charles river

FINAL REPORT

Test Facility Study No. 5002400

A 1-Month (3 Doses) Intramuscular Injection Toxicity Study of mRNA-1893 in Sprague-Dawley Rats followed by a 2-Week Recovery Period

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

TEST FACILITY:
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Sherbrooke Site (CR SHB)
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QUALITY ASSURANCE STATEMENT

Study Number: 5002400

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

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
07-Nov-2018 - 08-Nov-2018	Final Study Plan	09-Nov-2018	09-Nov-2018
15-Nov-2018	Study Plan Amendment 01	15-Nov-2018	15-Nov-2018
16-Nov-2018	Study Plan Amendment 02	16-Nov-2018	16-Nov-2018
19-Nov-2018	Addition of Study Plan to Provantis	20-Nov-2018	20-Nov-2018
19-Nov-2018	Body Temperature	20-Nov-2018	20-Nov-2018
19-Nov-2018	Blood Collection	20-Nov-2018	20-Nov-2018
20-Nov-2018	Dose Preparation	21-Nov-2018	21-Nov-2018
21-Nov-2018	Clinical Observations	21-Nov-2018	21-Nov-2018
29-Nov-2018	Study Plan Amendment 03	29-Nov-2018	29-Nov-2018
10-Dec-2018	Food Consumption	10-Dec-2018	10-Dec-2018
13-Dec-2018	Study Plan Amendment 04	13-Dec-2018	13-Dec-2018
21-Dec-2018	Study Plan Amendment 05	21-Dec-2018	21-Dec-2018
02-Jan-2019	Study Plan Amendment 06	02-Jan-2019	02-Jan-2019
08-Jan-2019	Study Plan Amendment 07	08-Jan-2019	08-Jan-2019
28-Jan-2019 - 05-Feb-2019	Data Review - Technical Operations	05-Feb-2019	05-Feb-2019
28-Jan-2019 - 05-Feb-2019	Data Review - Formulations	05-Feb-2019	05-Feb-2019
28-Jan-2019 - 05-Feb-2019	Data Review - Clinical Pathology	05-Feb-2019	05-Feb-2019
28-Jan-2019 - 05-Feb-2019	Data Review - Sample Management	05-Feb-2019	05-Feb-2019
28-Jan-2019 - 05-Feb-2019	Data Review - Veterinary Services	05-Feb-2019	05-Feb-2019
28-Jan-2019 - 05-Feb-2019	Data Review - Animal Care	05-Feb-2019	05-Feb-2019
28-Jan-2019 - 05-Feb-2019	Report Preparation	05-Feb-2019	05-Feb-2019
04-Feb-2019 - 05-Feb-2019	Phase Report - Ophthalmology	05-Feb-2019	05-Feb-2019
07-Feb-2019	Study Plan Amendment 08	07-Feb-2019	07-Feb-2019
07-Feb-2019	Study Plan Amendment 09	07-Feb-2019	07-Feb-2019
11-Feb-2019	Study Plan Amendment 10	11-Feb-2019	11-Feb-2019
20-Feb-2019	Data Review - Necropsy	20-Feb-2019	20-Feb-2019
20-Feb-2019	Data Review - Histology	20-Feb-2019	20-Feb-2019
20-Feb-2019	Data Review - Shipping/Receiving	20-Feb-2019	20-Feb-2019
20-Feb-2019	Report Preparation	20-Feb-2019	20-Feb-2019

QUALITY ASSURANCE STATEMENT - Study Number: 5002400

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
20-Feb-2019	Phase Report - Pathology	20-Feb-2019	20-Feb-2019
28-Feb-2019 - 01-Mar-2019	Data Review - Analytical Chemistry	01-Mar-2019	01-Mar-2019
28-Feb-2019 - 01-Mar-2019	Phase Report - Analytical Chemistry	01-Mar-2019	01-Mar-2019
01-Mar-2019 06-Mar-2019	Biomarkers	06-Mar-2019	06-Mar-2019
22-Mar-2019 25-Mar-2019	Report - Materials and Methods	26-Mar-2019	26-Mar-2019
25-Mar-2019	Data Review - Shipping/Receiving	26-Mar-2019	26-Mar-2019
25-Mar-2019 - 26-Mar-2019	Data Review - Bioanalysis & Immunology	27-Mar-2019	27-Mar-2019
25-Mar-2019 - 26-Mar-2019	Phase Report - Immunology	27-Mar-2019	27-Mar-2019
26-Mar-2019	Data Review - Sample Management	27-Mar-2019	27-Mar-2019
26-Mar-2019	Report Preparation	27-Mar-2019	27-Mar-2019
16-Apr-2019	Final Phase Report - Analytical Chemistry	16-Apr-2019	16-Apr-2019
16-Apr-2019	Final Phase Report - Ophthalmology	16-Apr-2019	16-Apr-2019
16-Apr-2019	Final Phase Report - Pathology	16-Apr-2019	16-Apr-2019
25-Apr-2019	Study Plan Amendment 11	25-Apr-2019	25-Apr-2019
26-Apr-2019	Study Plan Amendment 12	26-Apr-2019	26-Apr-2019
10-May-2019	Study Plan Amendment 13	10-May-2019	10-May-2019
10-May-2019	Report - Results	10-May-2019	10-May-2019
09-Sep-2019	Final Report	09-Sep-2019	09-Sep-2019
11-Sep-2019	Study Plan Amendment 14	11-Sep-2019	11-Sep-2019
12-Sep-2019	Study Plan Amendment 15	12-Sep-2019	12-Sep-2019
13-Sep-2019	Study Plan Amendment 16	13-Sep-2019	13-Sep-2019
17-Sep-2019	Study Plan Amendment 17	17-Sep-2019	17-Sep-2019

QUALITY ASSURANCE STATEMENT - Study Number: 5002400

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.

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[redacted]
Quality Assurance Auditor

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.

SEND datasets were not subject to QA Audit nor used as the basis for the Study Director interpretation of the study results.

Exceptions from the above regulations are listed below.

- 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 [redacted] were conducted using scientifically acceptable methods and in accordance with all applicable analytical procedures.
- Stability analysis under the conditions of use were not conducted for the dose formulations/concentrations used on this study.
- Pathology peer review

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

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

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[redacted] MSc
Study Director

1. RESPONSIBLE PERSONNEL

1.1. Test Facility

Study Director	[redacted] MSc
Test Facility Management	[redacted] BSc

1.2. Individual Scientists (IS) at Test Facility

Ophthalmology	[redacted] DMV, MS, DACVO Consultant Ophthalmologist Charles River Laboratories Montreal ULC, Senneville Site (CR MTL), Canada
Analytical Chemistry (Purity, Concentration and Particle Size Analysis)	[redacted] BSc Charles River Laboratories Montreal ULC, Senneville Site (CR MTL), Canada
Immunology (α1-Acid Glycoprotein and α-2 Macroglobulin Analysis)	[redacted] DEC Charles River Laboratories Montreal ULC Sherbrooke Site (CR SHB), Canada
Biomarkers (Cytokines Analysis And interpretation)	[redacted] DEC Charles River Laboratories Montreal ULC Sherbrooke Site (CR SHB), Canada
Pathology	[redacted] DVM, Dip Path, MSc, Diplomate ACVP Charles River Laboratories Montreal ULC, Senneville Site (CR MTL), Canada

1.3. PIs at Sponsor-designated Test Site

Immunogenicity [redacted]	[redacted] PhD Battelle Biomedical Research Center (BBRC) Clinical and Nonclinical Research, Healt West Jefferson, OH 43162, USA

2. SUMMARY

The objectives of this study were to determine the potential toxicity of mRNA-1893, when given by intramuscular injection for 1 month (3 doses administered every other week) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

The study design was as follows:

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study*		Recovery Study*	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1893	10	200	0.05	10	10	-	-
3	mRNA-1893	30	200	0.15	10	10	-	-
4	mRNA-1893	96	200	0.48	10	10	5	5

-: Not applicable.
* = 10/sex/Groups 1 to 4 were necropsied 1 day following the last dose, the remaining 5/sex/Groups 1 and 4 (recovery), were necropsied 2 weeks following the last dose.

The following parameters and end points were evaluated in this study: clinical signs, body weights, food consumption, ophthalmology, body temperature, clinical pathology parameters (hematology, coagulation, clinical chemistry, α1-acid glycoprotein and α2-macroglobulin), cytokines (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, and MCP-1), [redacted] gross necropsy findings, organ weights, and histopathologic examinations.

There were no mortalities and no mRNA-1893-related changes in body weight, food consumption and ophthalmology.

mRNA-1893-related inflammatory changes at the injection site occurred with a dose-related increased incidence/severity starting at the 10 µg/dose. The inflammation was characterized clinically by firmness and swelling sometimes as well as localized skin redness or scabbed in males and females. In addition to the aforementioned clinical signs, individual males and females were noted with increased vocalization. Also, two females were identified with an abnormal gait and one female was noted with a limited usage at the left hindlimb. Grossly the inflammation was characterized by the following findings: firm consistency, swelling, thick and dark focus. Microscopically, in all Groups, the clinical observations were correlated with mixed cell inflammation. An exacerbation of the inflammation was noted in animals treated with mRNA-1893 at ≥ 10 µg/dose based on the distribution and increased incidence and severity of the mixed cell inflammation compared to control animals. There was evidence of an extension of mixed cell inflammation from the injection site into the surrounding connective tissue affecting mainly sciatic nerve (recorded as mixed cell inflammation; perineurial) and iliac, inguinal and/or popliteal lymph nodes (recorded as inflammation mixed cell; perinodal) in males and females at ≥ 10 µg/dose. Minimal epidermal hyperplasia was also noted, particularly in high dose animals. Following a two-week dose free period, microscopic observations in main study animals (the injection site and peri nodal lymph nodes mixed cell inflammation and the epidermal hyperplasia) were considered partially resolved as there was a decreased incidence and severity detected.

In the lymph nodes draining the injection site (iliac, inguinal and/or popliteal), there were a higher incidence and/or severity of increased lymphoid cellularity in males and/or females at ≥ 10 µg/dose compared to control animals and focal/multifocal neutrophilic inflammation with necrosis in females at ≥ 30 µg/dose.

In the spleen, there was decreased cellularity of the periarteriolar lymphoid sheath in males and females at 96 µg/dose, increased cellularity of macrophages in red pulp of males at 96 µg/dose and females at ≥ 30 µg/dose, minimal to mild neutrophilic infiltration in the red pulp of males at ≥ 30 µg/dose and females at ≥ 10 µg/dose and minimal increased extramedullary hematopoiesis in males at ≥ 30 µg/dose. In the bone marrow, there was increased cellularity of myeloid lineage in males at ≥ 30 µg/dose and females at ≥ 10 µg/dose. The changes in the lymph node and bone marrow and the increased extramedullary hematopoiesis seen the spleen were regarded as secondary or reactive response to the injection site inflammation and correlated with the enlargement described grossly (lymph nodes).

At the end of the recovery period, the increased lymphoid cellularity in the lymph nodes (perinodal mixed cell inflammation) occurred with lower incidence and severity suggesting partial recovery. Microscopic findings seen in the spleen and bone marrow were no longer present after recovery indicating reversibility.

