
No Visible Lesions	6	0	2	8	6	.	.	8
Hemorrhage	1	1	0	0	2	.	.	0
.... minimal	0	1	0	0	1	.	.	0
.... mild	1	0	0	0	1	.	.	0
Macrophage aggregation	2	1	0	2	1	.	.	1
.... minimal	2	1	0	2	1	.	.	1
Infiltration, mixed cell	1	3	3	0	1	.	.	1
.... minimal	1	3	3	0	1	.	.	1
LYMPH NODE								
Examined	0	1	1	3	0	0	2	4
Inflammation, mixed cell	.	1	1	2	.	.	2	4
.... minimal	.	1	1	1	.	.	1	0

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE (Continued...)								
.... mild	.	0	0	1	.	.	1	4
Hyperplasia; lymphoid	.	1	0	1	.	.	0	0
.... mild	.	1	0	1	.	.	0	0
LYMPH NODE, INGUINAL								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	8	9	6	9	9	10	3
Not Examined: Not Present In Wet Tissues.	0	0	0	0	0	0	0	0
Inflammation, mixed cell	0	2	1	4	0	0	0	6
.... minimal	0	2	1	3	0	0	0	2
.... mild	0	0	0	1	0	0	0	4
Erythrocytosis	0	0	0	1	1	1	0	1
.... minimal	0	0	0	1	1	1	0	1
LYMPH NODE, MANDIBULAR								
Examined	10	0	0	10	10	1	1	10
No Visible Lesions	9	.	.	9	8	0	1	9
Hyperplasia; lymphoid	1	.	.	1	2	0	0	1
.... minimal	1	.	.	1	2	0	0	1
Erythrocytosis	0	.	.	0	0	1	0	0
.... minimal	0	.	.	0	0	1	0	0

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, MANDIBULAR (Continued...)								
.... mild	0	.	.	0	0	0	0	0
LYMPH NODE, MESENTERIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	8	.	.	10
Erythrocytosis	0	.	.	0	2	.	.	0
.... minimal	0	.	.	0	2	.	.	0
LYMPH NODE, POPLITEAL								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	9	1	2	0	10	0	1	1
Erythrocytosis	1	0	0	0	0	0	0	0
.... mild	1	0	0	0	0	0	0	0
Inflammation, mixed cell	0	9	8	10	0	10	9	9
.... minimal	0	1	3	2	0	3	1	4
.... mild	0	8	5	7	0	7	6	3
.... moderate	0	0	0	1	0	0	2	2
MUSCLE, SKELETAL								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
NERVE, OPTIC								

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
NERVE, OPTIC (Continued...)								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
NERVE, SCIATIC								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	1	0	0	10	0	0	3
Inflammation, mixed cell	0	9	10	10	0	10	10	7
.... minimal	0	8	9	9	0	9	9	6
.... mild	0	1	1	1	0	1	1	1
Infiltration, mononuclear cell	0	0	0	0	0	0	0	0
.... minimal	0	0	0	0	0	0	0	0
OVARY								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	9	.	.	10
Cyst	.	.	.	.	1	.	.	0
.... minimal	.	.	.	.	1	.	.	0
PANCREAS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Inflammation; islet of langerhans	1	.	.	0	0	.	.	0

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
PANCREAS (Continued...)								
.... minimal	1	.	.	0	0	.	.	0
SITE, INJECTION								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	9	0	0	0	7	1	0	0
Inflammation, mixed cell	1	10	10	10	3	9	10	10
.... minimal	1	1	0	0	2	1	0	0
.... mild	0	1	1	0	1	4	0	0
.... moderate	0	8	5	5	0	4	6	5
.... marked	0	0	4	5	0	0	4	5
Infiltration, mononuclear cell	0	0	0	0	0	0	0	0
.... minimal	0	0	0	0	0	0	0	0
.... mild	0	0	0	0	0	0	0	0
SKIN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	9	.	.	10
Crust	0	.	.	0	1	.	.	0
.... minimal	0	.	.	0	1	.	.	0
SMALL INTESTINE, DUODENUM								
Examined	10	0	0	10	10	0	0	10

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SMALL INTESTINE, DUODENUM (Continued...)								
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, ILEUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, JEJUNUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPINAL CORD, CERVICAL								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPINAL CORD, LUMBAR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	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	8	5	1	10	9	5	1

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
SPLEEN (Continued...)								
Decreased cellularity, periarteriolar lymphoid sheath	0	2	4	7	0	1	2	7
.... minimal	0	2	4	3	0	1	2	6
.... mild	0	0	0	4	0	0	0	1
Increased macrophages, periarteriolar lymphoid sheath	0	0	3	5	0	0	2	7
.... minimal	0	0	3	5	0	0	2	7
Inflammation; capsular, subacute	0	0	0	0	0	0	1	0
.... moderate	0	0	0	0	0	0	1	0
STOMACH								
Examined	10	0	0	10	10	2	0	10
No Visible Lesions	9	.	.	10	10	1	.	10
Hemorrhage	1	.	.	0	0	0	.	0
.... minimal	1	.	.	0	0	0	.	0
Inflammation; subacute	0	.	.	0	0	1	.	0
.... mild	0	.	.	0	0	1	.	0
TESTIS								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	9	.	.	.	.
Atrophy; tubular	0	.	.	1	.	.	.	.
.... moderate	0	.	.	1	.	.	.	.

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
THYMUS								
Examined	10	2	3	10	10	2	0	10
No Visible Lesions	6	0	0	6	9	0	.	7
Hemorrhage	4	2	3	4	1	2	.	3
.... minimal	4	2	3	3	1	2	.	2
.... mild	0	0	0	1	0	0	.	1
.... moderate	0	0	0	0	0	0	.	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	.	.	9	10	.	.	10
Infiltration, mixed cell	0	.	.	1	0	.	.	0
.... minimal	0	.	.	1	0	.	.	0
URINARY BLADDER								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
UTERUS								
Examined	.	.	.	.	10	0	0	10

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	50 ug/dose Group 3	150 ug/dose Group 4
Number of Animals:	10	10	10	10	10	10	10	10
UTERUS (Continued...)								
No Visible Lesions	.	.	.	.	10	.	.	10
VAGINA								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
ARTERY, AORTA				
Examined	0	0	0	0
BONE MARROW				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Increased hematopoiesis; myeloid	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
BONE, FEMUR				
Examined	0	0	0	0
BONE, STERNUM				
Examined	0	1	0	0
No Visible Lesions	.	1	.	.
BRAIN				
Examined	0	0	0	0
CERVIX				
Examined	.	.	0	0
EPIDIDYMIS				
Examined	0	0	.	.
ESOPHAGUS				

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
ESOPHAGUS (Continued...)				
Examined	0	0	0	0
EYE				
Examined	0	0	0	0
GALT				
Examined	0	0	0	0
GLAND, ADRENAL				
Examined	0	0	1	0
No Visible Lesions	.	.	1	.
GLAND, HARDERIAN				
Examined	0	0	0	0
GLAND, MAMMARY				
Examined	0	0	0	0
GLAND, PARATHYROID				
Examined	0	0	0	0
Not Examined: Not Present In Section.	0	0	0	0
GLAND, PITUITARY				
Examined	0	0	0	0
GLAND, PROSTATE				
Examined	0	0	.	.

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, SALIVARY, MANDIBULAR				
Examined	0	0	0	0
GLAND, SEMINAL VESICLE				
Examined	0	0	.	.
GLAND, THYROID				
Examined	0	0	0	0
HEART				
Examined	0	0	0	0
KIDNEY				
Examined	0	1	1	1
No Visible Lesions	.	0	1	1
Amphophilic vacuolar tubular carcinoma	.	0	0	0
Cyst	.	0	0	0
.... minimal	.	0	0	0
.... mild	.	0	0	0
.... moderate	.	0	0	0
Inflammation; interstitial	.	0	0	0
.... minimal	.	0	0	0
.... mild	.	0	0	0
Basophilia; tubular	.	0	0	0

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
KIDNEY (Continued...)				
.... minimal	.	0	0	0
Dilatation; pelvis	.	1	0	0
.... mild	.	1	0	0
LARGE INTESTINE, CECUM				
Examined	0	0	0	0
LARGE INTESTINE, COLON				
Examined	0	0	0	0
LARGE INTESTINE, RECTUM				
Examined	0	0	0	0
LIVER				
Examined	5	5	5	5
No Visible Lesions	4	4	5	5
Necrosis	1	0	0	0
.... minimal	1	0	0	0
.... mild	0	0	0	0
.... moderate	0	0	0	0
Infiltration, mononuclear cell	0	1	0	0
.... minimal	0	1	0	0
Tension lipidosis	0	0	0	0

Appendix 18
Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
LIVER (Continued...)				
.... minimal	0	0	0	0
Vacuolation, hepatocellular	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
LUNG				
Examined	0	2	0	0
No Visible Lesions	.	1	.	.
Hemorrhage	.	0	.	.
.... minimal	.	0	.	.
.... mild	.	0	.	.
Macrophage aggregation	.	0	.	.
.... minimal	.	0	.	.
Infiltration, mixed cell	.	1	.	.
.... minimal	.	1	.	.
LYMPH NODE				
Examined	0	0	0	0
LYMPH NODE, INGUINAL				
Examined	5	4	5	5
No Visible Lesions	3	3	5	5

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, INGUINAL (Continued...)				
Not Examined: Not Present In Wet Tissues.	0	1	0	0
Inflammation, mixed cell	0	1	0	0
.... minimal	0	1	0	0
.... mild	0	0	0	0
Erythrocytosis	2	0	0	0
.... minimal	2	0	0	0
LYMPH NODE, MANDIBULAR				
Examined	0	1	5	5
No Visible Lesions	.	0	0	0
Hyperplasia; lymphoid	.	0	1	0
.... minimal	.	0	1	0
Erythrocytosis	.	1	4	5
.... minimal	.	1	3	3
.... mild	.	0	1	2
LYMPH NODE, MESENTERIC				
Examined	0	0	0	0
LYMPH NODE, POPLITEAL				
Examined	5	5	5	5
No Visible Lesions	5	2	5	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, POPLITEAL (Continued...)				
Erythrocytosis	0	0	0	0
.... mild	0	0	0	0
Inflammation, mixed cell	0	3	0	5
.... minimal	0	3	0	5
.... mild	0	0	0	0
.... moderate	0	0	0	0
MUSCLE, SKELETAL				
Examined	0	0	0	0
NERVE, OPTIC				
Examined	0	0	0	0
NERVE, SCIATIC				
Examined	5	5	5	5
No Visible Lesions	5	0	5	1
Inflammation, mixed cell	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Infiltration, mononuclear cell	0	5	0	4
.... minimal	0	5	0	4
OVARY				

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
OVARY (Continued...)				
Examined	.	.	0	0
PANCREAS				
Examined	0	0	0	0
SITE, INJECTION				
Examined	5	5	5	5
No Visible Lesions	4	0	4	0
Inflammation, mixed cell	1	0	1	0
.... minimal	1	0	1	0
.... mild	0	0	0	0
.... moderate	0	0	0	0
.... marked	0	0	0	0
Infiltration, mononuclear cell	0	5	0	5
.... minimal	0	4	0	5
.... mild	0	1	0	0
SKIN				
Examined	0	0	0	0
SMALL INTESTINE, DUODENUM				
Examined	0	0	0	0
SMALL INTESTINE, ILEUM				

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
SMALL INTESTINE, ILEUM (Continued...)				
Examined	0	0	0	0
SMALL INTESTINE, JEJUNUM				
Examined	0	0	1	0
No Visible Lesions	.	.	1	.
SPINAL CORD, CERVICAL				
Examined	0	0	0	0
SPINAL CORD, LUMBAR				
Examined	0	0	0	0
SPINAL CORD, THORACIC				
Examined	0	0	0	0
SPLEEN				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Decreased cellularity, periarteriolar lymphoid sheath	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Increased macrophages, periarteriolar lymphoid sheath	0	0	0	0
.... minimal	0	0	0	0
Inflammation; capsular, subacute	0	0	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
SPLEEN (Continued...)				
.... moderate	0	0	0	0
STOMACH				
Examined	0	0	0	0
TESTIS				
Examined	0	0	.	.
THYMUS				
Examined	1	0	4	4
No Visible Lesions	1	.	0	0
Hemorrhage	0	.	4	4
.... minimal	0	.	1	3
.... mild	0	.	2	1
.... moderate	0	.	1	0
TONGUE				
Examined	0	0	0	0
TRACHEA				
Examined	0	0	0	0
URINARY BLADDER				
Examined	0	0	0	0
UTERUS				

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Removal Reason: RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	150 ug/dose Group 4	0 ug/dose Group 1	150 ug/dose Group 4
Number of Animals:	5	5	5	5
UTERUS (Continued...)				
Examined	.	.	0	0
VAGINA				
Examined	.	.	0	0

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Table 5

Summary of Microscopic Gradings by Organ/Group/Sex
5002033

Key Page

Measurement/Statistics

Measurement	Descriptive	Comparative	Arithmetic/Adjusted	Transformation
Pathology Observation	Count Positives			