In the liver, there was microvesicular periportal to midzonal hepatocellular vacuolation in males at 96 µg/dose and females at ≥ 30 µg/dose. In addition, hypertrophy of Kuppfer cells was observed in males at ≥ 30 µg/dose and females at ≥ 10 µg/dose. The vacuolation was still present at a lower incidence and severity at the end of the recovery period and the hypertrophy of the Kupffer cells was no longer observed suggesting partial and complete reversibility, respectively.

In the seminal vesicle, there was a minimal increased epithelial single cell necrosis in males at 96 µg/dose. This change was no longer present after the 2-week recovery period suggesting reversibility.

mRNA-1893-related hematology changes were noted for males and females starting at ≥ 10 µg/dose and included increases in neutrophil, monocyte and eosinophil (with concomitant increases in white blood cell counts), increases in red blood cell distribution width and a decreases in reticulocyte counts. Minimal to moderate decreases in lymphocytes were noted at 96 µg/dose. Minimal to moderate increases in activated partial thromboplastin time and in fibrinogen were noted in males and females given ≥ 10 µg/dose. Minimal increases in globulin and decreases in albumin in males and females given ≥ 10 µg/dose and were reflected by decrease in A/G ratio. Decrease in glucose was also noted for males and females at ≥ 30 µg/dose. A dose-dependent increases in α1-acidic glycoprotein and α2-macroglobulin were also noted on Day 30. Increases (minimal – mild) in body temperature postdose and increases in IL-1β, IL-6, MCP-1, IP-10, and MIP-1α at ≥ 10 µg/dose were was also observed and suggestive of inflammation. All clinical pathology parameters returned to normal levels except for neutrophil, monocytes and eosinophil counts, red cell distribution width that were higher than controls for males and/or females. Although these changes were still present in recovery animals, a decrease in severity was observed when compared to Main study animals, demonstrating ongoing recovery.

In conclusion, administration of mRNA-1893 by intramuscular injection for 1 month (over 3 doses) was clinically well tolerated (no mortality, changes in food consumption or deleterious

changes in body weights, hematology, coagulation or clinical chemistry parameters) in rats up to 96 µg/dose. At ≥ 10 µg/dose, dose-dependent clinical signs (swelling/firmness/redness/scabs) at the injection site, clinical pathology parameters, and cytokines levels along with minimal to mild increase in body temperatures were consistent with an inflammatory reaction. Dose-dependent target organ effects were limited to the injection site, the perineural tissue of the sciatic nerve, the iliac, inguinal and popliteal lymph nodes, the liver, the spleen, the seminal vesicle and the bone marrow of animals given mRNA-1893. At the end of the 2-week recovery period, all changes were partially or fully recovered.

3. INTRODUCTION

The objectives of this study were to determine the potential toxicity of mRNA-1893, when given by intramuscular injection for 1 month (3 doses administered every other week) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

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

- 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 S6 (R1). *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.
- Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). *Guidelines for Toxicity Studies of Drugs (Chapter 3, Repeated Dose Toxicity Studies)*.

The Study Director signed the study plan on 07 Nov 2018, and dosing was initiated on 19 Nov 2018 (Main male and recovery) and on 20 Nov 2018 (Main female). The in-life phase of the study was completed on 19 Dec 2018 (main animals) and on 31 Dec 2018 (recovery animals); the last date of necropsy. The experimental start date was 07 Nov 2018, and the experimental completion date is 11 Sep 2019. 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-1893
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) No.:	MTDP18195
Concentration:	0.48 mg/mL
Retest Date:	Jul 2019 (end of use bulk Test Item analysis was also performed under the current study).
Physical Description:	White to off-white lipid nanoparticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C Kept in a refrigerator set to maintain 4°C once thawed
Administration Dose Form:	Injection, Suspension, Liposomal

4.1.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Supplier:	Gibco
Lot No.:	1967654
Expiration Date:	30 Jun 2020
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

4.2. Test Item Characterization

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

4.3. End of Use Analysis of Test Item

Two vials of the Test Item were taken on the completion of the dosing period. Analysis of bulk Test Item for concentration, particle size and purity was performed.

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

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

Concentration, Particle size and Purity analysis was performed by IEX- HPLC, Dynamic Light Scattering (DLS) and IPRP-HPLC using validated analytical procedures.

Any residual analytical samples (and Test Item used in analysis) were discarded.

4.4. Reserve Samples

For each batch (lot) of Test and Reference Items, a reserve sample (1 mL or 1 vial as appropriate) 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, storage, and disposition of Test and Reference Items were maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item were returned to Moderna Therapeutics by an overnight express courier on gel packs (-20°C), with a temperature monitor.

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 (PBS) pH 7.2, was dispensed on days of dosing (i.e., Days 1, 15, and 29) for administration to Group 1 control animals and was used as required to dilute the bulk Test Item for administration to Groups 2 and 3 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. Alternatively, the aliquots were transferred directly to room temperature. Details of the preparation and dispensing of the Reference Item have been retained in the Study Records.
Any residual volumes were discarded.

4.6.2. Preparation of Test Item

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

The bulk Test Item was removed from the freezer and allowed to thaw at room temperature for no more than 1 hour. The bulk Test Item was diluted with phosphate buffered saline, pH 7.2, as necessary for administration. The dosing formulations were prepared on each day of dosing (i.e., Days 1, 15, and 29) and were stored in a refrigerator set to maintain 4°C. Aliquots were removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots (from Day 15 for Main females animals) were maintained directly at room temperature for up to 4 hours. The formulations were not vortexed or sonicated, but may have been gently swirled. Stock vials were used only once. Details of the preparation and dispensing of the Test Item have been retained in the Study Records.
Any residual volumes of formulated Test Item and bulk Test Item were stored in a refrigerator set at 4°C and were discarded prior to report finalization.

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[b]	Homogeneity[a]	Concentration	Sampling From
Day 1	Groups 2 to 4	All groups	Dosing container
Day 29	N/A	All groups	Dosing container

N/A = Not applicable.

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

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

Samples to be analyzed were transferred on ice pack to the analytical laboratory (CR MTL) as soon as possible following preparation.

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

4.6.3.1. Analytical Method

Analyses described below were performed by IEX-HPLC using a validated analytical procedure (AP.5002400.SP.02 validated under CR MTL Study No. 1802291).

4.6.3.2. Concentration and Homogenization Analysis

Duplicate sets of samples (0.5 mL) for each sampling time point were sent to the analytical laboratory; triplicate set of samples (0.5 mL) were retained at the Test Facility as backup samples. Samples were collected from the top, middle and bottom of the dosing container for each concentration except for Group 1 and on Day 29 (the last preparation of the study). Where only concentration analysis was required; the formulation was then only sampled from the middle.

Concentration results were considered acceptable when mean sample concentration results were within or equal to ± 15% of theoretical concentration. Each individual sample concentration result was considered acceptable when it was within or equal to ± 20%. Homogeneity results were considered acceptable when the relative standard deviation (RSD) of the mean value at each sampling location was ≤ 5%. After acceptance of the analytical results, backup samples were discarded.

4.6.3.3. Stability Analysis

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

4.7. Test System

4.7.1. Receipt

On 07 Nov 2018, one hundred and twenty Crl:CD(SD) Sprague-Dawley rats (60 males and 60 females) were received from Charles River Canada Inc., St. Constant, QC, Canada. At dosing initiation, animals were 7 weeks old and males weighed between 184 and 237 g and females weighed between 164 and 205 g.

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 to be used in this study was considered to be the minimum required to properly characterize the effects of the Test Item. This study has been designed such that it 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

Each animal was identified using a subcutaneously implanted electronic identification chip. When required, animals were temporarily identified using non-toxic indelible ink.

4.7.4. Environmental Acclimation

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

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

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

On Day 1, after spillage at dosing, one main study animal was replaced with an alternate animal as detailed in Section 4.8.

All rats remaining unassigned to groups after Day 4 were released from the study.

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. These housing conditions were maintained throughout the study. 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.

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, except when interrupted for designated procedures.

4.7.6.3. Food

Lab Diet Certified CR Rodent Diet 5CR4 was provided ad libitum throughout the study, except during designated procedures. Wet pellets and cucumber slices were also provided on Day 1 in order to help support animals with high volume blood sampling.

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

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

4.7.6.4. Water

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

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

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

4.7.6.5. 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 were documented in the study records. Over the course of the study, no veterinary treatments were necessary.

4.8. Experimental Design

Text Table 3
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	Animal Identification Nos.			
					Main Study*		Recovery Study*	
					Males	Females	Males	Females
1	Reference Item	0	200	0	1001-1010	1501-1510	1011-1015	1511-1515
2	mRNA-1893	10	200	0.05	2001-2010	2501-2503, 2604, 2505-2510	-	-
3	mRNA-1893	30	200	0.15	3001-3010	3501-3510	-	-
4	mRNA-1893	96	200	0.48	4001-4010	4501-4510	4011-4015	4511-4515

-: Not applicable.
* = 10/sex/Groups 1 to 4 were necropsied 1 day following the last dose, the remaining 5/sex/Groups 1 and 4 (recovery), were necropsied 2 weeks following the last dose.

4.8.1. Administration of Test and Reference Items

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

The injection area was marked as frequently as required to allow appropriate visualization of administration sites. Hair were 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.

Spillage of the formulation preparation (i.e., incomplete dose) was noted on Day 1 for Animal No. 2504, was noted on Day 1. The animal was replaced by a spare to become Animal No. 2604.

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 dose levels for this toxicology study were chosen to approximate clinical doses. The high dose of 100 µg/dose is expected to approximate the intended maximum human clinical dose and volume. At this dose level, minimal systemic toxicity is expected, but it was possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound. Similarly formulated vaccine test items have been tested in GLP studies at the test facility and are provided as a reference (5002033, 5002158, & 5002034). A two-week recovery period was selected based on previous studies in this model system and is anticipated to demonstrate reversibility of findings.

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

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

4.9.3. Detailed Examination of the Injection Sites

The animals were removed from the cage, and a detailed examination of the injection sites was performed once during the predosing period, on days of dosing; at least 24 and 72 hours postdose (end of each group), and weekly when there was no dosing and during the recovery period. Following Day 29 of dosing, no assessment was performed on main animals at 72 hours postdose as animals were sent to necropsy on Day 30. Existing clinical signs were verified and confirmed/closed at this examination and new clinical signs were recorded. The injection site region was observed for any scabs, lesions, discharges, colors and any visible abnormalities and palpated for any swellings.

4.9.4. Body Weights

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

4.9.5. Food Consumption

Food consumption was quantitatively measured (cage measurements) weekly throughout the dosing and recovery periods, starting on Day -1.

4.9.6. Ophthalmic Examinations

Once prestudy and again toward the end of Week 4 of the dosing period and again during the Week 2 of the recovery period (refer to Appendix 1), all animals were subjected to funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations. The mydriatic used was tropicamide 1%.

4.9.7. Body Temperature

On Days 1 and 29 at predose, 2, 6, and 24 hours post dose (end of each group), body temperature of all animals was recorded via subcutaneous implanted transponder (refer to Appendix 1 for exceptions). When body temperature was significantly outside normal range (37.0°C to 39.5°C) the temperature was monitored daily till return to normal (refer to Appendix 1 for exceptions).