Group Information

Short Name	Long Name	Report Headings		
1	1	0	ug/dose	Group 1
2	2	10	ug/dose	Group 2
3	3	50	ug/dose	Group 3
4	4	150	ug/dose	Group 4

Removal Reason Grouping

Grouping Name	Abbreviation	Removal Reasons
TERMINAL EUTHANASIA	TERM	TERMINAL EUTHANASIA
RECOVERY EUTHANASIA	REC	RECOVERY EUTHANASIA

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Appendix 1
Individual Absolute Organ Weights

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Individual Absolute Organ Weights Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed	OPMP	Only one of the paired organs present – Macroscopic pathology
AVS	Suspected aberrant value	OPOP	Only one of the paired organs present
COME	See Comment Value Excluded	OUM	Organ unidentifiable macroscopically
COMI	See Comment Value Included	MPE	Macroscopic pathology – Excluded from mean
LIBW	Lung infused before weighing	MPI	Macroscopic pathology – Included in mean
NC	Not calculable	TERR	Technical error
OA	Omitted activity	UPTD	Unable to perform due to technical difficulty
ONP	Organ not present	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study:

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	463	2.119	1.088	0.0678	0.0152	0.990	0.0103
	1002	586	2.216	1.162	0.0664	0.0151	1.222	0.0271
	1003	522	2.268	1.156	0.0581	0.0150	1.232	0.0205
	1004	512	2.139	1.109	0.0576	0.0166	0.928	0.0213
	1005	474	2.166	1.142	0.0672	0.0151	1.604	0.0249
	1006	475	2.218	1.128	0.0744	0.0135	1.399	0.0205
	1007	535	2.233	1.112	0.0699	0.0160	1.365	0.0285
	1008	477	2.100	1.119	0.0689	0.0164	1.210	0.0233
	1009	521	2.163	1.009	0.0704	0.0159	1.122	0.0229
	1010	527	2.207	1.317	0.0644	0.0149	1.194	0.0315
2M	2001	459	2.190	1.244	0.0495	0.0128	1.086	0.0179
	2002	468	2.214	1.192	0.0749	0.0160	1.096	0.0201
	2003	430	2.276	0.926	0.0550	0.0118	1.206	0.0173
	2004	464	2.258	1.139	0.0667	0.0160	1.447	0.0231
	2005	555	2.112	1.142	0.0484	0.0151	1.722	0.0242
	2006	433	2.149	1.044	0.0672	0.0123	0.911	0.0199
	2007	480	2.216	1.124	0.0644	0.0148	1.423	0.0203
	2008	498	2.256	1.208	0.0598	0.0147	1.324	0.0203
	2009	502	2.309	1.237	0.0566	0.0149	1.173	0.0282
	2010	500	2.224	1.089	0.0802	0.0128	1.180	0.0277

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	1001	1.612	2.784	12.956	1.715	--	0.937	3.625
	1002	1.979	3.450	22.824	2.139	--	1.024	3.777
	1003	1.844	3.063	14.858	1.786	--	1.088	3.706
	1004	1.675	2.909	14.158	1.695	--	0.911	3.541
	1005	1.742	2.866	12.140	1.692	--	1.186	4.304
	1006	1.586	3.014	14.293	1.785	--	0.955	3.784
	1007	1.785	3.580	14.995	1.656	--	0.799	3.736
	1008	1.680	2.434	13.692	1.621	--	0.710	3.718
	1009	1.616	2.879	14.476	1.548	--	0.872	3.757
	1010	1.724	3.509	16.179	1.728	--	1.051	3.980
2M	2001	1.550	3.033	13.499	1.684	--	1.000	4.120
	2002	1.503	2.729	16.181	1.726	--	0.946	3.824
	2003	1.541	2.682	11.503	1.575	--	0.926	3.430
	2004	1.597	2.875	12.667	1.717	--	1.062	3.437
	2005	1.676	2.942	17.560	1.812	--	0.881	4.047
	2006	1.617	2.803	11.951	1.550	--	0.826MPI	3.523
	2007	1.746	2.934	13.904	1.692	--	1.354	3.514
	2008	1.587	3.334	13.928	1.769	--	0.824	3.722
	2009	1.594	2.787	13.362	1.725	--	1.049	4.229
	2010	1.771	2.956	13.695	1.920	--	1.013	3.600

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1M	1001	0.471	--
	1002	0.841	--
	1003	0.739	--
	1004	0.579	--
	1005	0.468	--
	1006	0.422	--
	1007	0.453	--
	1008	0.393	--
	1009	0.497	--
	1010	0.424	--
2M	2001	0.599	--
	2002	0.479	--
	2003	0.514	--
	2004	0.541	--
	2005	0.435	--
	2006	0.555	--
	2007	0.586	--
	2008	0.464	--
	2009	0.777	--
	2010	0.661	--

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	566	2.083	1.022	0.0505	0.0128	1.151	0.0248
	3002	448	2.208	1.084	0.0680	0.0135	1.127	0.0262
	3003	483	2.230	1.081	0.0580	0.0120	1.145	0.0257
	3004	442	2.109	1.152	0.0598	0.0131	1.218	0.0182
	3005	426	2.123	1.148	0.0574	0.0108	1.076	0.0198
	3006	428	2.102	1.057	0.0640	0.0139	0.766	0.0199
	3007	501	2.200	1.162	0.0750	0.0113	1.136	0.0236
	3008	536	2.165	1.127	0.0731	0.0152	1.409	0.0244
	3009	491	2.290	1.057	0.0541	0.0138	1.383	0.0235
	3010	505	2.358	1.139	0.0749	0.0123	1.263	0.0241
4M	4001	455	2.114	1.022	0.0627	0.0148	1.139	0.0170
	4002	463	2.166	1.137	0.0817	0.0127	0.871	0.0240
	4003	491	2.190	1.072	0.0653	0.0152	1.138	0.0148
	4004	431	2.273	1.192	0.0836	0.0128	1.086	0.0213
	4005	430	2.113	1.101	0.0660	0.0119	1.476	0.0207
	4006	452	2.100	1.027	0.0715	0.0114	1.217	0.0187
	4007	453	2.097	1.100	0.0609	0.0151	0.997	0.0158
	4008	480	2.261	1.012	0.0826	0.0152	1.181	0.0286
	4009	456	2.226	1.065	0.0916	0.0108	1.494	0.0194
	4010	449	2.174	1.125	0.0624	0.0127	1.039	0.0287

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Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
3M	3001	1.662	3.176	18.531	1.823	--	1.193	3.971
	3002	1.442	3.017	13.050	1.800	--	1.191	3.219
	3003	1.570	3.431	13.967	1.714	--	1.174	3.407
	3004	1.659	2.686	14.538	1.628	--	0.992	3.508
	3005	1.407	2.604	11.619	1.747	--	1.061	3.636
	3006	1.442	3.242	13.783	1.645	--	1.085	3.476
	3007	1.864	3.289	15.984	1.713	--	0.971	4.220
	3008	1.613	2.938	15.882	1.655	--	1.222	3.624
	3009	1.519	2.952	15.434	1.639	--	1.284	3.552
	3010	1.578	3.100	14.988	1.824	--	0.806	3.371
4M	4001	1.410	3.091	14.396	1.679	--	1.029	3.313
	4002	1.655	3.106	14.682	1.651	--	1.049	3.766
	4003	1.706	3.034	14.333	1.643	--	1.018	4.112
	4004	1.538	2.770	12.621	1.703	--	1.036	3.557
	4005	1.422	2.934	12.436	1.552	--	0.856	3.603
	4006	1.407	2.865	14.642	1.709	--	1.130	3.434
	4007	1.745	3.320	17.275	1.751	--	1.210	3.588
	4008	1.686	3.340	16.315	1.807	--	1.372	2.839
	4009	1.578	3.042	14.175	1.653	--	1.117	3.761
	4010	1.572	2.814	13.734	1.754	--	1.126	3.667

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
3M	3001	0.561	--
	3002	0.461	--
	3003	0.572	--
	3004	0.531	--
	3005	0.390	--
	3006	0.669	--
	3007	0.454	--
	3008	0.512	--
	3009	0.485	--
	3010	0.497	--
4M	4001	0.687	--
	4002	0.589	--
	4003	0.343	--
	4004	0.652	--
	4005	0.349	--
	4006	0.533	--
	4007	0.500	--
	4008	0.518	--
	4009	0.440	--
	4010	0.402	--

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	299	1.976	--	0.0706	0.0201	--	0.0160
	1502	287	1.886	--	0.0648	0.0144	--	0.0162
	1503	279	1.912	--	0.0691	0.0151	--	0.0200
	1504	274	2.082	--	0.0621	0.0152	--	0.0109
	1505	287	2.053	--	0.0593	0.0171	--	0.0148
	1506	309	2.090	--	0.0833	0.0155	--	0.0200
	1507	281	1.920	--	0.0663	0.0155	--	0.0212
	1508	290	2.009	--	0.0646	0.0126	--	0.0166
	1509	306	1.912	--	0.0801	0.0201	--	0.0183
	1510	295	2.046	--	0.0637	0.0131	--	0.0150
2F	2501	317	1.959	--	0.0511	0.0156	--	0.0209
	2502	294	2.045	--	0.0679	0.0147	--	0.0162
	2503	325	2.025	--	0.0761	0.0170	--	0.0203
	2504	293	2.293	--	0.0687	0.0131	--	0.0175
	2505	259	2.050	--	0.0593	0.0237	--	0.0158
	2506	267	2.090	--	0.0504	0.0166	--	0.0176
	2507	277	2.111	--	0.0739	0.0201	--	0.0171
	2508	266	2.042	--	0.0717	0.0167	--	0.0161
	2509	281	1.912	--	0.0759	0.0151	--	0.0207
	2510	299	1.941	--	0.0741	0.0148	--	0.0191

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	1501	1.213	2.160	8.677	1.249	0.112	0.496	--
	1502	1.007	1.652	7.714	1.299	0.100	0.625	--
	1503	1.070	1.794	7.540	1.255	0.082	0.581	--
	1504	1.188	1.569	7.976	1.304	0.087	0.617	--
	1505	0.948	1.740	8.192	1.245	0.107	0.519	--
	1506	1.202	1.898	9.462	1.228	0.296MPI	0.534	--
	1507	1.095	1.866	8.283	1.364	0.115	0.534	--
	1508	1.033	1.708	7.721	1.175	0.125	0.550	--
	1509	1.153	1.969	9.679	1.300	0.081	0.574	--
	1510	0.960	1.767	8.138	1.339	0.105	0.680	--
2F	2501	1.081	1.863	9.030	1.329	0.099	0.797	--
	2502	1.043	2.065	9.046	1.232	0.130	0.677	--
	2503	1.131	2.258	9.589	1.501	0.109	0.730	--
	2504	1.093	1.805	7.528	1.397	0.097	0.676	--
	2505	1.028	1.634	7.625	1.184	0.101	0.626	--
	2506	0.965	1.618	7.784	1.313	0.117	0.740	--
	2507	1.073	1.943	8.019	1.142	0.132	0.704	--
	2508	0.923	1.658	8.583	1.260	0.108	0.865	--
	2509	1.008	1.882	8.196	1.302	0.113	0.613	--
	2510	0.935	1.724	8.371	1.193	0.087	0.702	--

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1F	1501	0.441	0.600
	1502	0.408	0.484
	1503	0.489	0.555
	1504	0.619	0.549
	1505	0.451	0.517
	1506	0.529	0.500
	1507	0.408	0.480
	1508	0.516	0.372
	1509	0.376	0.509
	1510	0.475	0.469
2F	2501	0.374	0.481
	2502	0.383	1.114
	2503	0.551	0.599
	2504	0.508	0.626
	2505	0.447	1.215
	2506	0.346	0.410
	2507	0.592	1.353
	2508	0.392	0.518
	2509	0.398	0.554
	2510	0.530	0.454

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	270	1.972	--	0.0587	0.0134	--	0.0150
	3502	245	1.965	--	0.0574	0.0130	--	0.0152
	3503	279	1.864	--	0.0581	0.0163	--	0.0142
	3504	288	2.005	--	0.0784	0.0155	--	0.0196
	3505	284	1.930	--	0.0690	0.0128	--	0.0199
	3506	307	1.994	--	0.0683	0.0119	--	0.0206
	3507	262	2.131	--	0.0748	0.0141	--	0.0182
	3508	285	1.950	--	0.0591	0.0150	--	0.0128
	3509	304	1.944	--	0.0660	0.0166	--	0.0182
	3510	261	2.009	--	0.0686	0.0138	--	0.0155
4F	4501	263	2.010	--	0.0715	0.0136	--	0.0160
	4502	262	2.048	--	0.0637	0.0150	--	0.0141
	4503	287	1.945	--	0.0723	0.0158	--	0.0169
	4504	296	1.938	--	0.0974	0.0160	--	0.0161
	4505	276	2.027	--	0.0859	0.0143	--	0.0182
	4506	267	1.943	--	0.0681	0.0146	--	0.0137
	4507	287	1.931	--	0.0585	0.0143	--	0.0166
	4508	256	1.993	--	0.0532	0.0111	--	0.0182
	4509	273	2.056	--	0.0836	0.0167	--	0.0278
	4510	266	2.012	--	0.0734	0.0148	--	0.0122

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
3F	3501	1.065	1.804MPI	7.414	1.117	0.090	0.692	--
	3502	0.884	1.683	6.086	1.198	0.077	0.907MPI	--
	3503	1.087	1.647	8.030	1.293	0.092	0.761	--
	3504	1.011	1.897	8.693	1.210	0.100	0.695	--
	3505	1.073	1.972	9.378	1.293	0.139	0.912	--
	3506	1.017	1.825	9.186	1.284	0.104	0.825	--
	3507	0.958	1.888	7.360	1.217	0.101	0.623	--
	3508	0.952	1.878	9.093	1.336	0.117	0.746	--
	3509	1.032	1.983	9.055	1.260	0.079	0.692	--
	3510	0.985	1.889	7.677	1.216	0.130	0.635	--
4F	4501	1.020	1.935	8.278	1.379	0.069	0.547	--
	4502	1.015	1.741	7.633	1.212	0.080	0.706	--
	4503	1.109	1.775	9.038	1.294	0.101	0.676	--
	4504	1.152	1.934	9.567	1.263	0.148	0.904	--
	4505	1.063	2.015	8.299	1.354	0.085	0.679	--
	4506	0.992	1.786	8.606	1.173	0.080	0.640	--
	4507	0.964	1.914	8.901	1.346	0.106	0.643	--
	4508	0.893	1.684	7.957	1.077	0.087	0.650	--
	4509	0.847	1.998	8.635	1.307	0.095	0.783	--
	4510	0.838	1.761	8.733	1.238	0.139	0.702	--

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
3F	3501	0.306	0.431
	3502	0.588	0.492
	3503	0.405	0.518
	3504	0.418	1.258
	3505	0.557	0.513
	3506	0.674	0.584
	3507	0.333	1.224
	3508	0.523	0.419
	3509	0.506	0.468
	3510	0.304	0.392
4F	4501	0.454	1.248
	4502	0.381	1.090
	4503	0.344	0.904
	4504	0.446	0.505
	4505	0.416	1.103
	4506	0.338	0.506
	4507	0.382	0.540
	4508	0.528	1.306
	4509	0.504	0.632
	4510	0.647	0.524

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	507	2.141	1.199	0.0600	0.0157	1.211	0.0221
	1012	485	2.139	1.162	0.0690	0.0131	1.045	0.0217
	1013	501	2.244	1.223	0.0606	0.0136	1.400	0.0283
	1014	541	2.210	1.299	0.0688	0.0158	1.410	0.0265
	1015	564	2.253	1.255	0.0597	0.0146	1.529	0.0218
4M	4011	482	2.304	1.159	0.0748	0.0110	1.212	0.0179
	4012	528	2.373	1.094	0.0576	0.0146	1.344	0.0255
	4013	553	2.258	1.188	0.0759	0.0159	1.286	0.0205
	4014	510	2.056	1.192	0.0550	0.0132	1.454	0.0170
	4015	473	2.126	1.174	0.0588	0.0132	1.390	0.0184

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1M	1011	1.505	2.847	14.151	1.660	--	0.805	3.771
	1012	1.665	3.038	12.952	1.714	--	0.703	3.831
	1013	1.629	3.492	13.780	1.799	--	1.025	3.776
	1014	1.763	3.540	14.252	1.769	--	1.092	3.808
	1015	1.892	3.150	17.356	1.848	--	0.860	3.999
4M	4011	1.398	2.754	12.441	1.577	--	0.869	3.688
	4012	1.777	3.295	13.723	1.786	--	1.023	3.357
	4013	1.632	3.070	15.108	1.792	--	0.863	3.800
	4014	1.644	2.946	15.050	1.725	--	1.096	3.506
	4015	1.508	2.542	12.988	1.398	--	1.111	3.470

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Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1M	1011	0.638	--
	1012	0.369	--
	1013	0.475	--
	1014	0.418	--
	1015	0.468	--
4M	4011	0.412	--
	4012	0.510	--
	4013	0.507	--
	4014	0.462	--
	4015	0.405	--

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Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 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	310	2.038	--	0.0709	0.0173	--	0.0177
	1512	297	1.930	--	0.0712	0.0153	--	0.0180
	1513	311	1.944	--	0.0611	0.0134	--	0.0138
	1514	317	1.972	--	0.0662	0.0144	--	0.0141
	1515	300	2.002	--	0.0653	0.0186	--	0.0156
4F	4511	293	1.868	--	0.0656	0.0131	--	0.0106
	4512	336	2.196	--	0.0782	0.0145	--	0.0194
	4513	262	1.963	--	0.0569	0.0136	--	0.0131
	4514	288	1.907	--	0.0707	0.0181	--	0.0152
	4515	289	2.154	--	0.0612	0.0154	--	0.0123

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	HEART g	KIDNEY g	LIVER g	LUNG g	OVARY g	SPLEEN g	TESTIS g
1F	1511	1.238	2.257	8.466	1.372	0.079	0.662	--
	1512	1.269	2.009	8.333	1.342	0.081	0.676	--
	1513	1.275	1.774	7.534	1.282	0.102	0.558	--
	1514	1.180	1.853	8.286	1.349	0.113	0.785	--
	1515	1.124	1.772	7.877	1.284	0.064	0.526	--
4F	4511	1.171	1.834	9.734	1.294	0.102	0.639	--
	4512	1.138	2.161	9.393	1.359	0.069	0.603	--
	4513	1.019	1.846	6.818	1.397	0.069	0.428	--
	4514	1.257	1.994	9.399	1.357	0.093	0.554	--
	4515	1.062	1.662	8.644	1.355	0.112	0.471	--

Appendix 18
Appendix 1
Individual Absolute Organ Weights: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	THYMUS g	UTERUS g
1F	1511	0.609	1.229
	1512	0.510	0.416
	1513	0.300	0.457
	1514	0.410	1.003
	1515	0.438	1.067
4F	4511	0.330	0.407
	4512	0.284	0.492
	4513	0.297	0.447
	4514	0.334	0.588
	4515	0.335	0.436

Appendix 18

Appendix 2
Individual Organ Weights Relative to Body Weight

Appendix 18

Individual Organ Weights Relative to Body Weight Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed	OPMP	Only one of the paired organs present – Macroscopic pathology
AVS	Suspected aberrant value	OPOP	Only one of the paired organs present
COME	See Comment Value Excluded	OUM	Organ unidentifiable macroscopically
COMI	See Comment Value Included	MPE	Macroscopic pathology – Excluded from mean
LIBW	Lung infused before weighing	MPI	Macroscopic pathology – Included in mean
NC	Not calculable	TERR	Technical error
OA	Omitted activity	UPTD	Unable to perform due to technical difficulty
ONP	Organ not present	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study:

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

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Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1001	0.4577	0.2350	0.01464	0.00328	0.2138	0.00222	0.3482
	1002	0.3782	0.1983	0.01133	0.00258	0.2085	0.00462	0.3377
	1003	0.4345	0.2215	0.01113	0.00287	0.2360	0.00393	0.3533
	1004	0.4178	0.2166	0.01125	0.00324	0.1813	0.00416	0.3271
	1005	0.4570	0.2409	0.01418	0.00319	0.3384	0.00525	0.3675
	1006	0.4669	0.2375	0.01566	0.00284	0.2945	0.00432	0.3339
	1007	0.4174	0.2079	0.01307	0.00299	0.2551	0.00533	0.3336
	1008	0.4403	0.2346	0.01444	0.00344	0.2537	0.00488	0.3522
	1009	0.4152	0.1937	0.01351	0.00305	0.2154	0.00440	0.3102
	1010	0.4188	0.2499	0.01222	0.00283	0.2266	0.00598	0.3271
2M	2001	0.4771	0.2710	0.01078	0.00279	0.2366	0.00390	0.3377
	2002	0.4731	0.2547	0.01600	0.00342	0.2342	0.00429	0.3212
	2003	0.5293	0.2153	0.01279	0.00274	0.2805	0.00402	0.3584
	2004	0.4866	0.2455	0.01438	0.00345	0.3119	0.00498	0.3442
	2005	0.3805	0.2058	0.00872	0.00272	0.3103	0.00436	0.3020
	2006	0.4963	0.2411	0.01552	0.00284	0.2104	0.00460	0.3734
	2007	0.4617	0.2342	0.01342	0.00308	0.2965	0.00423	0.3638
	2008	0.4530	0.2426	0.01201	0.00295	0.2659	0.00408	0.3187
	2009	0.4600	0.2464	0.01127	0.00297	0.2337	0.00562	0.3175
	2010	0.4448	0.2178	0.01604	0.00256	0.2360	0.00554	0.3542

Appendix 18
Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	1001	0.6013	2.7983	0.3704	--	0.2024	0.7829	0.1017
	1002	0.5887	3.8949	0.3650	--	0.1747	0.6445	0.1435
	1003	0.5868	2.8464	0.3421	--	0.2084	0.7100	0.1416
	1004	0.5682	2.7652	0.3311	--	0.1779	0.6916	0.1131
	1005	0.6046	2.5612	0.3570	--	0.2502	0.9080	0.0987
	1006	0.6345	3.0091	0.3758	--	0.2011	0.7966	0.0888
	1007	0.6692	2.8028	0.3095	--	0.1493	0.6983	0.0847
	1008	0.5103	2.8704	0.3398	--	0.1488	0.7795	0.0824
	1009	0.5526	2.7785	0.2971	--	0.1674	0.7211	0.0954
	1010	0.6658	3.0700	0.3279	--	0.1994	0.7552	0.0805
2M	2001	0.6608	2.9410	0.3669	--	0.2179	0.8976	0.1305
	2002	0.5831	3.4575	0.3688	--	0.2021	0.8171	0.1024
	2003	0.6237	2.6751	0.3663	--	0.2153	0.7977	0.1195
	2004	0.6196	2.7300	0.3700	--	0.2289	0.7407	0.1166
	2005	0.5301	3.1640	0.3265	--	0.1587	0.7292	0.0784
	2006	0.6473	2.7600	0.3580	--	0.1908MPI	0.8136	0.1282
	2007	0.6113	2.8967	0.3525	--	0.2821	0.7321	0.1221
	2008	0.6695	2.7968	0.3552	--	0.1655	0.7474	0.0932
	2009	0.5552	2.6618	0.3436	--	0.2090	0.8424	0.1548
	2010	0.5912	2.7390	0.3840	--	0.2026	0.7200	0.1322

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Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	UTERUS %
1M	1001	--
	1002	--
	1003	--
	1004	--
	1005	--
	1006	--
	1007	--
	1008	--
	1009	--
	1010	--
2M	2001	--
	2002	--
	2003	--
	2004	--
	2005	--
	2006	--
	2007	--
	2008	--
	2009	--
	2010	--

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Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
3M	3001	0.3680	0.1806	0.00892	0.00226	0.2034	0.00438	0.2936
	3002	0.4929	0.2420	0.01518	0.00301	0.2516	0.00585	0.3219
	3003	0.4617	0.2238	0.01201	0.00248	0.2371	0.00532	0.3251
	3004	0.4771	0.2606	0.01353	0.00296	0.2756	0.00412	0.3753
	3005	0.4984	0.2695	0.01347	0.00254	0.2526	0.00465	0.3303
	3006	0.4911	0.2470	0.01495	0.00325	0.1790	0.00465	0.3369
	3007	0.4391	0.2319	0.01497	0.00226	0.2267	0.00471	0.3721
	3008	0.4039	0.2103	0.01364	0.00284	0.2629	0.00455	0.3009
	3009	0.4664	0.2153	0.01102	0.00281	0.2817	0.00479	0.3094
	3010	0.4669	0.2255	0.01483	0.00244	0.2501	0.00477	0.3125
4M	4001	0.4646	0.2246	0.01378	0.00325	0.2503	0.00374	0.3099
	4002	0.4678	0.2456	0.01765	0.00274	0.1881	0.00518	0.3575
	4003	0.4460	0.2183	0.01330	0.00310	0.2318	0.00301	0.3475
	4004	0.5274	0.2766	0.01940	0.00297	0.2520	0.00494	0.3568
	4005	0.4914	0.2560	0.01535	0.00277	0.3433	0.00481	0.3307
	4006	0.4646	0.2272	0.01582	0.00252	0.2692	0.00414	0.3113
	4007	0.4629	0.2428	0.01344	0.00333	0.2201	0.00349	0.3852
	4008	0.4710	0.2108	0.01721	0.00317	0.2460	0.00596	0.3513
	4009	0.4882	0.2336	0.02009	0.00237	0.3276	0.00425	0.3461
	4010	0.4842	0.2506	0.01390	0.00283	0.2314	0.00639	0.3501