4.10. Laboratory Evaluations

4.10.1. Clinical Pathology

4.10.1.1. 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	Blood Markers
1 to 4[a]	Day 30	X	X	X	X
1 and 4	Day 43	X	X	X	X

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

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

4.10.1.2. Hematology

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

Text Table 5
Hematology Parameters

Red blood cell count	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. Animal No.4508 had its blood smear examined to investigate results.

4.10.1.3. Coagulation

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

Text Table 6
Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample Quality

4.10.1.4. Clinical Chemistry

Blood samples (target volume of 1.5 mL collected in serum separator tube) were processed for serum, and the serum was analyzed for the parameters specified in Text Table 7.

Text Table 7
Clinical Chemistry Parameters

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

4.10.1.5. Blood Markers (α1-acid Glycoprotein and α2-macroglobulin)

Blood (target volume of 0.7 mL collected in serum separator tube) was obtained via the abdominal aorta following isoflurane anesthesia at scheduled euthanasia.

Blood samples were allowed to clot at ambient room temperature. After collection, samples were transferred to the appropriate laboratory for processing. Samples were centrifuged as per standard procedures. Serum was aliquoted into 3 aliquots (target of 75 µL aliquot for the

first two aliquots and a leftover (when available). Samples were stored in a freezer set to maintain -20°C, pending analysis.

Analyses for α1-acid glycoprotein and α2-macroglobulin were conducted using a validated electrochemiluminescence (ECL) assay (Study No. 3600390). The procedure to be followed along with the assay acceptance criteria was detailed in CR SHB Analytical Procedure AP.5002400.rtsAPP.01. Samples were analyzed in duplicate.

Any residual/retained samples were discarded prior to report finalization.

4.10.2. Laboratory Investigations (Cytokine Analysis)

Blood was collected from the jugular vein from 5 animals/group/sex. After collection, blood samples for plasma were transferred on wet ice to the appropriate laboratory for processing. Samples were collected according in Text Table 8.

Text Table 8
Sample Collection Schedule

Target Blood Volume (mL)			**0.5**
Anticoagulant			**K_2EDTA**
Centrifugation Setting			**As per Standard Procedures**
Timepoints			
Day	**Hrs (postdose)**	**No. of Males/ Females**	IL-1ß, IL-6, TNF-α, IP-10, MIP-1α, MCP-1
1	2	5/5	X
	6	5/5	X
15	2	5/5	X
	6	5/5	X
29	2	5/5	X
	6	5/5	X
43[a]	N/A	5/5	X
Matrix			Plasma
Volume per aliquot (µL)			100 µL
Number of aliquot(s)			2x100µL and a leftover (when available)
Storage condition (set to maintain)			-80°C
Responsible Lab			CR SHB

N/A = Not applicable.
[a] Samples were only collected on recovery animals.

The number of aliquots and volumes were targets that may have been adjusted based on sample volume availability.

The samples were analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1α, and MCP-1 were conducted using a scientifically acceptable multiplex Luminex method (non-GLP). The procedures followed during the course of this study along with the assays acceptance criteria were detailed in CR SHB Analytical Procedure AP.5002400.Cyt.01. Samples were analyzed in duplicate.

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

4.10.2.1. [redacted]

Blood (target volume of 0.5 mL collected in serum separator tube) was collected from animals by jugular venipuncture (on prestudy) and from the abdominal aorta, when the samples were collected at termination on Day 30 (main animals only) and Day 43 (recovery animals).

Samples were mixed gently and kept under ambient conditions until centrifugation, which was carried out as soon as practical. The samples were centrifuged for 10 minutes in a refrigerated centrifuge (set to maintain 4°C) at 1200g during the prestudy occasion. Samples phases were not correctly separated during this occasion, then samples were centrifuged at 2400g the others occasions. The resultant serum was separated, transferred to uniquely labeled clear polypropylene tubes, and frozen immediately over dry ice and transferred to a freezer set to maintain -80°C until shipment. Samples were shipped on dry ice to Battelle Biomedical Research Center (BBRC), West Jefferson, OH, USA.

The samples were analyzed for [redacted] using a microneutralization assay qualified for the detection of [redacted] in human serum-(Battelle Study No. B05188).

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

4.11. Terminal Procedures

Terminal procedures are summarized in Text Table 9.

Text Table 9
Terminal Procedures for Main Study and Recovery Animals

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

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

4.11.1. Unscheduled Deaths

No main study or recovery animals were sent to unscheduled euthanasia over the course of the study.

4.11.2. Scheduled Euthanasia

Main study and recovery animals had a terminal body weight recorded. The animals underwent exsanguination from the abdominal aorta following isoflurane anesthesia and blood sample collection. 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.

4.11.3. 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.

4.11.4. Organ Weights

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

Text Table 10
Organs Weighed at Necropsy

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

[a] Paired organ weight.

4.11.5. 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 (except for the bone marrow smears), unless otherwise indicated.

Text Table 11
Tissue Collection and Preservation

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

[a] Preserved in Davidson's fixative.
[b] Preserved in Modified Davidson's fixative.
[c] Lymph node draining the last administration site used (bilateral collection;unilateral examination).
[d] Quadriceps.
[e] Both sites collected. Only the last administration site used was evaluated.

4.11.6. Histology

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

4.11.7. Histopathology

Histopathological evaluation was performed by a board-certified veterinary pathologist. Bone marrow, liver, spleen, lymph nodes (iliac, inguinal, and popliteal), injection site, sciatic nerve in males and females and seminal vesicles in males were identified by the study pathologist during microscopic evaluation as potential target tissues. They were evaluated and reported.

4.11.8. Peer Review

A pathology peer review was conducted by [redacted] DVM, PhD from Moderna Therapeutics, Cambridge, MA, USA.

The peer review documentation is included as an appendix to the Report.

4.11.9. Bone Marrow Smear Analysis

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

5. CONSTRUCTED VARIABLES

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

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

6. STATISTICAL ANALYSIS

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

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

Text Table 12
Statistical Matrix

Variables for Inferential Analysis	Statistical Method Parametric/Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
Blood Markers (α1-acid glycoprotein and α2-macroglobulin)	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.

The groups were compared using an overall one-way ANOVA F-test when Levene's test was not significant or the Kruskal-Wallis test when it was significant. When the overall F-test or Kruskal-Wallis test was found to be significant, then pairwise comparisons were conducted using Dunnett's or Dunn's test, respectively.

Datasets with two groups were compared using a Dunnett's test (referred to as t-test in Nevis 2012 tables) or Dunn's test (referred to as Wilcoxon Rank-Sum test in Nevis 2012 tables).

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	10	In-life; clinical pathology; postmortem Statistical analyses of numerical in-life, clinical pathology and postmortem data
Dispense	10	Test Material receipt, accountability and/or formulation activities
SRS (CR MTL in-house application built with SAS) and SAS system for Windows	1.4	Statistical analyses of biomarkers
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
Deviation Information Library	2.1	Deviations

8. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, electronic data, documentation, Study Plan and amendments, retained samples and specimens, and final reports from this study will be transferred to CR MTL archives by no later than the date of final report issue. At least one year after issue of the final report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Electronic data generated by the Test Facility were archived as noted above, except that the data collected using Provantis 10, the study deviation recorded electronically using the "Deviation Information Library" version 2.1 and reporting files stored on SDMS, which were archived at the Charles River Laboratories facility location in Wilmington, MA, USA.

All records and reports generated from phases or segments performed by Sponsor-designated subcontractors were not returned to the Test Facility for archiving. Archival location and duration are detailed in the applicable PI report(s).

9. RESULTS

9.1. Dose Formulation Analyses

(Appendix 3)

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.

For homogeneity, the RSD of concentrations for all samples in each group tested was within the acceptance criteria of ≤ 5%.

9.2. End of Use Bulk Test Item Analysis

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

9.3. Mortality

(Appendix 4)

There were no mortalities during the course of the study.

9.4. Clinical Observations

(Table 1 and Appendix 5)

At 96 µg/dose, the following clinical signs were observed: slight to severe firm swelling at the dosing site on Days 2, 4, 7, 16, and or 30; slight to moderate soft swelling at the dosing site on Days 4 and 30 for males only and on female No. 4506 on Day 2; skin redness and/or skin thickening and/or scabbed at the dosing sites starting on Day 2 and observed throughout the dosing period. In addition to the aforementioned clinical signs, individual females were noted with increased vocalization on Days 16 or 30. Some males were noted with increased vocalization on Days 2 or 30. One male (No. 4007) and two females (No. 4505 and 4510) were identified with an abnormal gait on Day 30, also female No. 4501 was noted with a limited usage at the left hindlimb on Day 16.

At 30 µg/dose, clinical signs were similar in incidence but observed at a lower severity when compared to 96 µg/dose. The following clinical signs were noted: slight to moderate soft or firm swelling at the dosing sites starting on Day 2; skin redness at the dosing sites on Day 30.

At 10 µg/dose, the incidence and severity of the clinical signs were minimal when compared to the higher dose levels and were limited to slight soft swelling at the dosing sites, starting on Day 2; slight to moderate firm swelling at the dosing sites on Day 30; skin redness and/or scabbed at dosing sites were noted on Days 2, 4, 7, and 16.

During the 2-week recovery period, clinical signs such as slight firm swelling at the dosing sites was still observed for three females (No. 4511, 4513, and 4514) given 96 µg/dose but with a lower severity and only on Day 32.

9.5. Body Weights and Body Weight Gains

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

There were no mRNA-1893-related body weight changes during the course of the study.

9.6. Food Consumption

(Table 4 and Appendix 8)

There were no mRNA-1893-related changes in food consumption during the course of this study.

9.7. Body Temperature

(Table 5 and Appendix 9)

mRNA-1893-related minimal, dose-dependent increases in mean body temperatures (compared to control values) were generally noted 6 hours postdose in males given ≥ 10 µg/dose on both Day 1 and Day 29 (from 37.47 to 39.13°C) and generally returned to predose values at 24-hour postdose; except for a few animals at 10 and 30 µg/dose, where body temperatures returned to baseline 48 hours postdose on Day 1.

9.8. Ophthalmic Examinations

(Appendix 14)

There were no mRNA-1893-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. Hematology

(Table 6 and Appendix 10)

mRNA-1893-related hematology changes were noted at ≥ 10 µg/dose and included increases in neutrophil (NEUT), monocyte (MONO) and eosinophil (EOS) (with concomitant increases in white blood cell [WBC] counts), increases in red blood cell distribution width (RDW), decreases in reticulocyte (RETIC) counts and in lymphocytes (LYMPH) count. These changes are illustrated in Text Table 14.

Text Table 14
Hematology Changes in Rats Administered mRNA-1893

Dose (µg/dose)	0		10		30		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
WBC (10^3/µL)								
Day 30	7.276	6.404	1.12	1.27	**1.77**	**1.75**	**2.21**	1.34
Day 43	7.184	5.124					1.37	**1.56**
NEUT (10^3/µL)								
Day 30	0.917	0.868	2.54	**3.34**	**7.15**	**7.53**	**11.61**	**6.34**
Day 43	1.068	0.780					**1.77**	**2.11**
LYMPH (10^3/µL)								
Day 30	6.142	5.302	-	**-**	-	-	0.80	**0.51**
Day 43	5.852	4.146					**-**	**-**
MONO (10^3/µL)								
Day 30	0.097	0.098	1.46	1.32	**1.95**	**1.65**	**2.40**	**-**
Day 43	0.122	0.098					**1.80**	**1.76**
EOS (10^3/µL)								
Day 30	0.055	0.069	**2.05**	**2.73**	**3.04**	**3.09**	**3.13**	**2.53**
Day 43	0.066	0.034					1.52	**2.82**
RDW (%)								
Day 30	12.26	10.87	-	**-**	**1.09**	**1.09**	**1.16**	**1.16**
Day 43	12.74	11.38					**1.13**	**1.18**
RETIC (10^9/µL)								
Day 30	263.81	204.79	-	**-**	-	-	**0.77**	**-**
Day 43	223.86	203.90					-	-

For control group means are shown, for mRNA-1893 dosed groups X change as compared to control group.
–: Indicates results were considered not to be meaningfully different from mean control value.
Bolded values were statistically significant.
Shaded boxes indicate no collection at these time point for corresponding groups.

mRNA-1893-related moderate to marked increases in NEUT (up to 11.61x mean controls), EOS (up to 3.13x mean controls), and moderate increases in MONO (up to 2.40x mean controls) led to minimal to moderate increases in WBC counts in males and females given ≥ 10 µg/dose (up to 2.21x mean controls). mRNA-1893-related minimal to moderate decreases in LYMPH (down to 0.51x mean controls).

mRNA-1893-related minimal increases in RDW was noted at ≥ 30 µg/dose (up to 1.16x mean controls) and minimal decreases in RETIC were noted in males at 96 µg/dose (0.77x mean controls). Although, there were no correlative changes in mean corpuscular volume, nor red blood cell count, the changes in RDW noted were supportive of an increased variability of the red cell size.

At the end of the 2-week recovery period (Day 43), mRNA-1893-related minimal to moderate increases in NEUT (up to 2.11x mean controls), MONO (up to 1.80x mean controls), EOS (up to 2.82x mean controls) and RDW (up to 1.18x mean to control) were still noted at 96 µg/dose. Other changes were considered fully recovered.

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-1893-related.

9.10. Coagulation

(Table 7 and Appendix 11)

mRNA-1893-related increases in activated partial thromboplastin time (APTT) and in fibrinogen (FIB) were noted at ≥ 10 µg/dose. The changes are illustrated in Text Table 15.

Text Table 15
Coagulation Changes in Rats Administered mRNA-1893

Dose (µg/dose)	0		10		30		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
APTT (sec)								
Day 30	15.79	15.32	-	**1.08**	**1.10**	**1.20**	**1.28**	**1.28**
Day 43	15.06	15.90					-	-
FIB (mg/dL)								
Day 30	310.7	219.7	**1.75**	1.65	**2.36**	**2.81**	**2.81**	**3.24**
Day 43	293.8	203.0					-	-

For control group means are shown, for mRNA-1893 dosed groups X change as compared to control group.
–: Indicates results were considered not to be meaningfully different from mean control value.
Bolded values were statistically significant.
Shaded boxes indicate no collection at these time point for corresponding groups.

mRNA-1893 dose related minimal increases in APTT were noted for males at ≥ 30 µg/dose (up to 1.28x mean controls) and females at ≥ 10 µg/dose (up to 1.28x mean controls). mRNA-1893-dose-related moderate increases in FIB were noted at ≥ 10 µg/dose (up to 3.24x mean controls).

There were no nRMA-1893-related changes at the end of the 2-week recovery period.

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-1893-related.

9.11. Clinical Chemistry

(Table 8 and Appendix 12)

mRNA-1893-related increases in globulin (GLOB) and decreases in albumin (ALB) at ≥ 10 µg/dose and were reflected by decrease in A/G ratio. mRNA-1893-related decrease in glucose (GLU) was also noted for females at ≥ 30 µg/dose. These changes are illustrated in Text Table 16.

Text Table 16
Clinical Chemistry Changes in Rats Administered mRNA-1893

Dose (µg/dose)	0		10		30		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
GLU (mg/dL)								
Day 30	201.9	192.2	-	-	0.98	**0.86**	-	**0.76**
Day 43	216.0	184.2					-	0.80
ALB (g/dL)								
Day 30	3.77	4.67	-	-	**0.91**	**0.90**	**0.90**	**0.89**
Day 43	3.92	4.84					-	-
GLOB (g/dL)								
Day 30	1.65	1.53	**1.14**	1.11	**1.33**	**1.36**	**1.51**	**1.44**
Day 43	1.66	1.62					-	-
A/G Ratio								
Day 30	2.30	3.11	**0.83**	0.84	**0.68**	**0.65**	**0.60**	**0.61**
Day 43	2.40	3.02					-	-

For control group means are shown, for mRNA-1893 dosed groups X change as compared to control group.
–: Indicates results were considered not to be meaningfully different from mean control value.
Bolded values were statistically significant.
Shaded boxes indicate no collection at these time point for corresponding groups.

mRNA-1893-related minimal to moderate decreases in GLU were noted in females at ≥ 30 µg/dose (down to 0.76x mean controls), minimal increases in GLOB were noted at ≥ 10 µg/dose (up to 1.51x mean controls) accompanied with minimal decreases in ALB at ≥ 30 µg/dose (down to 0.89x mean controls). The changes in ALB and GLOB resulted in a decrease in the A/G ratio (down to 0.60x mean controls) at ≥ 10 µg/dose. At the end of the 2-week recovery period (Day 43), minimal decreased in GLU was still noted at 96 µg/dose for females (down to 0.80x mean controls). Other changes were considered fully recovered.

Any other differences in the clinical chemistry parameters were judged to be due to individual or biological variability or lacked true dose relationship and therefore were considered not mRNA-1893-related.

9.12. α1-acidic Glycoprotein and α2-macroglobulin Analysis

(Table 9, Appendix 13, and Appendix 15)

mRNA-1893-related dose-dependent increases in α1-acidic glycoprotein (AGP) and α2-macroglobulin (A2M) were noted on Day 30 at ≥ 30 µg/dose. These changes are illustrated in Text Table 17.

Text Table 17
Blood Marker Changes in Rats Administered mRNA-1893

Dose (µg/dose)	0		10		30		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
AGP (ng/mL)								
Day 30	33308.095	25825.490	-	-	**11.5**	**11.7**	**20.7**	**25.2**
Day 43	34976.510	22092.828					0.9	0.9
A2M (ng/mL)								
Day 30	15123.563	8803.271	-	-	**18.5**	**8.0**	**80.8**	**56.4**
Day 43	8305.714	7422.756					**2.8**	1.7

For control group means are shown, for mRNA-1893 dosed groups X change as compared to control group.
–: Indicates results were considered not to be meaningfully different from mean control value.
Bolded values were statistically significant.
Shaded boxes indicate no collection at these time point for corresponding groups.

mRNA-1893-related changes consisted of mild to moderate dose-dependent increases in AGP (range: 11.5x-25.2x mean control) and A2M (range: 8.0x-80.8x. mean control) observed at ≥ 30 µg/dose. Overall, there were no significant differences in AGP and A2M concentrations between males and females.

At the end of 2-week recovery period (Day 43), mean concentration of AGP and A2M in female animal given 96 µg/dose were still slightly above the control value which suggests a partial recovery. AGP mean concentration return to normal value at the end of 2-week recovery for male animals but A2M mean concentration were still noted significant higher than control value.

9.13. Cytokines

(Appendix 16)

mRNA-1893-related increases were noted in cytokines IL-1β, IL-6, IP-10, MCP-1, and MIP-1α. There were no mRNA-1893-related increases in TNF-α concentration were observed. The upper limit of the baseline ranges are presented in Text Table 18. Fold increases of cytokines (IL-1β, IL-6, IP-10, MCP-1, MIP-1α and TNF-α) are presented in Text Table 19.

Text Table 18
Cytokines Upper Limit of Baseline Ranges

	IL-1β (pg/mL)	**IL-6 (pg/mL)**	**IP-10 (pg/mL)**	**MCP-1 (pg/mL)**	**MIP-1α (pg/mL)**	**TNF-α (pg/mL)**
Males	70.25	519.27	359.59	1356.80	17.25	2.93
Females	122.28	2512.41	267.15	703.15	11.72	8.88

Text Table 19
Fold Increase of Cytokines

Analyte	Gender	Day	Time Point	Group 1		Group 2		Group 3		Group 4	
				Reference Item		10 µg/dose		30 µg/dose		96 µg/dose	
				Inc	Fold	Inc	Fold	Inc	Fold	Inc	Fold
IL-1ß	Male	Day 1	2 hrs	0/5	-	0/5	-	0/5	-	1/5	4.2
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 15	2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	1/5	6.8	2/5	1.7-2.8
	Day 29		2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	1/5	1.6	0/5	-	1/5	2.1	1/5	10.3
	Day 43			0/5	-	-	-	-	-	0/5	-
	Female	Day 1	2 hrs	0/5	-	1/5	1.6	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	1/5	4.4
		Day 15	2 hrs	1/5	1.1	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	1/5	2.1	1/5	11.5
	Day 29		2 hrs	1/5	1.6	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	2/5	1.2-4.5	1/5	5.0
	Day 43			0/5	-	-	-	-	-	0/5	-
IL-6	Male	Day 1	2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
	Day 15		2 hrs	1/5	1.6	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	1/5	1.7
	Day 29		2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	1/5	2.0	0/5	-
		Day 43		0/5	-	-	-	-	-	0/5	-
	Female	Day 1	2 hrs	0/5	-	1/5	1.4	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 15	2 hrs	0/5	-	0/5	-	1/5	3.0	0/5	-
			6 hrs	1/5	1.7	0/5	-	0/5	-	0/5	-
		Day 29	2 hrs	0/5	-	0/5	-	1/5	1.5	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 43		1/5	1.6	-	-	-	-	0/5	-

Inc = Incidence/Total number of animals (male or female) Fold = Value/Upper limit of the baseline range (Min fold-Max fold).