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Appendix 2
Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
3M	3001	0.5611	3.2740	0.3221	--	0.2108	0.7016	0.0991
	3002	0.6734	2.9129	0.4018	--	0.2658	0.7185	0.1029
	3003	0.7104	2.8917	0.3549	--	0.2431	0.7054	0.1184
	3004	0.6077	3.2891	0.3683	--	0.2244	0.7937	0.1201
	3005	0.6113	2.7275	0.4101	--	0.2491	0.8535	0.0915
	3006	0.7575	3.2203	0.3843	--	0.2535	0.8121	0.1563
	3007	0.6565	3.1904	0.3419	--	0.1938	0.8423	0.0906
	3008	0.5481	2.9631	0.3088	--	0.2280	0.6761	0.0955
	3009	0.6012	3.1434	0.3338	--	0.2615	0.7234	0.0988
	3010	0.6139	2.9679	0.3612	--	0.1596	0.6675	0.0984
4M	4001	0.6793	3.1640	0.3690	--	0.2262	0.7281	0.1510
	4002	0.6708	3.1711	0.3566	--	0.2266	0.8134	0.1272
	4003	0.6179	2.9191	0.3346	--	0.2073	0.8375	0.0699
	4004	0.6427	2.9283	0.3951	--	0.2404	0.8253	0.1513
	4005	0.6823	2.8921	0.3609	--	0.1991	0.8379	0.0812
	4006	0.6338	3.2394	0.3781	--	0.2500	0.7597	0.1179
	4007	0.7329	3.8135	0.3865	--	0.2671	0.7921	0.1104
	4008	0.6958	3.3990	0.3765	--	0.2858	0.5915	0.1079
	4009	0.6671	3.1086	0.3625	--	0.2450	0.8248	0.0965
	4010	0.6267	3.0588	0.3906	--	0.2508	0.8167	0.0895

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	UTERUS %
3M	3001	--
	3002	--
	3003	--
	3004	--
	3005	--
	3006	--
	3007	--
	3008	--
	3009	--
	3010	--
4M	4001	--
	4002	--
	4003	--
	4004	--
	4005	--
	4006	--
	4007	--
	4008	--
	4009	--
	4010	--

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	1501	0.6609	--	0.02361	0.00672	--	0.00535	0.4057
	1502	0.6571	--	0.02258	0.00502	--	0.00564	0.3509
	1503	0.6853	--	0.02477	0.00541	--	0.00717	0.3835
	1504	0.7599	--	0.02266	0.00555	--	0.00398	0.4336
	1505	0.7153	--	0.02066	0.00596	--	0.00516	0.3303
	1506	0.6764	--	0.02696	0.00502	--	0.00647	0.3890
	1507	0.6833	--	0.02359	0.00552	--	0.00754	0.3897
	1508	0.6928	--	0.02228	0.00434	--	0.00572	0.3562
	1509	0.6248	--	0.02618	0.00657	--	0.00598	0.3768
	1510	0.6936	--	0.02159	0.00444	--	0.00508	0.3254
2F	2501	0.6180	--	0.01612	0.00492	--	0.00659	0.3410
	2502	0.6956	--	0.02310	0.00500	--	0.00551	0.3548
	2503	0.6231	--	0.02342	0.00523	--	0.00625	0.3480
	2504	0.7826	--	0.02345	0.00447	--	0.00597	0.3730
	2505	0.7915	--	0.02290	0.00915	--	0.00610	0.3969
	2506	0.7828	--	0.01888	0.00622	--	0.00659	0.3614
	2507	0.7621	--	0.02668	0.00726	--	0.00617	0.3874
	2508	0.7677	--	0.02695	0.00628	--	0.00605	0.3470
	2509	0.6804	--	0.02701	0.00537	--	0.00737	0.3587
	2510	0.6492	--	0.02478	0.00495	--	0.00639	0.3127

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	1501	0.7224	2.9020	0.4177	0.0375	0.1659	--	0.1475
	1502	0.5756	2.6878	0.4526	0.0348	0.2178	--	0.1422
	1503	0.6430	2.7025	0.4498	0.0294	0.2082	--	0.1753
	1504	0.5726	2.9109	0.4759	0.0318	0.2252	--	0.2259
	1505	0.6063	2.8544	0.4338	0.0373	0.1808	--	0.1571
	1506	0.6142	3.0621	0.3974	0.0958MPI	0.1728	--	0.1712
	1507	0.6641	2.9477	0.4854	0.0409	0.1900	--	0.1452
	1508	0.5890	2.6624	0.4052	0.0431	0.1897	--	0.1779
	1509	0.6435	3.1631	0.4248	0.0265	0.1876	--	0.1229
	1510	0.5990	2.7586	0.4539	0.0356	0.2305	--	0.1610
2F	2501	0.5877	2.8486	0.4192	0.0312	0.2514	--	0.1180
	2502	0.7024	3.0769	0.4190	0.0442	0.2303	--	0.1303
	2503	0.6948	2.9505	0.4618	0.0335	0.2246	--	0.1695
	2504	0.6160	2.5693	0.4768	0.0331	0.2307	--	0.1734
	2505	0.6309	2.9440	0.4571	0.0390	0.2417	--	0.1726
	2506	0.6060	2.9154	0.4918	0.0438	0.2772	--	0.1296
	2507	0.7014	2.8949	0.4123	0.0477	0.2542	--	0.2137
	2508	0.6233	3.2267	0.4737	0.0406	0.3252	--	0.1474
	2509	0.6698	2.9167	0.4633	0.0402	0.2181	--	0.1416
	2510	0.5766	2.7997	0.3990	0.0291	0.2348	--	0.1773

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	UTERUS %
1F	1501	0.2007
	1502	0.1686
	1503	0.1989
	1504	0.2004
	1505	0.1801
	1506	0.1618
	1507	0.1708
	1508	0.1283
	1509	0.1663
	1510	0.1590
2F	2501	0.1517
	2502	0.3789
	2503	0.1843
	2504	0.2137
	2505	0.4691
	2506	0.1536
	2507	0.4884
	2508	0.1947
	2509	0.1972
	2510	0.1518

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Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
3F	3501	0.7304	--	0.02174	0.00496	--	0.00556	0.3944
	3502	0.8020	--	0.02343	0.00531	--	0.00620	0.3608
	3503	0.6681	--	0.02082	0.00584	--	0.00509	0.3896
	3504	0.6962	--	0.02722	0.00538	--	0.00681	0.3510
	3505	0.6796	--	0.02430	0.00451	--	0.00701	0.3778
	3506	0.6495	--	0.02225	0.00388	--	0.00671	0.3313
	3507	0.8134	--	0.02855	0.00538	--	0.00695	0.3656
	3508	0.6842	--	0.02074	0.00526	--	0.00449	0.3340
	3509	0.6395	--	0.02171	0.00546	--	0.00599	0.3395
	3510	0.7697	--	0.02628	0.00529	--	0.00594	0.3774
4F	4501	0.7643	--	0.02719	0.00517	--	0.00608	0.3878
	4502	0.7817	--	0.02431	0.00573	--	0.00538	0.3874
	4503	0.6777	--	0.02519	0.00551	--	0.00589	0.3864
	4504	0.6547	--	0.03291	0.00541	--	0.00544	0.3892
	4505	0.7344	--	0.03112	0.00518	--	0.00659	0.3851
	4506	0.7277	--	0.02551	0.00547	--	0.00513	0.3715
	4507	0.6728	--	0.02038	0.00498	--	0.00578	0.3359
	4508	0.7785	--	0.02078	0.00434	--	0.00711	0.3488
	4509	0.7531	--	0.03062	0.00612	--	0.01018	0.3103
	4510	0.7564	--	0.02759	0.00556	--	0.00459	0.3150

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Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
3F	3501	0.6681MPI	2.7459	0.4137	0.0333	0.2563	--	0.1133
	3502	0.6869	2.4841	0.4890	0.0314	0.3702MPI	--	0.2400
	3503	0.5903	2.8781	0.4634	0.0330	0.2728	--	0.1452
	3504	0.6587	3.0184	0.4201	0.0347	0.2413	--	0.1451
	3505	0.6944	3.3021	0.4553	0.0489	0.3211	--	0.1961
	3506	0.5945	2.9922	0.4182	0.0339	0.2687	--	0.2195
	3507	0.7206	2.8092	0.4645	0.0385	0.2378	--	0.1271
	3508	0.6589	3.1905	0.4688	0.0411	0.2618	--	0.1835
	3509	0.6523	2.9786	0.4145	0.0260	0.2276	--	0.1664
	3510	0.7238	2.9414	0.4659	0.0498	0.2433	--	0.1165
4F	4501	0.7357	3.1475	0.5243	0.0262	0.2080	--	0.1726
	4502	0.6645	2.9134	0.4626	0.0305	0.2695	--	0.1454
	4503	0.6185	3.1491	0.4509	0.0352	0.2355	--	0.1199
	4504	0.6534	3.2321	0.4267	0.0500	0.3054	--	0.1507
	4505	0.7301	3.0069	0.4906	0.0308	0.2460	--	0.1507
	4506	0.6689	3.2232	0.4393	0.0300	0.2397	--	0.1266
	4507	0.6669	3.1014	0.4690	0.0369	0.2240	--	0.1331
	4508	0.6578	3.1082	0.4207	0.0340	0.2539	--	0.2063
	4509	0.7319	3.1630	0.4788	0.0348	0.2868	--	0.1846
	4510	0.6620	3.2831	0.4654	0.0523	0.2639	--	0.2432

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Individual Organ Weights Relative to Body Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	UTERUS %
3F	3501	0.1596
	3502	0.2008
	3503	0.1857
	3504	0.4368
	3505	0.1806
	3506	0.1902
	3507	0.4672
	3508	0.1470
	3509	0.1539
	3510	0.1502
4F	4501	0.4745
	4502	0.4160
	4503	0.3150
	4504	0.1706
	4505	0.3996
	4506	0.1895
	4507	0.1882
	4508	0.5102
	4509	0.2315
	4510	0.1970

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Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1011	0.4223	0.2365	0.01183	0.00310	0.2389	0.00436	0.2968
	1012	0.4410	0.2396	0.01423	0.00270	0.2155	0.00447	0.3433
	1013	0.4479	0.2441	0.01210	0.00271	0.2794	0.00565	0.3251
	1014	0.4085	0.2401	0.01272	0.00292	0.2606	0.00490	0.3259
	1015	0.3995	0.2225	0.01059	0.00259	0.2711	0.00387	0.3355
4M	4011	0.4780	0.2405	0.01552	0.00228	0.2515	0.00371	0.2900
	4012	0.4494	0.2072	0.01091	0.00277	0.2545	0.00483	0.3366
	4013	0.4083	0.2148	0.01373	0.00288	0.2325	0.00371	0.2951
	4014	0.4031	0.2337	0.01078	0.00259	0.2851	0.00333	0.3224
	4015	0.4495	0.2482	0.01243	0.00279	0.2939	0.00389	0.3188

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Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1M	1011	0.5615	2.7911	0.3274	--	0.1588	0.7438	0.1258
	1012	0.6264	2.6705	0.3534	--	0.1449	0.7899	0.0761
	1013	0.6970	2.7505	0.3591	--	0.2046	0.7537	0.0948
	1014	0.6543	2.6344	0.3270	--	0.2018	0.7039	0.0773
	1015	0.5585	3.0773	0.3277	--	0.1525	0.7090	0.0830
4M	4011	0.5714	2.5811	0.3272	--	0.1803	0.7651	0.0855
	4012	0.6241	2.5991	0.3383	--	0.1938	0.6358	0.0966
	4013	0.5552	2.7320	0.3241	--	0.1561	0.6872	0.0917
	4014	0.5776	2.9510	0.3382	--	0.2149	0.6875	0.0906
	4015	0.5374	2.7459	0.2956	--	0.2349	0.7336	0.0856

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Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	UTERUS %
1M	1011	--
	1012	--
	1013	--
	1014	--
	1015	--
4M	4011	--
	4012	--
	4013	--
	4014	--
	4015	--

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Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1F	1511	0.6574	--	0.02287	0.00558	--	0.00571	0.3994
	1512	0.6498	--	0.02397	0.00515	--	0.00606	0.4273
	1513	0.6251	--	0.01965	0.00431	--	0.00444	0.4100
	1514	0.6221	--	0.02088	0.00454	--	0.00445	0.3722
	1515	0.6673	--	0.02177	0.00620	--	0.00520	0.3747
4F	4511	0.6375	--	0.02239	0.00447	--	0.00362	0.3997
	4512	0.6536	--	0.02327	0.00432	--	0.00577	0.3387
	4513	0.7492	--	0.02172	0.00519	--	0.00500	0.3889
	4514	0.6622	--	0.02455	0.00628	--	0.00528	0.4365
	4515	0.7453	--	0.02118	0.00533	--	0.00426	0.3675

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Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	KIDNEY %	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %
1F	1511	0.7281	2.7310	0.4426	0.0255	0.2135	--	0.1965
	1512	0.6764	2.8057	0.4519	0.0273	0.2276	--	0.1717
	1513	0.5704	2.4225	0.4122	0.0328	0.1794	--	0.0965
	1514	0.5845	2.6139	0.4256	0.0356	0.2476	--	0.1293
	1515	0.5907	2.6257	0.4280	0.0213	0.1753	--	0.1460
4F	4511	0.6259	3.3222	0.4416	0.0348	0.2181	--	0.1126
	4512	0.6432	2.7955	0.4045	0.0205	0.1795	--	0.0845
	4513	0.7046	2.6023	0.5332	0.0263	0.1634	--	0.1134
	4514	0.6924	3.2635	0.4712	0.0323	0.1924	--	0.1160
	4515	0.5751	2.9910	0.4689	0.0388	0.1630	--	0.1159