Analyte	Gender	Day	Time Point	Group 1		Group 2		Group 3		Group 4	
				Reference Item		10 µg/dose		30 µg/dose		96 µg/dose	
				Inc	Fold	Inc	Fold	Inc	Fold	Inc	Fold
IP-10	Male	Day 1	2 hrs	0/5	-	0/5	-	1/5	1.2	1/5	1.1
			6 hrs	0/5	-	0/5	-	2/5	1.2-1.5	5/5	1.1-1.9
		Day 15	2 hrs	0/5	-	0/5	-	0/5	-	2/5	1.1-1.2
			6 hrs	1/5	1.1	0/5	-	2/5	1.3-2.2	4/5	1.3-2.7
		Day 29	2 hrs	0/5	-	0/5	-	1/5	1.1	0/5	-
			6 hrs	1/5	1.1	0/5	-	2/4	1.2-1.7	4/5	1.4-3.6
		Day 43		0/5	-	-	-	-	-	0/5	-
	Female	Day 1	2 hrs	0/5	-	1/5	1.2	0/5	-	0/5	-
			6 hrs	0/5	-	2/5	1.2-1.3	3/5	1.5-2.3	4/5	1.2-6.0
		Day 15	2 hrs	0/5	-	3/5	1.1-2.3	0/5	-	0/5	-
			6 hrs	0/5	-	2/5	1.1-1.4	4/5	1.3-3.8	5/5	1.1-6.8
		Day 29	2 hrs	1/5	1.1	2/5	1.3	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	3/5	1.9-4.5	5/5	2.2-9.8
		Day 43		0/5	-	-	-	-	-	0/5	-
MCP-1	Male	Day 1	2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	1/5	1.1	0/5	-	2/5	1.1-1.2
		Day 15	2 hrs	1/5	1.7	1/5	1.2	1/5	1.2	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 29	2 hrs	1/5	1.1	0/5	-	1/5	1.2	0/5	-
			6 hrs	0/5	-	0/5	-	2/5	1.1-1.4	1/5	1.2
		Day 43		0/5	-	-	-	-	-	0/5	-
	Female	Day 1	2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	1/5	2.1
		Day 15	2 hrs	0/5	-	1/5	2.1	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	2/5	2.2-3.5
		Day 29	2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 43		0/5	-	-	-	-	-	0/5	-
MIP-1α	Male	Day 1	2 hrs	0/5	-	0/5	-	0/5	-	1/5	8.8
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 15	2 hrs	1/5	1.6	0/5	-	0/5	-	1/5	2.4
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 29	2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 43		0/5	-	-	-	-	-	0/5	-
	Female	Day 1	2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 15	2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 29	2 hrs	0/5	-	0/5	-	0/5	-	0/5	-
			6 hrs	0/5	-	0/5	-	0/5	-	0/5	-
		Day 43		0/5	-	-	-	-	-	0/5	-

Inc = Incidence/Total number of animals (male or female) Fold = Value/Upper limit of the baseline range (Min fold-Max fold).

9.13.1. IL-1ß

mRNA-1893-related increase in IL-1β concentration was observed at ≥30 µg/dose at 6 hours SOI on Days 15 and 29 and at 96 µg/dose at 2 hours SOI on Day 1 for males and at 6 hours SOI on Day 1 for females. Peak increases were observed at 6 hours SOI on Day 29 in males and Day 15 in females. IL-1β concentration fold increases, gender combined, over the upper limit of baseline levels ranged from 1.6, 1.2-6.8, and 1.7-11.5 at 10, 30, and 96 µg/dose, respectively. All animals returned to baseline levels at Day 43.

9.13.2. IL-6

mRNA-1893-related increases in IL-6 concentration were observed at 30 µg/dose on Day 15 2 hours SOI (females) and on Day 29 6 hours SOI (males). Increases were also observed at 96 µg/dose at 6 hours SOI on Day 15 for males only. IL-6 concentration fold increases, gender combined, over the upper limit of baseline levels ranged from 1.5-3.0, and 1.7 at 30, and 96 µg/dose, respectively. All animals returned to baseline levels at Day 43.

9.13.3. IP-10

mRNA-1893-related increases in IP-10 concentration were observed at ≥ 30 µg/dose at 2 and 6 hours SOI on Days 1, 15, and 29 for males. In females, mRNA-1893-related increases in IP-10 concentration were observed at 10 µg/dose at 2 and 6 hours SOI on Days 1, 15, and 29 and at ≥30 µg/dose at 6 hours SOI on Days 1, 15, and 29. IP-10 concentration fold increases, gender combined, over the upper limit of baseline levels ranged from 1.1-4.5, and 1.1-9.8 at 30, and 96 µg/dose, respectively. All animals returned to baseline levels at Day 43.

9.13.4. MCP-1

mRNA-1893-related increases in MCP-1 concentration were observed in females only at 10 µg/dose on Day 15 at 2 hours SOI and at 96 µg/dose on Days 1 and 15 at 6 hours SOI. MCP-1 concentration fold increases, in females only, over the upper limit of baseline levels ranged from 1.1-2.1, 1.1-1.4, and 1.1-3.5 at 10, 30 and 96 µg/dose, respectively. All animals returned to baseline levels at Day 43.

9.13.5. MIP-1α

mRNA-1893-related increases in MIP-1α concentration were observed at 96 µg/dose at 2 hours SOI on Days 1 and 15 in males only. MIP-1α concentration fold increases over the upper limit of baseline levels ranged from 2.4-8.8 at 96 µg/dose for the male. All animals returned to baseline levels at Day 43.

9.14. Anti-therapeutic Antibody (ATA)

(Appendix 17)

All samples from control group animals generated results that were < limit of detection (LOD). All samples collected at Day 30 and Day 43 timepoints from animals that received the Test Item mRNA-1893 had detectable [redacted] for samples from 10 µg/dose group, Day 30 ranged from 138 to 11 891; for samples from 30 µg/dose group, Day 30 ranged from 62 to 4 545; for samples from 96 µg/dose group, Day 30 ranged from 488 to 4 953. At the end of 2-week recovery period (Day 43), samples from 96 µg/dose group ranged from 3,809 to 14 249.

9.15. Gross Pathology

9.15.1. Terminal Necropsy (Day 30)

(Appendix 18)

mRNA-1893-related gross pathology findings are summarized in Text Table 20.

Text Table 20
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**	**30**	**96**	**0**	**10**	**30**	**96**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, injection (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency; firm	0	1	6	9	0	2	1	7
Swelling	0	4	5	7	0	4	5	7
Thick	0	0	3	8	0	1	10	10
Focus, dark	0	0	0	0	0	0	1	0
Lymph node, iliac (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	0	0	3	0	1	1	6
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	0	0	1	0	0	0	2
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	1	0	0	0	0	1	2

Macroscopic findings considered to be related to mRNA-1893 were seen in the injection site (firm consistency, swelling, thick and/or dark focus) and draining lymph nodes (iliac, inguinal and/or popliteal) of injection site (enlargement) of males and females at ≥ 10 µg/dose.

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 Item and Test Item-treated animals and, therefore, were considered not mRNA-1893.

9.15.2. Recovery Necropsy (Day 43)

(Appendix 18)

mRNA-1893-related gross pathology findings in the iliac lymph node at the terminal euthanasia was still observed at the end of the 2-week recovery period (Day 43) and is summarized in Text Table 21.

Text Table 21
Summary of Gross Pathology Findings – Scheduled Euthanasia (Day 43)

	Males		Females	
Group	**1**	**4**	**1**	**4**
Dose (µg/dose)	**0**	**96**	**0**	**96**
No. Animals per Group	**5**	**5**	**5**	**5**
Lymph node, iliac (No. Examined)	5	5	5	5
Enlargement	0	1	0	0

mRNA-1893-related enlarged iliac lymph node was observed in 1 male at 96 µg/dose.

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 Item and Test Item treated animals and, therefore, were considered unrelated to administration of mRNA-1893.

9.16. Organ Weights

9.16.1. Terminal Necropsy (Day 30)

(Appendix 18)

mRNA-1893-related organ weight changes are summarized in Text Table 22.

Text Table 22
Summary of Organ Weight Data – Scheduled Euthanasia (Day 30)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**10**	**30**	**96**	**10**	**30**	**96**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Spleen (No. Weighed)	10	10	10	10	10	10
Absolute value	-0.7552	6.3021	14.0625	-0.6424	7.5482	10.4925
% of body weight	-1.88364	7.62303	**14.68763**	2.34641	**13.71379**	**15.82386**
% of brain weight	-1.92392	4.06712	12.83219	2.14876	11.45926	14.05730

[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.

Organ weight changes considered to be related to mRNA-1893 were seen in the spleen.

mRNA-1893-related increase in mean spleen weights (absolute, relative to body and brain weights) was noted in males at 96 µg/dose and females at ≥ 30 µg/dose. These higher spleen weights had no gross or microscopic correlates.

No other mRNA-1893-related organ weights changes were noted. There were isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, the organ weight differences observed were considered incidental and unrelated to administration of mRNA-1893.

9.16.2. Recovery Necropsy (Day 43)

(Appendix 18)

There were no mRNA-1893-related organ weight changes observed at the end of the recovery period (Day 43).

The organ weight differences observed were considered incidental and unrelated to the administration of mRNA-1893.

9.17. Histopathology

9.17.1. Terminal Necropsy (Day 30)

(Appendix 18)

mRNA-1893-related microscopic findings are summarized in Text Table 23.

Text Table 23
Summary of Microscopic Findings – Scheduled Euthanasia (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**30**	**96**	**0**	**10**	**30**	**96**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, injection (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell; dermal	(0)[a]	(1)	(0)	(2)	(0)	(2)	(0)	(2)
Minimal	0	1	0	1	0	2	0	2
Mild	0	0	0	1	0	0	0	0
Inflammation, mixed cell; subcutis/perimuscular	(1)	(10)	(10)	(10)	(5)	(10)	(10)	(10)
Minimal	1	2	0	0	5	1	1	0
Mild	0	4	7	2	0	8	7	3
Moderate	0	4	3	8	0	1	2	7
Inflammation, mixed cell; muscular	(0)	(10)	(10)	(10)	(0)	(10)	(10)	(10)
Minimal	0	4	5	1	0	7	5	2
Mild	0	6	5	9	0	3	5	8
Hyperplasia; epidermal	(0)	(0)	(0)	(3)	(0)	(2)	(2)	(7)
Minimal	0	0	0	3	0	2	2	7
Lymph node, iliac (No. Examined)	10	10	10	10	10	10	10	10
Increased cellularity; lymphoid	(0)	(1)	(4)	(9)	(3)	(5)	(9)	(6)
Minimal	0	1	2	2	2	5	1	3
Mild	0	0	1	6	1	0	8	3
Moderate	0	0	1	0	0	0	0	0
Marked	0	0	0	1	0	0	0	0
Inflammation, mixed cell; perinodal	(0)	(0)	(0)	(1)	(0)	(1)	(6)	(8)
Minimal	0	0	0	1	0	1	6	7
Mild	0	0	0	0	0	0	0	1
Inflammation, neutrophilic	(0)	(0)	(0)	(0)	(0)	(0)	(5)	(7)
Minimal	0	0	0	0	0	0	4	3
Mild	0	0	0	0	0	0	1	3
Moderate	0	0	0	0	0	0	0	1
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	9
Increased cellularity; lymphoid	(0)	(0)	(2)	(9)	(0)	(0)	(0)	(2)
Minimal	0	0	2	3	0	0	0	2
Mild	0	0	0	6	0	0	0	0
Inflammation, neutrophilic	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)
Minimal	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	0	0	0	1
Inflammation, mixed cell; perinodal	(0)	(0)	(1)	(0)	(0)	(0)	(0)	(2)
Minimal	0	0	1	0	0	0	0	1
Moderate	0	0	0	0	0	0	0	1
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell; perinodal	(0)	(9)	(10)	(9)	(0)	(10)	(10)	(10)
Minimal	0	6	6	6	0	7	7	4
Mild	0	3	4	3	0	3	3	6
Increased cellularity; lymphoid	(0)	(0)	(1)	(1)	(0)	(3)	(6)	(0)
Minimal	0	0	1	1	0	3	6	0
Inflammation, neutrophilic	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(2)
Minimal	0	0	0	0	0	0	1	2