Appendix 18
Appendix 2
Individual Organ Weights Relative to Body Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	UTERUS %
1F	1511	0.3965
	1512	0.1401
	1513	0.1469
	1514	0.3164
	1515	0.3557
4F	4511	0.1389
	4512	0.1464
	4513	0.1706
	4514	0.2042
	4515	0.1509

Appendix 18

Appendix 3
Individual Organ Weights Relative to Brain Weight

Appendix 18

Individual Organ Weights Relative to Brain Weight Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed	OPMP	Only one of the paired organs present – Macroscopic pathology
AVS	Suspected aberrant value	OPOP	Only one of the paired organs present
COME	See Comment Value Excluded	OUM	Organ unidentifiable macroscopically
COMI	See Comment Value Included	MPE	Macroscopic pathology – Excluded from mean
LIBW	Lung infused before weighing	MPI	Macroscopic pathology – Included in mean
NC	Not calculable	TERR	Technical error
OA	Omitted activity	UPTD	Unable to perform due to technical difficulty
ONP	Organ not present	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study:

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

Appendix 18
Appendix 3
Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1001	51.3450	3.19962	0.71732	46.7202	0.48608	76.0736	131.3827
	1002	52.4368	2.99639	0.68141	55.1444	1.22292	89.3051	155.6859
	1003	50.9700	2.56173	0.66138	54.3210	0.90388	81.3051	135.0529
	1004	51.8467	2.69285	0.77606	43.3848	0.99579	78.3076	135.9981
	1005	52.7239	3.10249	0.69714	74.0536	1.14958	80.4247	132.3176
	1006	50.8566	3.35437	0.60866	63.0748	0.92426	71.5059	135.8882
	1007	49.7985	3.13032	0.71652	61.1285	1.27631	79.9373	160.3224
	1008	53.2857	3.28095	0.78095	57.6190	1.10952	80.0000	115.9048
	1009	46.6482	3.25474	0.73509	51.8724	1.05871	74.7110	133.1022
	1010	59.6738	2.91799	0.67512	54.1006	1.42728	78.1151	158.9941
2M	2001	56.8037	2.26027	0.58447	49.5890	0.81735	70.7763	138.4932
	2002	53.8392	3.38302	0.72267	49.5032	0.90786	67.8862	123.2611
	2003	40.6854	2.41652	0.51845	52.9877	0.76011	67.7065	117.8383
	2004	50.4429	2.95394	0.70859	64.0833	1.02303	70.7263	127.3251
	2005	54.0720	2.29167	0.71496	81.5341	1.14583	79.3561	139.2992
	2006	48.5807	3.12704	0.57236	42.3918	0.92601	75.2443	130.4328
	2007	50.7220	2.90614	0.66787	64.2148	0.91606	78.7906	132.4007
	2008	53.5461	2.65071	0.65160	58.6879	0.89982	70.3457	147.7837
	2009	53.5730	2.45128	0.64530	50.8012	1.22131	69.0342	120.7016
	2010	48.9658	3.60612	0.57554	53.0576	1.24550	79.6313	132.9137

Appendix 18
Appendix 3
Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	1001	611.4205	80.9344	--	44.2190	171.0713	22.2275	--
	1002	1029.9639	96.5253	--	46.2094	170.4422	37.9513	--
	1003	655.1146	78.7478	--	47.9718	163.4039	32.5838	--
	1004	661.8981	79.2426	--	42.5900	165.5446	27.0687	--
	1005	560.4801	78.1163	--	54.7553	198.7073	21.6066	--
	1006	644.4094	80.4779	--	43.0568	170.6041	19.0261	--
	1007	671.5181	74.1603	--	35.7815	167.3086	20.2866	--
	1008	652.0000	77.1905	--	33.8095	177.0476	18.7143	--
	1009	669.2557	71.5673	--	40.3144	173.6939	22.9773	--
	1010	733.0766	78.2963	--	47.6212	180.3353	19.2116	--
2M	2001	616.3927	76.8950	--	45.6621	188.1279	27.3516	--
	2002	730.8491	77.9584	--	42.7281	172.7191	21.6350	--
	2003	505.4042	69.2004	--	40.6854	150.7030	22.5835	--
	2004	560.9832	76.0407	--	47.0328	152.2143	23.9593	--
	2005	831.4394	85.7955	--	41.7140	191.6193	20.5966	--
	2006	556.1191	72.1266	--	38.4365MPI	163.9367	25.8260	--
	2007	627.4368	76.3538	--	61.1011	158.5740	26.4440	--
	2008	617.3759	78.4131	--	36.5248	164.9823	20.5674	--
	2009	578.6921	74.7077	--	45.4309	183.1529	33.6509	--
	2010	615.7824	86.3309	--	45.5486	161.8705	29.7212	--

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
3M	3001	49.0639	2.42439	0.61450	55.2568	1.19059	79.7888	152.4724
	3002	49.0942	3.07971	0.61141	51.0417	1.18659	65.3080	136.6395
	3003	48.4753	2.60090	0.53812	51.3453	1.15247	70.4036	153.8565
	3004	54.6230	2.83547	0.62115	57.7525	0.86297	78.6629	127.3589
	3005	54.0744	2.70372	0.50871	50.6830	0.93264	66.2741	122.6566
	3006	50.2854	3.04472	0.66127	36.4415	0.94672	68.6013	154.2341
	3007	52.8182	3.40909	0.51364	51.6364	1.07273	84.7273	149.5000
	3008	52.0554	3.37644	0.70208	65.0808	1.12702	74.5035	135.7044
	3009	46.1572	2.36245	0.60262	60.3930	1.02620	66.3319	128.9083
	3010	48.3036	3.17642	0.52163	53.5623	1.02205	66.9211	131.4673
4M	4001	48.3444	2.96594	0.70009	53.8789	0.80416	66.6982	146.2157
	4002	52.4931	3.77193	0.58633	40.2124	1.10803	76.4081	143.3980
	4003	48.9498	2.98174	0.69406	51.9635	0.67580	77.8995	138.5388
	4004	52.4417	3.67796	0.56313	47.7783	0.93709	67.6639	121.8654
	4005	52.1060	3.12352	0.56318	69.8533	0.97965	67.2977	138.8547
	4006	48.9048	3.40476	0.54286	57.9524	0.89048	67.0000	136.4286
	4007	52.4559	2.90415	0.72008	47.5441	0.75346	83.2141	158.3214
	4008	44.7590	3.65325	0.67227	52.2335	1.26493	74.5688	147.7222
	4009	47.8437	4.11500	0.48518	67.1159	0.87152	70.8895	136.6577
	4010	51.7479	2.87029	0.58418	47.7921	1.32015	72.3091	129.4388

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
3M	3001	889.6303	87.5180	--	57.2732	190.6385	26.9323	--
	3002	591.0326	81.5217	--	53.9402	145.7880	20.8786	--
	3003	626.3229	76.8610	--	52.6457	152.7803	25.6502	--
	3004	689.3314	77.1930	--	47.0365	166.3348	25.1778	--
	3005	547.2916	82.2892	--	49.9764	171.2671	18.3702	--
	3006	655.7088	78.2588	--	51.6175	165.3663	31.8268	--
	3007	726.5455	77.8636	--	44.1364	191.8182	20.6364	--
	3008	733.5797	76.4434	--	56.4434	167.3903	23.6490	--
	3009	673.9738	71.5721	--	56.0699	155.1092	21.1790	--
	3010	635.6234	77.3537	--	34.1815	142.9601	21.0772	--
4M	4001	680.9839	79.4229	--	48.6755	156.7171	32.4976	--
	4002	677.8393	76.2235	--	48.4303	173.8689	27.1930	--
	4003	654.4749	75.0228	--	46.4840	187.7626	15.6621	--
	4004	555.2574	74.9230	--	45.5785	156.4892	28.6846	--
	4005	588.5471	73.4501	--	40.5111	170.5159	16.5168	--
	4006	697.2381	81.3810	--	53.8095	163.5238	25.3810	--
	4007	823.7959	83.5002	--	57.7015	171.1016	23.8436	--
	4008	721.5834	79.9204	--	60.6811	125.5639	22.9102	--
	4009	636.7925	74.2588	--	50.1797	168.9578	19.7664	--
	4010	631.7387	80.6808	--	51.7939	168.6753	18.4913	--

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	1501	--	3.57287	1.01721	--	0.80972	61.3866	109.3117
	1502	--	3.43584	0.76352	--	0.85896	53.3934	87.5928
	1503	--	3.61402	0.78975	--	1.04603	55.9623	93.8285
	1504	--	2.98271	0.73007	--	0.52354	57.0605	75.3602
	1505	--	2.88846	0.83293	--	0.72090	46.1763	84.7540
	1506	--	3.98565	0.74163	--	0.95694	57.5120	90.8134
	1507	--	3.45313	0.80729	--	1.10417	57.0313	97.1875
	1508	--	3.21553	0.62718	--	0.82628	51.4186	85.0174
	1509	--	4.18933	1.05126	--	0.95711	60.3033	102.9812
	1510	--	3.11339	0.64027	--	0.73314	46.9208	86.3636
2F	2501	--	2.60847	0.79632	--	1.06687	55.1812	95.0995
	2502	--	3.32029	0.71883	--	0.79218	51.0024	100.9780
	2503	--	3.75802	0.83951	--	1.00247	55.8519	111.5062
	2504	--	2.99608	0.57130	--	0.76319	47.6668	78.7178
	2505	--	2.89268	1.15610	--	0.77073	50.1463	79.7073
	2506	--	2.41148	0.79426	--	0.84211	46.1722	77.4163
	2507	--	3.50071	0.95216	--	0.81004	50.8290	92.0417
	2508	--	3.51126	0.81783	--	0.78844	45.2008	81.1949
	2509	--	3.96967	0.78975	--	1.08264	52.7197	98.4310
	2510	--	3.81762	0.76249	--	0.98403	48.1710	88.8202

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	1501	439.1194	63.2085	5.6680	25.1012	--	22.3178	30.3644
	1502	409.0138	68.8759	5.3022	33.1389	--	21.6331	25.6628
	1503	394.3515	65.6381	4.2887	30.3870	--	25.5753	29.0272
	1504	383.0932	62.6321	4.1787	29.6350	--	29.7310	26.3689
	1505	399.0258	60.6430	5.2119	25.2801	--	21.9679	25.1827
	1506	452.7273	58.7560	14.1627MPI	25.5502	--	25.3110	23.9234
	1507	431.4063	71.0417	5.9896	27.8125	--	21.2500	25.0000
	1508	384.3206	58.4868	6.2220	27.3768	--	25.6844	18.5167
	1509	506.2238	67.9916	4.2364	30.0209	--	19.6653	26.6213
	1510	397.7517	65.4448	5.1320	33.2356	--	23.2160	22.9228
2F	2501	460.9495	67.8407	5.0536	40.6840	--	19.0914	24.5533
	2502	442.3472	60.2445	6.3570	33.1051	--	18.7286	54.4743
	2503	473.5309	74.1235	5.3827	36.0494	--	27.2099	29.5802
	2504	328.3035	60.9246	4.2303	29.4810	--	22.1544	27.3005
	2505	371.9512	57.7561	4.9268	30.5366	--	21.8049	59.2683
	2506	372.4402	62.8230	5.5981	35.4067	--	16.5550	19.6172
	2507	379.8674	54.0976	6.2530	33.3491	--	28.0436	64.0928
	2508	420.3232	61.7042	5.2889	42.3604	--	19.1969	25.3673
	2509	428.6611	68.0962	5.9100	32.0607	--	20.8159	28.9749
	2510	431.2725	61.4632	4.4822	36.1669	--	27.3055	23.3900

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
3F	3501	--	2.97667	0.67951	--	0.76065	54.0061	91.4807MPI
	3502	--	2.92112	0.66158	--	0.77354	44.9873	85.6489
	3503	--	3.11695	0.87446	--	0.76180	58.3155	88.3584
	3504	--	3.91022	0.77307	--	0.97756	50.4239	94.6135
	3505	--	3.57513	0.66321	--	1.03109	55.5959	102.1762
	3506	--	3.42528	0.59679	--	1.03310	51.0030	91.5246
	3507	--	3.51009	0.66166	--	0.85406	44.9554	88.5969
	3508	--	3.03077	0.76923	--	0.65641	48.8205	96.3077
	3509	--	3.39506	0.85391	--	0.93621	53.0864	102.0062
	3510	--	3.41463	0.68691	--	0.77153	49.0294	94.0269
4F	4501	--	3.55721	0.67662	--	0.79602	50.7463	96.2687
	4502	--	3.11035	0.73242	--	0.68848	49.5605	85.0098
	4503	--	3.71722	0.81234	--	0.86889	57.0180	91.2596
	4504	--	5.02580	0.82559	--	0.83075	59.4427	99.7936
	4505	--	4.23779	0.70548	--	0.89788	52.4420	99.4080
	4506	--	3.50489	0.75142	--	0.70510	51.0551	91.9197
	4507	--	3.02952	0.74055	--	0.85966	49.9223	99.1196
	4508	--	2.66934	0.55695	--	0.91320	44.8068	84.4957
	4509	--	4.06615	0.81226	--	1.35214	41.1965	97.1790
	4510	--	3.64811	0.73559	--	0.60636	41.6501	87.5249