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**30**	**96**	**0**	**10**	**30**	**96**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Nerve, sciatic (No. Examined)	10	10	10	10	10	10	10	10
Inflammation, mixed cell; perineurial	(1)	(10)	(10)	(9)	(1)	(10)	(10)	(10)
Minimal	1	1	2	4	1	5	2	2
Mild	0	4	1	3	0	1	3	6
Moderate	0	5	7	2	0	4	5	2
Spleen (No. Examined)	10	10	10	10	10	10	10	10
Extramedullary hematopoiesis; increased	(0)	(0)	(1)	(3)	(0)	(0)	(0)	(0)
Minimal	0	0	1	3	0	0	0	0
Infiltration, neutrophilic; red pulp	(0)	(0)	(10)	(10)	(0)	(7)	(10)	(10)
Minimal	0	0	8	3	0	7	8	5
Mild	0	0	2	7	0	0	2	5
Decreased cellularity; periarteriolar lymphoid sheath	(0)	(0)	(0)	(4)	(0)	(0)	(0)	(2)
Minimal	0	0	0	3	0	0	0	2
Mild	0	0	0	1	0	0	0	0
Increased cellularity; red pulp	(0)	(0)	(0)	(4)	(0)	(0)	(1)	(7)
Minimal	0	0	0	2	0	0	1	6
Mild	0	0	0	2	0	0	0	1
Bone marrow (No. Examined)	10	10	10	10	10	10	10	10
Increased cellularity; myeloid	(0)	(0)	(2)	(8)	(0)	(1)	(1)	(10)
Minimal	0	0	2	8	0	1	1	10
Liver (No. Examined)	10	10	10	10	10	10	10	10
Hypertrophy; Kupffer cell	(0)	(0)	(2)	(4)	(0)	(2)	(6)	(7)
Minimal	0	0	2	4	0	2	4	6
Mild	0	0	0	0	0	0	2	1
Vacuolation; hepatocellular, periportal to midzonal	(0)	(1)	(1)	(7)	(1)	(1)	(5)	(9)
Minimal	0	1	1	5	1	1	3	8
Mild	0	0	0	2	0	0	2	1
Gland, seminal vesicle (No. Examined)	10	10	10	10	N/A	N/A	N/A	N/A
Single cell necrosis; increased	(0)	(0)	(0)	(4)	N/A	N/A	N/A	N/A
Minimal	0	0	0	4	N/A	N/A	N/A	N/A

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

Microscopic changes related to the administration of mRNA-1893 were seen in the injection site, sciatic nerve, draining lymph nodes of injection site (iliac, inguinal, and popliteal lymph nodes), liver, spleen and bone marrow of males and females and seminal vesicle of males.

In the injection site, there was minimal to moderate mixed cell inflammation in males and females given Reference and Test Items. An exacerbation of the inflammation was noted in animals dosed with mRNA-1893 at ≥ 10 µg/dose based on the distribution and increased incidence and severity of the mixed cell inflammation compared to control animals. In Test Item-dosed animals, the mixed cell inflammation which was accompanied by edema, rarely hemorrhage and formation of microabscesses, was found in the dermis, subcutaneous and perimuscular tissue and skeletal muscle. Minimal epidermal hyperplasia was also noted, particularly in high dose animals. This inflammatory reaction correlated with findings described grossly in the injection site (firm consistency, swelling, thick and dark focus). There was evidence of an extension of mixed cell inflammation from the injection site into the surrounding connective tissue affecting mainly sciatic nerve (recorded as mixed cell inflammation;

perineurial) and iliac, inguinal and/or popliteal lymph nodes (recorded as inflammation mixed cell; perinodal) in males and females at ≥ 10 µg/dose. The popliteal lymph nodes were the most frequently affected lymph nodes followed by the iliac lymph nodes. Of note, the mixed cell inflammation was sometimes extending also into other tissues adjacent to the injection site (perifemoral tissue, inguinal skin/mammary gland and quadriceps femoris muscle).

In the lymph nodes draining the injection site (iliac, inguinal and/or popliteal), there were an higher incidence and/or severity of increased lymphoid cellularity in males and/or females at ≥ 10 µg/dose compared to Reference Item animals and minimal to moderate focal/multifocal neutrophilic inflammation with necrosis in females at ≥ 30 µg/dose. These lymph node changes were regarded as secondary or reactive response to the injection site inflammation and correlated with the enlargement described grossly.

In the liver, there was minimal to mild microvesicular periportal to midzonal hepatocellular vacuolation in males at 96 µg/dose and females at ≥ 30 µg/dose. In addition, minimal to mild hypertrophy of Kuppfer cells was observed in males at ≥ 30 µg/dose and females at ≥ 10 µg/dose. The Kupffer cells were enlarged with a prominent nucleus and abundant vacuolated and/or granular cytoplasm.

In the spleen, there was minimal to mild decreased cellularity of the periarteriolar lymphoid sheath in males and females at 96 µg/dose, minimal to mild increased cellularity of macrophages in red pulp of males at 96 µg/dose and females at ≥ 30 µg/dose, minimal to mild neutrophilic infiltration in the red pulp of males at ≥ 30 µg/dose and females at ≥ 10 µg/dose and minimal increased extramedullary hematopoiesis in males at ≥ 30 µg/dose.

In the bone marrow, there was minimal increased cellularity of myeloid lineage in males at ≥30 µg/dose and females at ≥ 10 µg/dose. This change as well as the increased extramedullary hematopoiesis seen the spleen was considered to be a secondary response to the inflammation observed in the injection site.

In the seminal vesicle, there was a minimal increased epithelial single cell necrosis in males at 96 µg/dose.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in Reference Item and Test Item animals and, therefore, were considered unrelated to administration of mRNA-1893.

9.17.2. Recovery Necropsy (Day 43)

(Appendix 18)

Microscopic findings noted at the terminal euthanasia were still observed at the end of the recovery period (Day 43) and are summarized in Text Table 24.

Text Table 24
Summary of Microscopic Findings – Scheduled Euthanasia (Day 43)

	Males		Females	
Group	**1**	**4**	**1**	**4**
Dose (µg/dose)	**0**	**96**	**0**	**96**
No. Animals per Group	**5**	**5**	**5**	**5**
Site, injection (No. Examined)	5	5	5	5
Inflammation, mixed cell; subcutis/perimuscular	(0)[a]	(5)	(0)	(5)
Minimal	0	5	0	5
Inflammation, mixed cell; muscular	(0)	(0)	(0)	(1)
Minimal	0	0	0	1
Infiltration, mononuclear cell; muscular	(1)	(4)	(3)	(4)
Minimal	1	4	3	3
Mild	0	0	0	1
Hyperplasia; epidermal	(0)	(1)	(0)	(0)
Minimal	0	1	0	0
Lymph node, iliac (No. Examined)	5	5	5	5
Increased cellularity; lymphoid	(0)	(3)	(0)	(2)
Minimal	0	3	0	1
Mild	0	0	0	1
Inflammation, mixed cell; perinodal	(0)	(1)	(0)	(2)
Minimal	0	1	0	2
Lymph node, inguinal (No. Examined)	5	5	5	5
Inflammation, mixed cell; perinodal	(0)	(0)	(0)	(1)
Minimal	0	0	0	1
Lymph node, popliteal (No. Examined)	5	5	5	5
Inflammation, mixed cell; perinodal	(0)	(2)	(0)	(4)
Minimal	0	2	0	4
Increased cellularity; lymphoid	(0)	(1)	(0)	(0)
Minimal	0	1	0	0
Nerve, sciatic (No. Examined)	5	5	5	5
Inflammation, mixed cell; perineurial	(0)	(5)	(0)	(5)
Minimal	0	5	0	5
Liver (No. Examined)	5	5	5	5
Vacuolation; hepatocellular, periportal to midzonal	(0	(1)	(0)	(3)
Minimal	0	1	0	3

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

After 2 weeks of recovery, mRNA-1893 microscopic changes were observed in males and/or females at the injection site (mixed cell inflammation without edema or mononuclear cell infiltration and epidermal hyperplasia), in the surrounding connective tissue of sciatic nerve (perineurial mixed cell inflammation) and iliac, inguinal and popliteal lymph nodes (perinodal mixed cell inflammation); in iliac and popliteal lymph nodes (increased lymphoid cellularity) and liver (periportal to midzonal hepatocellular vacuolation). These remaining findings occurred with a decreased incidence and/or severity indicating partial recovery.

Microscopic findings seen in the spleen, bone marrow and seminal vesicle at terminal euthanasia were not present after the recovery period indicating reversibility.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in Reference Item and Test Item animals and, therefore, were considered unrelated to administration of mRNA-1893.

10. CONCLUSION

In conclusion, administration of mRNA-1893 by intramuscular injection for 1 month (over 3 doses) was clinically well tolerated (no mortality, changes in food consumption or deleterious changes in body weights, hematology, coagulation or clinical chemistry parameters) in rats up to 96 µg/dose. At ≥ 10 µg/dose, dose-dependent clinical signs (swelling/firmness/redness/scabs) at the injection site, clinical pathology parameters, and cytokines levels along with minimal to mild increase in body temperatures were consistent with an inflammatory reaction. Dose-dependent target organ effects were limited to the injection site, the perineural tissue of the sciatic nerve, the iliac, inguinal and popliteal lymph nodes, the liver, the spleen, the seminal vesicle and the bone marrow of animals given mRNA-1893. At the end of the 2-week recovery period, all changes were partially or fully recovered.

Figure 1
Summary of Body Weights

5002400

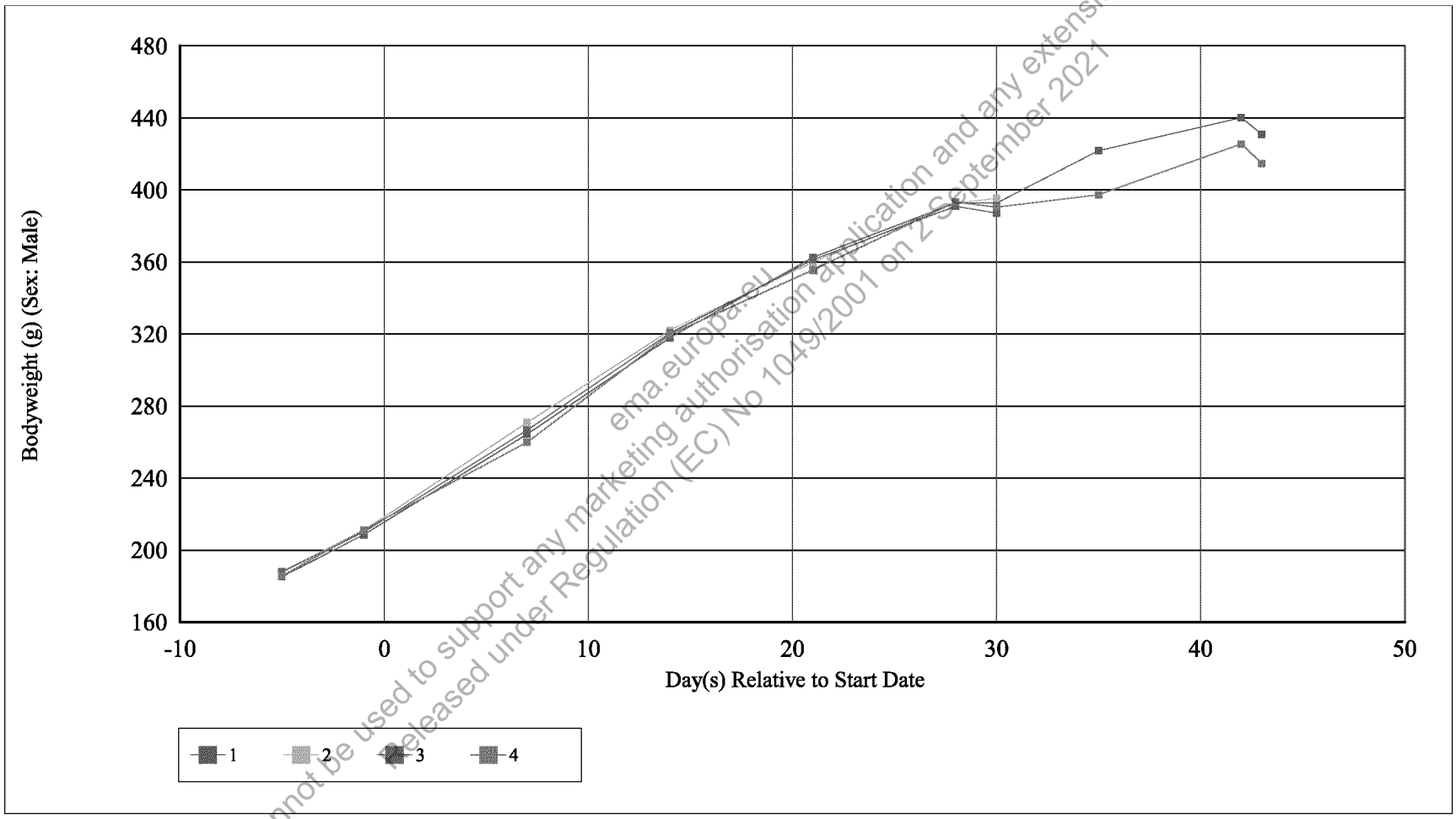

Figure 2
Summary of Body Weights

5002400

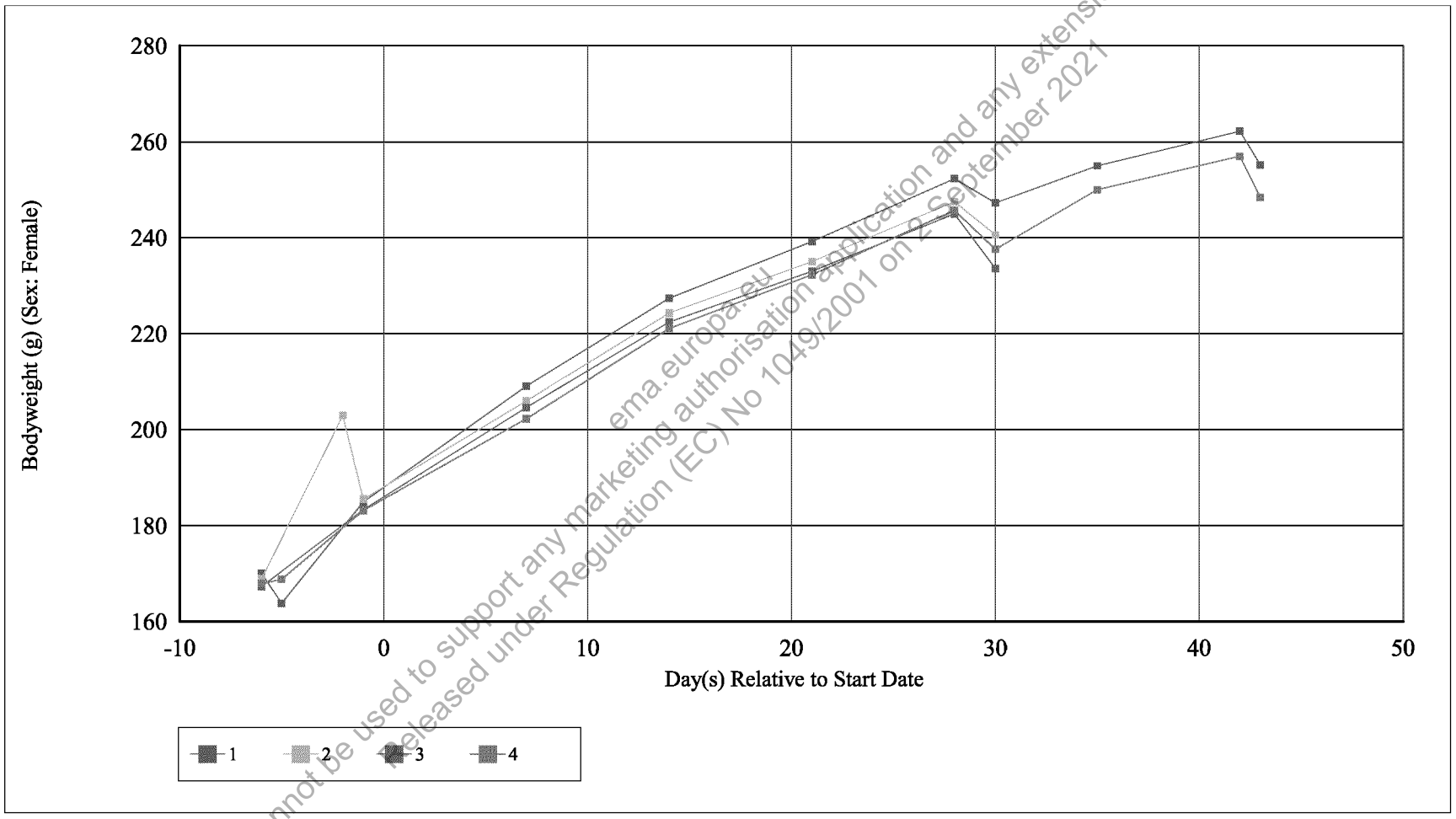

Table 1

Summary of Clinical Observations

5002400

Observation Type: All Types From Day -13 (Start Date) to 43 (Start Date)	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Vocalization								
Number of Animals Affected	0	0	0	6	0	0	0	2
Number of Times Recorded	0	0	0	6	0	0	0	2
% of Affected Animals	0	0	0	40	0	0	0	13
First to Last seen	-	-	-	2 - 30	-	-	-	16 - 30
Limited Usage								
Number of Animals Affected	0	0	0	0	0	0	0	1
Number of Times Recorded	0	0	0	0	0	0	0	2
% of Affected Animals	0	0	0	0	0	0	0	7
First to Last seen	-	-	-	-	-	-	-	16 - 16
Muscle Tone								
Number of Animals Affected	0	1	0	0	0	0	0	0
Number of Times Recorded	0	4	0	0	0	0	0	0
% of Affected Animals	0	10	0	0	0	0	0	0
First to Last seen	-	-3 - -3	-	-	-	-	-	-
Breathing, Shallow								
Number of Animals Affected	0	1	0	0	0	0	0	0
Number of Times Recorded	0	1	0	0	0	0	0	0
% of Affected Animals	0	10	0	0	0	0	0	0
First to Last seen	-	-3 - -3	-	-	-	-	-	-
Fur, Staining								
Number of Animals Affected	0	0	1	1	0	0	0	3
Number of Times Recorded	0	0	1	1	0	0	0	3
% of Affected Animals	0	0	10	7	0	0	0	20
First to Last seen	-	-	7 - 7	43 - 43	-	-	-	30 - 43
Fur, Thin Cover								
Number of Animals Affected	1	1	0	0	4	1	1	2

Table 1

Summary of Clinical Observations

5002400

Observation Type: All Types From Day -13 (Start Date) to 43 (Start Date)	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Fur, Thin Cover (Continued...)								
Number of Times Recorded	4	1	0	0	12	1	2	6
% of Affected Animals	7	10	0	0	27	10	10	13
First to Last seen	42 - 43	7 - 7	-	-	14 - 43	21 - 21	28 - 30	14 - 30
Skin, Lesion w/ Discharge								
Number of Animals Affected	0	0	0	0	1	0	0	0
Number of Times Recorded	0	0	0	0	1	0	0	0
% of Affected Animals	0	0	0	0	7	0	0	0
First to Last seen	-	-	-	-	15 - 15	-	-	-
Skin, Dry								
Number of Animals Affected	0	0	0	0	0	0	0	4
Number of Times Recorded	0	0	0	0	0	0	0	8
% of Affected Animals	0	0	0	0	0	0	0	27
First to Last seen	-	-	-	-	-	-	-	4 - 7
Skin, Pallor								
Number of Animals Affected	0	1	0	0	0	0	0	0
Number of Times Recorded	0	1	0	0	0	0	0	0
% of Affected Animals	0	10	0	0	0	0	0	0
First to Last seen	-	-3 - -3	-	-	-	-	-	-
Skin Thickening								
Number of Animals Affected	0	0	0	14	0	0	0	10
Number of Times Recorded	0	0	0	14	0	0	0	15
% of Affected Animals	0	0	0	93	0	0	0	67
First to Last seen	-	-	-	2 - 2	-	-	-	2 - 7
Skin, Discolored								
Number of Animals Affected	0	1	0	5	0	3	4	14
Number of Times Recorded	0	1	0	7	0	5	4	47

Table 1

Summary of Clinical Observations

5002400

Observation Type: All Types From Day -13 (Start Date) to 43 (Start Date)	Male 0 ug/dose Group 1	Male 10 ug/dose Group 2	Male 30 ug/dose Group 3	Male 96 ug/dose Group 4	Female 0 ug/dose Group 1	Female 10 ug/dose Group 2	Female 30 ug/dose Group 3	Female 96 ug/dose Group 4
Skin, Discolored (Continued...)								
% of Affected Animals	0	10	0	33	0	30	40	93
First to Last seen	-	4 - 4	-	-1 - 43	-	2 - 30	30 - 30	2 - 30
Skin, Scab								
Number of Animals Affected	3	4	5	3	3	2	6	4
Number of Times Recorded	6	6	6	9	4	2	18	15
% of Affected Animals	20	40	50	20	20	20	60	27
First to Last seen	7 - 18	-1 - 7	-1 - 16	-1 - 35	-1 - 30	-1 - 21	-1 - 30	-1 - 30
Swollen								
Number of Animals Affected	0	1	7	15	0	10	10	15
Number of Times Recorded	0	1	9	36	0	23	37	62
% of Affected Animals	0	10	70	100	0	100	100	100
First to Last seen	-	30 - 30	30 - 30	2 - 30	-	2 - 30	2 - 30	2 - 32
Eyeball, Abnormal Color								
Number of Animals Affected	0	1	0	0	0	0	0	0
Number of Times Recorded	0	2	0	0	0	0	0	0
% of Affected Animals	0	10	0	0	0	0	0	0
First to Last seen	-	-3 - -3	-	-	-	-	-	-
Weak								
Number of Animals Affected	0	1	0	0	0	0	0	0
Number of Times Recorded	0	1	0	0	0	0	0	0
% of Affected Animals	0	10	0	0	0	0	0	0
First to Last seen	-	-3 - -3	-	-	-	-	-	-
Abnormal Gait								
Number of Animals Affected	0	0	0	1	0	0	0	2
Number of Times Recorded	0	0	0	1	0	0	0	2
% of Affected Animals	0	0	0	7	0	0	0	13