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Main Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
3F	3501	375.9635	56.6430	4.5639	35.0913	--	15.5172	21.8560
	3502	309.7201	60.9669	3.9186	46.1578MPI	--	29.9237	25.0382
	3503	430.7940	69.3670	4.9356	40.8262	--	21.7275	27.7897
	3504	433.5661	60.3491	4.9875	34.6633	--	20.8479	62.7431
	3505	485.9067	66.9948	7.2021	47.2539	--	28.8601	26.5803
	3506	460.6820	64.3932	5.2156	41.3741	--	33.8014	29.2879
	3507	345.3778	57.1093	4.7396	29.2351	--	15.6265	57.4378
	3508	466.3077	68.5128	6.0000	38.2564	--	26.8205	21.4872
	3509	465.7922	64.8148	4.0638	35.5967	--	26.0288	24.0741
	3510	382.1304	60.5276	6.4709	31.6078	--	15.1319	19.5122
4F	4501	411.8408	68.6070	3.4328	27.2139	--	22.5871	62.0896
	4502	372.7051	59.1797	3.9063	34.4727	--	18.6035	53.2227
	4503	464.6787	66.5296	5.1928	34.7558	--	17.6864	46.4781
	4504	493.6533	65.1703	7.6367	46.6460	--	23.0134	26.0578
	4505	409.4228	66.7982	4.1934	33.4978	--	20.5229	54.4154
	4506	442.9233	60.3706	4.1173	32.9388	--	17.3958	26.0422
	4507	460.9529	69.7048	5.4894	33.2988	--	19.7825	27.9648
	4508	399.2474	54.0391	4.3653	32.6141	--	26.4927	65.5294
	4509	419.9903	63.5700	4.6206	38.0837	--	24.5136	30.7393
	4510	434.0457	61.5308	6.9085	34.8907	--	32.1571	26.0437

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Appendix 3
Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1011	56.0019	2.80243	0.73330	56.5624	1.03223	70.2943	132.9752
	1012	54.3245	3.22581	0.61244	48.8546	1.01449	77.8401	142.0290
	1013	54.5009	2.70053	0.60606	62.3886	1.26114	72.5936	155.6150
	1014	58.7783	3.11312	0.71493	63.8009	1.19910	79.7738	160.1810
	1015	55.7035	2.64980	0.64802	67.8651	0.96760	83.9769	139.8136
4M	4011	50.3038	3.24653	0.47743	52.6042	0.77691	60.6771	119.5313
	4012	46.1020	2.42731	0.61525	56.6372	1.07459	74.8841	138.8538
	4013	52.6129	3.36138	0.70416	56.9531	0.90788	72.2764	135.9610
	4014	57.9767	2.67510	0.64202	70.7198	0.82685	79.9611	143.2879
	4015	55.2211	2.76576	0.62088	65.3810	0.86548	70.9313	119.5673

Appendix 18
Appendix 3
Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1M	1011	660.9528	77.5339	--	37.5993	176.1326	29.7992	--
	1012	605.5166	80.1309	--	32.8658	179.1024	17.2511	--
	1013	614.0820	80.1693	--	45.6774	168.2709	21.1676	--
	1014	644.8869	80.0452	--	49.4118	172.3077	18.9140	--
	1015	770.3506	82.0240	--	38.1713	177.4967	20.7723	--
4M	4011	539.9740	68.4462	--	37.7170	160.0694	17.8819	--
	4012	578.2975	75.2634	--	43.1100	141.4665	21.4918	--
	4013	669.0877	79.3623	--	38.2197	168.2905	22.4535	--
	4014	732.0039	83.9008	--	53.3074	170.5253	22.4708	--
	4015	610.9125	65.7573	--	52.2578	163.2173	19.0499	--

Appendix 18
Appendix 3
Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1F	1511	--	3.47890	0.84887	--	0.86850	60.7458	110.7458
	1512	--	3.68912	0.79275	--	0.93264	65.7513	104.0933
	1513	--	3.14300	0.68930	--	0.70988	65.5864	91.2551
	1514	--	3.35700	0.73022	--	0.71501	59.8377	93.9655
	1515	--	3.26174	0.92907	--	0.77922	56.1439	88.5115
4F	4511	--	3.51178	0.70128	--	0.56745	62.6874	98.1799
	4512	--	3.56102	0.66029	--	0.88342	51.8215	98.4062
	4513	--	2.89862	0.69282	--	0.66735	51.9103	94.0397
	4514	--	3.70739	0.94913	--	0.79706	65.9150	104.5621
	4515	--	2.84123	0.71495	--	0.57103	49.3036	77.1588

Appendix 18
Appendix 3
Individual Organ Weights Relative to Brain Weight: Recovery Study

Group 1 - Reference Item
Group 2 - mRNA-1653 10 µg/dose
Group 3 - mRNA-1653 50 µg/dose
Group 4 - mRNA-1653 150 µg/dose

Group / Sex	Animal No.	LIVER %	LUNG %	OVARY %	SPLEEN %	TESTIS %	THYMUS %	UTERUS %
1F	1511	415.4073	67.3209	3.8763	32.4828	--	29.8822	60.3042
	1512	431.7617	69.5337	4.1969	35.0259	--	26.4249	21.5544
	1513	387.5514	65.9465	5.2469	28.7037	--	15.4321	23.5082
	1514	420.1826	68.4077	5.7302	39.8073	--	20.7911	50.8621
	1515	393.4565	64.1359	3.1968	26.2737	--	21.8781	53.2967
4F	4511	521.0921	69.2719	5.4604	34.2077	--	17.6660	21.7880
	4512	427.7322	61.8852	3.1421	27.4590	--	12.9326	22.4044
	4513	347.3255	71.1666	3.5150	21.8034	--	15.1299	22.7713
	4514	492.8684	71.1589	4.8768	29.0509	--	17.5144	30.8338
	4515	401.2999	62.9062	5.1996	21.8663	--	15.5525	20.2414

Appendix 18

Appendix 4
Individual Gross and Microscopic Findings

Appendix 18

Individual Gross and Microscopic Findings Explanation Page

Abbreviation	Description	Abbreviation	Description
AB	Abdominal region	LJ	Lower jaw
AX	Axillary region	LN	Lymph node
BC	Body cavity	LT	Left
BI	Bilateral	LU	Lumbar region
CGEP	Complete gross examination performed	MF	Multifocal
CR	Cranium	MU	Muzzle
DC	Dorsal cervical region	NBF	Neutral buffered formalin
DT	Dorsal thoracic region	Ø	In diameter
F	Focal	PO	Periorbital region
FL	Forelimb	RT	Right
FP	Forepaw	SA	Sacral region
G	Gross Pathology	SC	Scapular region
GALT	Gut associated lymphoid tissue	SI	Small intestine
GL	Gland	SR	Scrotum
HL	Hindlimb	TGL	Trackable Gross Lesion
HP	Hindpaw	UG	Urogenital region
IG	Inguinal region	VC	Ventral cervical region
IS	Interscapular region	VT	Ventral thoracic region
LI	Large Intestine		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study:

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1653	10
3	mRNA-1653	50
4	mRNA-1653	150

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Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	1001	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Focus; dark : 3 to 4, bilateral (TGL)
THYMUS : Focus; dark : >10, right (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LYMPH NODE, POPLITEAL : Erythrocytosis; mild [LYMPH NODE, POPLITEAL : Focus; dark : 3 to 4, bilateral (G)]

THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 18
Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	1002	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LUNG : Focus; dark : 3 to >10. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LUNG : Hemorrhage; focal, mild [LUNG : Focus; dark : 3 to >10. (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; 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; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	1003	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0 ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death	30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Inflammation; interstitial, focal, minimal
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 18
Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	1004	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1 to 2, right middle, right caudal, left lobe. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Basophilia; tubular, focal, minimal
LUNG : Infiltration, mixed cell; focal, minimal : with eosinophilic material [LUNG : Focus; dark : 1 to 2, right middle, right caudal, left lobe. (G)]
NERVE, OPTIC : One Of A Pair Available For Evaluation.
NERVE, OPTIC : Examined

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; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	1005	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Dilatation; pelvis : Right (TGL)
LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
THYMUS : Focus; dark : >10, right (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Dilatation; mild, pelvis [KIDNEY : Dilatation; pelvis : Right (G)]
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, right (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	1006	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Focus; depressed : 1, dark, surrounded by a pale rim, right. (TGL)
LUNG : Focus; dark : 1 to 3. (TGL)
LYMPH NODE, MANDIBULAR : Enlargement : Right. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Cyst; focal, mild [KIDNEY : Focus; depressed : 1, dark, surrounded by a pale rim, right. (G)]
KIDNEY : Inflammation; interstitial, focal, mild
LUNG : Macrophage aggregation; focal, minimal
LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, minimal [LYMPH NODE, MANDIBULAR : Enlargement : Right. (G)]
THYMUS : Hemorrhage; multifocal, minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1 to 3. (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; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

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Appendix 4

Individual Gross and Microscopic Findings
5002033

None

Appendix 18
Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	1007	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Inflammation; interstitial, focal, minimal
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LUNG : Macrophage aggregation; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	1008	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Inflammation; interstitial, focal, minimal
NERVE, OPTIC : One Of A Pair Available For Evaluation.
NERVE, OPTIC : Examined

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, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1009	Group:	1	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	0 ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death	30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Vacuolation, hepatocellular; minimal
PANCREAS : Inflammation; focal, minimal, islet of langerhans
SITE, INJECTION : Inflammation, mixed cell; multifocal, minimal
STOMACH : Hemorrhage; focal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1010	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Cyst; focal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, 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, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 1011	Group: 1		Sex: Male
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, INGUINAL : Erythrocytosis; minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1012	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1013	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, INGUINAL : Erythrocytosis; minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1014	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Necrosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, INGUINAL : One Of A Pair Available For Evaluation.
LYMPH NODE, INGUINAL : Examined

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1015	Group: 1	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

THYMUS : Focus; dark : 5, right (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, INGUINAL : One Of A Pair Available For Evaluation.
LYMPH NODE, INGUINAL : Examined
NO CORRELATE : No correlating lesion [THYMUS : Focus; dark : 5, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SITE, INJECTION; SPLEEN; THYMUS

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1501	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LUNG : Infiltration, mixed cell; focal, minimal : with eosinophilic material

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1502	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Discoloration; dark : left (TGL)
SITE, INJECTION : Focus; dark : 1, left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Vacuolation, hepatocellular; minimal
LUNG : Hemorrhage; focal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, mild
NO CORRELATE : No correlating lesion [LYMPH NODE, POPLITEAL : Discoloration; dark : left (G) | SITE, INJECTION : Focus; dark : 1, left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1503	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Enlargement : Right (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, minimal [LYMPH NODE, MANDIBULAR : Enlargement : Right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1504	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 3 to 5, left lobe, right caudal (TGL)
SKIN : Scab; pale : 2 to 3, hindlimb bilateral, adjacent to injection sites (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Necrosis; multifocal, mild : subcapsular with hemorrhage
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LIVER : Vacuolation, hepatocellular; minimal
LUNG : Hemorrhage; focal, mild [LUNG : Focus; dark : 3 to 5, left lobe, right caudal (G)]
SKIN : Crust; focal, minimal [SKIN : Scab; pale : 2 to 3, hindlimb bilateral, adjacent to injection sites (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; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1505	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1506	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

OVARY : Cyst; pale : 1, left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
OVARY : Cyst; focal, minimal [OVARY : Cyst; pale : 1, left (G)]
SITE, INJECTION : Inflammation, mixed cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1507	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Enlargement : Right (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Basophilia; tubular, focal, minimal
LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, minimal [LYMPH NODE, MANDIBULAR : Enlargement : Right (G)]
LYMPH NODE, MESENTERIC : Erythrocytosis; minimal
NERVE, OPTIC : One Of A Pair Available For Evaluation.
NERVE, OPTIC : 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; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1508	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Tension lipidosis; focal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, 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, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1509	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Basophilia; tubular, focal, minimal
LUNG : Macrophage aggregation; focal, minimal
LYMPH NODE, INGUINAL : Erythrocytosis; minimal
LYMPH NODE, MESENTERIC : Erythrocytosis; minimal
NERVE, OPTIC : One Of A Pair Available For Evaluation.
NERVE, OPTIC : Examined
OVARY : One Of A Pair Available For Evaluation.
OVARY : Examined
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE MARROW; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 1510	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

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, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SITE, INJECTION; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 1511	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Erythrocytosis; mild [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
THYMUS : Hemorrhage; multifocal, mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 1512	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]

SITE, INJECTION : Inflammation, mixed cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 1513	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
THYMUS : Hemorrhage; multifocal, mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	1514	Group: 1	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 0 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, ADRENAL : Focus; dark : 2, left (TGL)
KIDNEY : Focus; depressed : 1, dark, linear, right (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
SMALL INTESTINE, JEJUNUM : Focus; dark : 1, middle, wall (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]

THYMUS : Hemorrhage; multifocal, moderate [THYMUS : Focus; dark : >10 (G)]

NO CORRELATE : No correlating lesion [GLAND, ADRENAL : Focus; dark : 2, left (G) | KIDNEY : Focus; depressed : 1, dark, linear, right (G) | SMALL INTESTINE, JEJUNUM : Focus; dark : 1, middle, wall (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; GLAND, ADRENAL; KIDNEY; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SITE, INJECTION; SMALL INTESTINE, JEJUNUM; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 1515	Group: 1		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 0 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
THYMUS : Focus; dark : >10, left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, left (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; NERVE, SCIATIC; SITE, INJECTION; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 2001	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [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

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Individual Gross and Microscopic Findings
5002033

Animal: 2002	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1 to 8. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LUNG : Hemorrhage; focal, minimal [LUNG : Focus; dark : 1 to 8. (G)]
LUNG : Infiltration, mixed cell; focal, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : Left. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; NERVE, SCIATIC; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	2003	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]

NERVE, SCIATIC : Inflammation, mixed cell; multifocal, mild
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Swelling : Left (G) | 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

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Individual Gross and Microscopic Findings
5002033

Animal:	2004	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1 to 3, right middle, right caudal, right accessory. (TGL)
LYMPH NODE : Enlargement : Iliac left. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LUNG : Infiltration, mixed cell; multifocal, minimal [LUNG : Focus; dark : 1 to 3, right middle, right caudal, right accessory. (G)]
LYMPH NODE : Inflammation, mixed cell; minimal [LYMPH NODE : Enlargement : Iliac left. (G)]
LYMPH NODE : Hyperplasia; lymphoid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : Left. (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 2005	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	2006	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; pale : 2 to 5, left lobe, right cranial, right caudal (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)
SITE, INJECTION : Swelling : Left. (TGL)
SPLEEN : Nodule; [a] : 1, dark, firm, pedunculated. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LUNG : Infiltration, mixed cell; focal, minimal : with eosinophilic material [LUNG : Focus; pale : 2 to 5, left lobe, right cranial, right caudal (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Left. (G)]

NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : Left. (G) | SITE, INJECTION : Swelling : Left. (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
NO CORRELATE : No correlating lesion [SPLEEN : Nodule; [a] : 1, dark, firm, pedunculated. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 2007	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (TGL)
SITE, INJECTION : Swelling : Left (TGL)
THYMUS : Focus; dark : >10, right (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Swelling : Left (G)]
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, right (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 2008	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LUNG : Focus; dark : 1 to 2. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LUNG : Macrophage aggregation; focal, minimal [LUNG : Focus; dark : 1 to 2. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : Left. (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 2009	Group: 2	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 10 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Bilateral (TGL)
THYMUS : Focus; dark : 1, right (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal [LYMPH NODE, INGUINAL : Enlargement : Left (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Bilateral (G)]
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, mild
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 1, right (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	2010	Group: 2	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, medial lobe. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)
SITE, INJECTION : Swelling : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, medial lobe. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, minimal
NO CORRELATE : No correlating lesion [SITE, INJECTION : Swelling : Left. (G) | 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

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Individual Gross and Microscopic Findings
5002033

Animal:	2501	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SITE, INJECTION

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	2502	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LARGE INTESTINE, RECTUM : Parasite : 4
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
STOMACH : Focus; pale : >10, mucosa, glandular (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, mild [SITE, INJECTION : Abnormal consistency; firm : left (G)]
NO CORRELATE : No correlating lesion [STOMACH : Focus; pale : >10, mucosa, glandular (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, INGUINAL; SPLEEN; STOMACH

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	2503	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, mild : with edema

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	2504	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : left (G)]
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	2505	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LYMPH NODE, INGUINAL : Erythrocytosis; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 2506	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 10 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left (TGL)
THYMUS : Focus; dark : 8 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, mild : with edema [SITE, INJECTION : Abnormal consistency; firm : left (G)]
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 8 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	2507	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	2508	Group: 2	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 10 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, mild : with edema

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 2509	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 10 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema, necrotic debris and hemorrhage [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

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Individual Gross and Microscopic Findings
5002033

Animal: 2510	Group: 2		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 10 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left (TGL)
STOMACH : Focus; dark : 2, mucosa, glandular (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, mild
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : left (G)]
STOMACH : Inflammation; subacute, multifocal, mild [STOMACH : Focus; dark : 2, mucosa, glandular (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	3001	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; pale : >10, left lobe, right caudal, right middle (TGL)
LUNG : Discoloration; pale : right accessory (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; minimal
LUNG : Infiltration, mixed cell; multifocal, minimal [LUNG : Focus; pale : >10, left lobe, right caudal, right middle (G) | LUNG : Discoloration; pale : right accessory (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, 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

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Individual Gross and Microscopic Findings
5002033

Animal:	3002	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 2, near hilus, right lateral. (TGL)
LUNG : Focus; dark : 1 to 3. (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)
THYMUS : Focus; dark : 2, right lobe. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 2, near hilus, right lateral. (G)]
LUNG : Infiltration, mixed cell; focal, minimal [LUNG : Focus; dark : 1 to 3. (G)]
LYMPH NODE : Inflammation, mixed cell; minimal [LYMPH NODE : Enlargement : Iliac left. (G)]
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal [LYMPH NODE, INGUINAL : Enlargement : Left. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : bilateral (G)]
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left. (G)]
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 2, right lobe. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

None

Histo Pathology - The following Tissues were Not Examined:

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Individual Gross and Microscopic Findings
5002033

None

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Individual Gross and Microscopic Findings
5002033

Animal:	3003	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
LYMPH NODE, POPLITEAL : Focus; dark : >10, left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal : with hemorrhage [LYMPH NODE, POPLITEAL : Enlargement : Bilateral (G) | LYMPH NODE, POPLITEAL : Focus; dark : >10, left (G)]
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema, necrotic debris and hemorrhage [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	3004	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal: Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LUNG : Focus; dark : 1 to 4. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)
SITE, INJECTION : Swelling : Left. (TGL)
THYMUS : Focus; dark : >10, left lobe. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema [SITE, INJECTION : Abnormal consistency; firm : Left. (G) | SITE, INJECTION : Swelling : Left. (G)]
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, left lobe. (G)]
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1 to 4. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LUNG; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	3005	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
THYMUS : Focus; dark : 5 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 5 (G)]

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

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Individual Gross and Microscopic Findings
5002033

Animal:	3006	Group:	3	Sex: Male
Species:	Rat	Strain:	Sprague-Dawley	
		Dose:	50 ug/dose	
		Removal Reason:	Terminal Euthanasia	
		Day (Week) of Death	30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)
SITE, INJECTION : Swelling : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [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

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Individual Gross and Microscopic Findings
5002033

Animal:	3007	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; dark : >10, papillary process of caudate, adjacent to focus depressed (TGL)
LIVER : Focus; depressed : 1, pale, linear, papillary process of caudate (TGL)
LIVER : Focus; pale : 1 to >10, fissure, right medial, papillary process of caudate (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
LIVER : Necrosis; multifocal, moderate [LIVER : Focus; pale : 1 to >10, fissure, right medial, papillary process of caudate (G) | LIVER : Focus; dark : >10, papillary process of caudate, adjacent to focus depressed (G) | LIVER : Focus; depressed : 1, pale, linear, papillary process of caudate (G)]
LYMPH NODE, INGUINAL : One Of A Pair Available For Evaluation.
LYMPH NODE, INGUINAL : Examined
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Bilateral (G)]
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	3008	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1 to 2, right accessory, right caudal, left lobe. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; minimal
LUNG : Infiltration, mixed cell; focal, minimal [LUNG : Focus; dark : 1 to 2, right accessory, right caudal, left lobe. (G)]
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, mild : with edema [SITE, INJECTION : Abnormal consistency; firm : Left. (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 3009	Group: 3	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 50 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Enlargement : Bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Bilateral (G)]
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [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

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Individual Gross and Microscopic Findings
5002033

Animal:	3010	Group: 3	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1 to 2. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)
SITE, INJECTION : Swelling : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, mild
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Swelling : Left. (G) | SITE, INJECTION : Abnormal consistency; firm : Left. (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1 to 2. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LUNG; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 3501	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 50 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Cyst; pale : 3, right (TGL)
LIVER : Focus; pale : 1, fissure, right medial (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
KIDNEY : Amphophilic vacuolar tubular carcinoma; malignant without metastasis, incidental [KIDNEY : Cyst; pale : 3, right (G)]
LIVER : Necrosis; focal, minimal : subcapsular
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, fissure, right medial (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema, necrotic debris and hemorrhage [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	3502	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
SITE, INJECTION : Thick : left (TGL)
SPLEEN : Focus; pale : >10, surface (TGL)
SPLEEN : Adhesion : to abdominal fat (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LYMPH NODE : Inflammation, mixed cell; mild [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, mild
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G) | SITE, INJECTION : Thick : left (G)]
SPLEEN : Inflammation; capsular, subacute, multifocal, moderate [SPLEEN : Focus; pale : >10, surface (G) | SPLEEN : Adhesion : to abdominal fat (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	3503	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema, necrotic debris and hemorrhage [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
NO CORRELATE : No correlating lesion [LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 3504	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 50 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [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

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Individual Gross and Microscopic Findings
5002033

Animal:	3505	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, POPLITEAL : Focus; dark : 1, left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate : with hemorrhage [LYMPH NODE, POPLITEAL : Focus; dark : 1, left (G)]
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and hemorrhage [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	3506	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [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; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 3507	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 50 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
LIVER : Tension lipidosis; focal, minimal [LIVER : Focus; pale : 1, near hilus, right lateral (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : Left (G)]
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

LYMPH NODE, INGUINAL

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	3508	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Discoloration; dark : corticomedullary junction, bilateral (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
KIDNEY : Cyst; focal, minimal
KIDNEY : Basophilia; tubular, focal, minimal
LYMPH NODE : Inflammation, mixed cell; minimal [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
NO CORRELATE : No correlating lesion [KIDNEY : Discoloration; dark : corticomedullary junction, bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 3509	Group: 3		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 50 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [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

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Individual Gross and Microscopic Findings
5002033

Animal:	3510	Group: 3	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 50 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
SITE, INJECTION : Material accumulation; clot : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema, necrotic debris and hemorrhage [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G) | SITE, INJECTION : Material accumulation; clot : 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

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Individual Gross and Microscopic Findings
5002033

Animal:	4001	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Bilateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Necrosis; focal, minimal : subcapsular
LIVER : Vacuolation, hepatocellular; mild
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal [LYMPH NODE, INGUINAL : Enlargement : Left (G)]

LYMPH NODE, INGUINAL : Erythrocytosis; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Bilateral (G)]
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; mild
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

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Appendix 4

Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	4002	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial. (TGL)
LYMPH NODE : Enlargement : Iliac left. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)
SITE, INJECTION : Swelling : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE : Inflammation, mixed cell; mild [LYMPH NODE : Enlargement : Iliac left. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema [SITE, INJECTION : Abnormal consistency; firm : Left. (G) | SITE, INJECTION : Swelling : Left. (G)]
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, fissure, right medial. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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Appendix 4

Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4003	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Basophilia; tubular, focal, minimal
LYMPH NODE, INGUINAL : One Of A Pair Available For Evaluation.
LYMPH NODE, INGUINAL : Examined
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
THYMUS : Hemorrhage; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, 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; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

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Individual Gross and Microscopic Findings
5002033

Histo Pathology - The following Tissues were Not Examined:

None

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Appendix 4

Individual Gross and Microscopic Findings
5002033

Animal:	4004	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)
SITE, INJECTION : Swelling : Left. (TGL)
SITE, INJECTION : Thick : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left. (G) | SITE, INJECTION : Swelling : Left. (G) | SITE, INJECTION : Thick : Left. (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; mild

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4005	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, 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; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4006	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Focus; dark : 1, left. (TGL)
KIDNEY : Focus; depressed : >10, surface, cortex, medulla, left (TGL)
KIDNEY : Focus; pale : 1, linear, left. (TGL)
LYMPH NODE : Enlargement : Iliac left. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)
SITE, INJECTION : Swelling : Left. (TGL)
SITE, INJECTION : Thick : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Cyst; multifocal, moderate [KIDNEY : Focus; dark : 1, left. (G) | KIDNEY : Focus; pale : 1, linear, left. (G) | KIDNEY : Focus; depressed : >10, surface, cortex, medulla, left (G)]
KIDNEY : Inflammation; interstitial, multifocal, mild
LIVER : Vacuolation, hepatocellular; mild
LYMPH NODE : Inflammation, mixed cell; minimal [LYMPH NODE : Enlargement : Iliac left. (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, mild
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema [SITE, INJECTION : Abnormal consistency; firm : Left. (G) | SITE, INJECTION : Swelling : Left. (G) | SITE, INJECTION : Thick : Left. (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; mild

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 4007	Group: 4	Sex: Male
Species: Rat	Strain: Sprague-Dawley	
	Dose: 150 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 1, edge, left lobe (TGL)
LUNG : Focus; pale : 1, right middle (TGL)
LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
KIDNEY : Basophilia; tubular, focal, minimal
LUNG : Macrophage aggregation; multifocal, minimal [LUNG : Focus; pale : 1, right middle (G)]
LYMPH NODE, INGUINAL : Inflammation, mixed cell; mild [LYMPH NODE, INGUINAL : Enlargement : Left (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; mild
THYMUS : Hemorrhage; multifocal, mild [THYMUS : Focus; dark : >10 (G)]
TRACHEA : Infiltration, mixed cell; multifocal, minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 1, edge, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4008	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE : Enlargement : Iliac left , deep cervical left. (TGL)
LYMPH NODE, MANDIBULAR : Enlargement : right (TGL)
SITE, INJECTION : Swelling : Left. (TGL)
SITE, INJECTION : Thick : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Vacuolation, hepatocellular; mild
LYMPH NODE : Hyperplasia; lymphoid, mild [LYMPH NODE : Enlargement : Iliac left , deep cervical left. (G)]
LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, minimal [LYMPH NODE, MANDIBULAR : Enlargement : right (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [SITE, INJECTION : Swelling : Left. (G) | SITE, INJECTION : Thick : Left. (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
TESTIS : Atrophy; tubular, bilateral, multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4009	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
KIDNEY : Basophilia; tubular, multifocal, minimal
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal [LYMPH NODE, INGUINAL : Enlargement : Left (G)]

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4010	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; pale : 2 to 3, right caudal, left lobe. (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left. (TGL)
SITE, INJECTION : Swelling : Left. (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
LUNG : Macrophage aggregation; focal, minimal [LUNG : Focus; pale : 2 to 3, right caudal, left lobe. (G)]
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Swelling : Left. (G) | SITE, INJECTION : Abnormal consistency; firm : Left. (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
THYMUS : Hemorrhage; multifocal, minimal
NO CORRELATE : No correlating lesion

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TESTIS; TONGUE; TRACHEA; URINARY BLADDER

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Individual Gross and Microscopic Findings
5002033

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4011	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Dilatation; pelvis : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Dilatation; mild, pelvis [KIDNEY : Dilatation; pelvis : Left (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; multifocal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4012	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; pale : 3, left lobe (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LUNG : Infiltration, mixed cell; focal, minimal [LUNG : Focus; pale : 3, left lobe (G)]
LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
NERVE, SCIATIC : Infiltration, mononuclear cell; multifocal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4013	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; pale : 2, left lobe (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, INGUINAL : One Of A Pair Available For Evaluation.
LYMPH NODE, INGUINAL : Examined
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; multifocal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal
NO CORRELATE : No correlating lesion [LUNG : Focus; pale : 2, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LUNG; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4014	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; multifocal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4015	Group: 4	Sex: Male
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

BONE, STERNUM : Abnormal appearance; bent (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LIVER : Infiltration, mononuclear cell; multifocal, minimal : with necrotic cell
NERVE, SCIATIC : Infiltration, mononuclear cell; multifocal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, mild
NO CORRELATE : No correlating lesion [BONE, STERNUM : Abnormal appearance; bent (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; BONE, STERNUM; LYMPH NODE, POPLITEAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, INGUINAL - Not Present In Wet Tissues.

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Individual Gross and Microscopic Findings
5002033

Animal: 4501	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 150 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)
THYMUS : Focus; dark : 1, left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE, INGUINAL : Inflammation, mixed cell; mild [LYMPH NODE, INGUINAL : Enlargement : Left (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 1, left (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, 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; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

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Individual Gross and Microscopic Findings
5002033

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

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Individual Gross and Microscopic Findings
5002033

Animal:	4502	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE : Enlargement : iliac left (TGL)
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 study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE : Inflammation, mixed cell; mild : with necrotic cells [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : left (G)]

NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
NO CORRELATE : No correlating lesion [LYMPH NODE, INGUINAL : Enlargement : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4503	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, 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, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal: 4504	Group: 4		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 150 ug/dose		
	Removal Reason: Terminal Euthanasia		
	Day (Week) of Death 30 (5)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : 2 to 3, left lobe, right caudal (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)
SITE, INJECTION : Thick : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LUNG : Infiltration, mixed cell; focal, minimal : with eosinophilic material [LUNG : Focus; dark : 2 to 3, left lobe, right caudal (G)]
LYMPH NODE : Inflammation, mixed cell; mild : with necrotic cells [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, INGUINAL : Inflammation, mixed cell; mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, mild
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [SITE, INJECTION : Thick : left (G) | SITE, INJECTION : Swelling : left (G) | SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4505	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, near hilus, right lateral (TGL)
LYMPH NODE, INGUINAL : Enlargement : Left (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE, INGUINAL : Inflammation, mixed cell; mild [LYMPH NODE, INGUINAL : Enlargement : Left (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]

NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
NO CORRELATE : No correlating lesion [LIVER : Focus; pale : 1, near hilus, right lateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4506	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, linear, left lateral (TGL)
LUNG : Focus; dark : 2, left lobe (TGL)
LYMPH NODE : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Necrosis; focal, mild : subcapsular [LIVER : Focus; pale : 1, linear, left lateral (G)]
LIVER : Infiltration, mononuclear cell; multifocal, minimal
LIVER : Vacuolation, hepatocellular; mild
LUNG : Macrophage aggregation; focal, minimal
LYMPH NODE : Inflammation, mixed cell; mild [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, INGUINAL : Erythrocytosis; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
NO CORRELATE : No correlating lesion [LUNG : Focus; dark : 2, left lobe (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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Individual Gross and Microscopic Findings
5002033

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; LYMPH NODE, POPLITEAL; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
5002033

Animal:	4507	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LIVER : Focus; pale : 1, fissure, right medial (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, minimal
LIVER : Vacuolation, hepatocellular; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; mild
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; mild
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; 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, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal:	4508	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, INJECTION : Abnormal consistency; firm : left (TGL)
SITE, INJECTION : Swelling : left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
LIVER : Vacuolation, hepatocellular; mild
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : left (G) | SITE, INJECTION : Swelling : left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, INGUINAL; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; THYMUS; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal:	4509	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Terminal Euthanasia	
		Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
SITE, INJECTION : Abnormal consistency; firm : Left (TGL)
SITE, INJECTION : Swelling : Left (TGL)
THYMUS : Focus; dark : 1, left (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
GLAND, PARATHYROID : One Of A Pair Available For Evaluation.
GLAND, PARATHYROID : Examined
LIVER : Vacuolation, hepatocellular; mild
LYMPH NODE, INGUINAL : Inflammation, mixed cell; mild
LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, minimal [LYMPH NODE, MANDIBULAR : Enlargement : Bilateral (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; moderate [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]
SITE, INJECTION : Inflammation, mixed cell; multifocal, marked : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : Left (G) | SITE, INJECTION : Swelling : Left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
SPLEEN : Increased macrophages, periarteriolar lymphoid sheath; minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 1, left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

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ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

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Individual Gross and Microscopic Findings
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Animal: 4510	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 150 ug/dose	
	Removal Reason: Terminal Euthanasia	
	Day (Week) of Death 30 (5)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE : Enlargement : iliac left (TGL)
SITE, INJECTION : Abnormal consistency; firm : left (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE MARROW : Increased hematopoiesis; myeloid, mild
LIVER : Vacuolation, hepatocellular; mild
LYMPH NODE : Inflammation, mixed cell; mild [LYMPH NODE : Enlargement : iliac left (G)]
LYMPH NODE, INGUINAL : Inflammation, mixed cell; minimal
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Inflammation, mixed cell; multifocal, minimal
SITE, INJECTION : Inflammation, mixed cell; multifocal, moderate : with edema and necrotic debris [SITE, INJECTION : Abnormal consistency; firm : left (G)]
SPLEEN : Decreased cellularity, periarteriolar lymphoid sheath; minimal
THYMUS : Hemorrhage; multifocal, mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BRAIN; CERVIX; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, HARDERIAN; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SPINAL CORD, CERVICAL; SPINAL CORD, LUMBAR; SPINAL CORD, THORACIC; STOMACH; TONGUE; TRACHEA; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

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None

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Individual Gross and Microscopic Findings
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Animal: 4511	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 150 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Bilateral (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Erythrocytosis; mild [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Bilateral (G)]
NERVE, SCIATIC : Infiltration, mononuclear cell; multifocal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal
THYMUS : Hemorrhage; multifocal, mild [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Animal: 4512	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 150 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Dilatation; pelvis : Bilateral (TGL)
LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)
THYMUS : Focus; dark : >10, right (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, INGUINAL : One Of A Pair Available For Evaluation.
LYMPH NODE, INGUINAL : Examined
LYMPH NODE, MANDIBULAR : Erythrocytosis; mild [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; multifocal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10, right (G)]
NO CORRELATE : No correlating lesion [KIDNEY : Dilatation; pelvis : Bilateral (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; KIDNEY; LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Animal: 4513	Group: 4		Sex: Female
Species: Rat	Strain: Sprague-Dawley		
	Dose: 150 ug/dose		
	Removal Reason: Recovery Euthanasia		
	Day (Week) of Death 43 (7)		

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, INGUINAL : One Of A Pair Available For Evaluation.
LYMPH NODE, INGUINAL : Examined
LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : >10, bilateral (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; NERVE, SCIATIC; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Animal:	4514	Group: 4	Sex: Female
Species:	Rat	Strain: Sprague-Dawley	
		Dose: 150 ug/dose	
		Removal Reason: Recovery Euthanasia	
		Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : 4, right (TGL)
LYMPH NODE, POPLITEAL : Enlargement : Left (TGL)
THYMUS : Focus; dark : 9 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 4, right (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal [LYMPH NODE, POPLITEAL : Enlargement : Left (G)]
NERVE, SCIATIC : Infiltration, mononuclear cell; multifocal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : 9 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Animal: 4515	Group: 4	Sex: Female
Species: Rat	Strain: Sprague-Dawley	
	Dose: 150 ug/dose	
	Removal Reason: Recovery Euthanasia	
	Day (Week) of Death 43 (7)	

Gross Pathology Animal Details:

Animal Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MANDIBULAR : Focus; dark : 2, right (TGL)
THYMUS : Focus; dark : >10 (TGL)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LYMPH NODE, MANDIBULAR : Erythrocytosis; minimal [LYMPH NODE, MANDIBULAR : Focus; dark : 2, right (G)]
LYMPH NODE, POPLITEAL : Inflammation, mixed cell; minimal
NERVE, SCIATIC : Infiltration, mononuclear cell; multifocal, minimal
SITE, INJECTION : Infiltration, mononuclear cell; multifocal, minimal
THYMUS : Hemorrhage; multifocal, minimal [THYMUS : Focus; dark : >10 (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

BONE MARROW; LIVER; LYMPH NODE, INGUINAL; SPLEEN

Histo Pathology - The following Tissues were Not Examined:

None

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Key Page

Codes

(TGL) = Trackable Gross Lesion, (MPF) = Major Pathological Finding, (?) = Questionable, (E) = Excluded, (C) = Clinical Observation, (M) = Mass, (G) = Gross Pathology, (H) = Histo Pathology

Group Information

Short Name	Long Name
1	1
2	2
3	3
4	4

Appendix 19

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Toxicology/Pathology Department
200 Tech Square • Cambridge, MA 02139
Phone 617-714-6500 • Fax 617-583-1998

PEER-REVIEW STATEMENT

Study Number: 5002033

Study Title: A 1-month (3 doses) Study of mRNA-1653 by Intramuscular Injection in Sprague Dawley Rat with a 2-Week Recovery Period

EXPERIMENTAL DESIGN:

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µl)	Dose Concentration (µg/mL)	No. of Animals			
					Main Study[a]		Recovery Study[b]	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1653	10	200	50	10	10	-	-
3	mRNA-1653	50	200	250	10	10	-	-
4	mRNA-1653	150	200	750	10	10	5	5

[a] = 10/sex/groups 1 to 4 necropsied 1 day following the last dose
[b] = The remaining 5/sex/groups 1 to 4 necropsied 2 weeks following the last dose.

PURPOSE: The purpose of this peer review was to assess the overall quality and consistency of the microscopic data and determine the validity of the study pathologist's conclusions.

METHODS:

1. Study plan and amendments, narrative pathology report, histology records, clinical observations, and organ weight data were reviewed
2. Review of all tissues from the Male and Female Groups 1 and Group 4, animal numbers: 1003,1006,1010,1503,1508, 4003, 4006, 4010, 4503, 4506, and 4509.

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3. The following organs from all animals in all Groups were reviewed: Bone Marrow, Injection Site, Mesenteric lymph nodes (Group 1 and 4 males only), Sciatic nerve (Group 1 and 4 only), Liver, Spleen and lymph node popliteal. In the Recovery, Groups: Sciatic nerve, Liver, Spleen, Injection site and Popliteal Lymph node were examined

4. Following review of the histological sections and corresponding histopathology-related study data, findings were discussed with the study pathologist.

RESULTS:

Differences of opinion were resolved and mutual agreement on terminology and diagnoses were achieved. The histopathology tables and corresponding narrative contained in the pathology report reflect diagnoses and conclusions agreed to by the peer reviewer and study pathologist

(b) (6)

Date : September 19 2017

Date : 27 Sep 2017