Table 1

Summary of Clinical Observations

5002400

Observation Type: All Types From Day -13 (Start Date) to 43 (Start Date)	Male				Female			
	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4	0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Abnormal Gait (Continued...)								
First to Last seen	-	-	-	30 - 30	-	-	-	30 - 30
Activity Decreased								
Number of Animals Affected	0	1	0	0	0	0	0	0
Number of Times Recorded	0	1	0	0	0	0	0	0
% of Affected Animals	0	10	0	0	0	0	0	0
First to Last seen	-	-3 - -3	-	-	-	-	-	-
Pinna, Missing (PT)								
Number of Animals Affected	0	0	0	0	2	0	1	0
Number of Times Recorded	0	0	0	0	23	0	10	0
% of Affected Animals	0	0	0	0	13	0	10	0
First to Last seen	-	-	-	-	-12 - 43	-	14 - 30	-

Table 2
Summary of Body Weights

5002400
Bodyweight (g)

Sex: Male		Day(s) Relative to Start Date						
		-5	-1	7	14	21	28	30
0	Mean	185.3	208.5	264.4	317.9	362.6	392.9	392.8
ug/dose	SD	15.4	16.5	19.9	25.8	33.2	36.9	35.3
	N	15	15	15	15	15	15	10
Group 1		-	-	-	-	-	-	-
10	Mean	188.1	211.1	271.0	322.1	359.9	392.8	395.4
ug/dose	SD	10.7	12.6	17.0	23.4	30.1	39.0	38.0
	N	10	10	10	10	10	10	10
Group 2	%Diff	1.5	1.2	2.5	1.3	-0.7	0.0	0.7
30	Mean	187.9	210.1	266.6	320.5	361.2	390.9	387.2
ug/dose	SD	9.9	11.2	12.9	16.6	25.0	32.9	33.9
	N	10	10	10	10	10	10	10
Group 3	%Diff	1.4	0.8	0.8	0.8	-0.4	-0.5	-1.4
96	Mean	185.5	211.2	259.9	319.7	355.5	393.4	390.5
ug/dose	SD	15.0	14.5	16.9	18.7	21.9	26.2	31.6
	N	15	15	15	15	15	15	10
Group 4	%Diff	0.1	1.3	-1.7	0.6	-2.0	0.1	-0.6

Anova & Dunnett

Table 2
Summary of Body Weights

5002400
Bodyweight (g)

Sex: Male		Day(s) Relative to Start Date		
		35	42	43
0	Mean	421.8	440.2	431.0
ug/dose	SD	57.5	65.4	63.0
	N	5	5	5
Group 1		-	-	-
10	Mean	-	-	-
ug/dose	SD	-	-	-
	N	-	-	-
Group 2	%Diff	-	-	-
30	Mean	-	-	-
ug/dose	SD	-	-	-
	N	-	-	-
Group 3	%Diff	-	-	-
96	Mean	397.4	425.6	414.8
ug/dose	SD	23.5	28.3	23.0
	N	5	5	5
Group 4	%Diff	-5.8	-3.3	-3.8

Anova & Dunnett

Table 2
Summary of Body Weights

5002400
Bodyweight (g)

Sex: Female		Day(s) Relative to Start Date						
		-6 [G]	-5 [G]	-2 [G1]	-1 [G]	7 [G]	14 [G]	21 [G]
0	Mean	170.1	163.8	-	184.9	209.1	227.4	239.2
ug/dose	SD	9.5	9.6	-	12.1	13.3	13.5	12.8
	N	10	5	-	15	15	15	15
Group 1		-	-	-	-	-	-	-
10	Mean	168.9	-	203.0n	185.5	206.0	224.3	235.0
ug/dose	SD	8.3	-	-	9.0	9.2	11.5	13.9
	N	10	-	1	10	10	10	10
Group 2	%Diff	-0.7	-	-	0.3	-1.5	-1.4	-1.8
30	Mean	167.3	-	-	183.3	204.6	222.4	233.0
ug/dose	SD	5.3	-	-	7.3	6.8	10.5	9.4
	N	10	-	-	10	10	10	10
Group 3	%Diff	-1.6	-	-	-0.8	-2.1	-2.2	-2.6
96	Mean	167.9	168.8	-	183.1	202.3	221.1	232.3
ug/dose	SD	10.8	6.5	-	11.3	15.4	18.9	20.5
	N	10	5	-	15	15	15	15
Group 4	%Diff	-1.3	3.1	-	-1.0	-3.2	-2.8	-2.9

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn: n - Inappropriate for statistics

Table 2
Summary of Body Weights

5002400
Bodyweight (g)

Sex: Female		Day(s) Relative to Start Date				
		28 [G]	30 [G1]	35 [G]	42 [G]	43 [G1]
0	Mean	252.3	247.3	255.0	262.2	255.2
ug/dose	SD	12.4	9.9	16.7	14.0	12.8
	N	15	10	5	5	5
Group 1		-	-	-	-	-
10	Mean	247.5	240.6	-	-	-
ug/dose	SD	15.5	15.4	-	-	-
	N	10	10	-	-	-
Group 2	%Diff	-1.9	-2.7	-	-	-
30	Mean	245.0	233.6	-	-	-
ug/dose	SD	9.9	10.5	-	-	-
	N	10	10	-	-	-
Group 3	%Diff	-2.9	-5.5	-	-	-
96	Mean	245.7	237.6	250.0	257.0	248.4
ug/dose	SD	22.3	27.4	4.7	4.2	2.4
	N	15	10	5	5	5
Group 4	%Diff	-2.6	-3.9	-2.0	-2.0	-2.7

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Table 3
Summary of Body Weight Gains

5002400
Bodyweight Gain (Interval)

Sex: Male		Day(s) Relative to Start Date						
		-5 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	-1 → 28	28 → 30
0	Mean	23.2	55.9	53.5	44.7	30.3	184.4	-0.2
ug/dose	SD	3.6	9.3	9.0	9.4	6.5	31.3	4.7
	N	15	15	15	15	15	15	10
Group 1		-	-	-	-	-	-	-
10	Mean	23.0	59.9	51.1	37.8	32.9	181.7	2.6
ug/dose	SD	5.3	7.8	8.7	8.4	10.0	31.1	4.0
	N	10	10	10	10	10	10	10
Group 2		-	-	-	-	-	-	-
30	Mean	22.2	56.5	53.9	40.7	29.7	180.8	-3.7
ug/dose	SD	3.9	7.2	9.0	10.2	8.9	31.6	3.3
	N	10	10	10	10	10	10	10
Group 3		-	-	-	-	-	-	-
96	Mean	25.7	48.7	59.8	35.8	37.9*	182.2	-9.2**
ug/dose	SD	5.8	9.9	7.5	8.9	6.1	25.9	5.3
	N	15	15	15	15	15	15	10
Group 4		-	-	-	-	-	-	-

Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Table 3
Summary of Body Weight Gains

5002400
Bodyweight Gain (Interval)

Sex: Male		Day(s) Relative to Start Date			
		28 → 35	35 → 42	28 → 42	42 → 43
0	Mean	29.0	18.4	47.4	-9.2
ug/dose	SD	11.0	9.7	19.6	5.8
	N	5	5	5	5
Group 1		-	-	-	-
10	Mean	-	-	-	-
ug/dose	SD	-	-	-	-
	N	-	-	-	-
Group 2		-	-	-	-
30	Mean	-	-	-	-
ug/dose	SD	-	-	-	-
	N	-	-	-	-
Group 3		-	-	-	-
96	Mean	16.6	28.2	44.8	-10.8
ug/dose	SD	10.9	6.5	16.5	5.6
	N	5	5	5	5
Group 4		-	-	-	-

Anova & Dunnett

Table 3
Summary of Body Weight Gains

5002400
Bodyweight Gain (Interval)

Sex: Female		Day(s) Relative to Start Date						
		-5 → -1	-6 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	-1 → 28
0	Mean	12.6	19.0	24.2	18.3	11.8	13.1	67.4
ug/dose	SD	4.9	4.2	5.6	3.4	5.1	4.4	6.2
	N	5	10	15	15	15	15	15
Group 1		-	-	-	-	-	-	-
10	Mean	-	16.6	20.5	18.3	10.7	12.5	62.0
ug/dose	SD	-	4.5	3.8	5.3	3.7	6.1	11.4
	N	-	10	10	10	10	10	10
Group 2		-	-	-	-	-	-	-
30	Mean	-	16.0	21.3	17.8	10.6	12.0	61.7
ug/dose	SD	-	4.8	5.2	9.1	4.9	6.5	5.8
	N	-	10	10	10	10	10	10
Group 3		-	-	-	-	-	-	-
96	Mean	10.6	17.0	19.3	18.7	11.3	13.4	62.7
ug/dose	SD	3.2	5.8	5.4	5.3	5.7	5.6	13.4
	N	5	10	15	15	15	15	15
Group 4		-	-	-	-	-	-	-

Anova & Dunnett

Table 3
Summary of Body Weight Gains

5002400
Bodyweight Gain (Interval)

Sex: Female		Day(s) Relative to Start Date				
		28 → 30 [G]	28 → 35 [G1]	35 → 42 [G1]	28 → 42 [G1]	42 → 43 [G]
0	Mean	-6.0	4.8	7.2	12.0	-7.0
ug/dose	SD	3.4	3.6	4.5	3.8	6.0
	N	10	5	5	5	5
Group 1		-	-	-	-	-
10	Mean	-6.9	-	-	-	-
ug/dose	SD	6.4	-	-	-	-
	N	10	-	-	-	-
Group 2		-	-	-	-	-
30	Mean	-11.4	-	-	-	-
ug/dose	SD	8.7	-	-	-	-
	N	10	-	-	-	-
Group 3		-	-	-	-	-
96	Mean	-9.3	6.6	7.0	13.6	-8.6
ug/dose	SD	3.9	1.5	2.3	3.6	3.8
	N	10	5	5	5	5
Group 4		-	-	-	-	-

[G] - Kruskal-Wallis & Dunn
[G1] - Anova & Dunnett

Table 4
Summary of Food Consumption

5002400
Food Mean Daily Consumption (g/animal/day)

Sex: Male		Day(s) Relative to Start Date						
		-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29	28 → 35	35 → 42
0	Mean	26.50	28.52	29.63	29.55	28.30	29.46	29.57
ug/dose	SD	1.98	2.57	2.26	2.47	3.71	1.86	2.87
	N	15	15	15	15	10	5	5
Group 1		.	.	.	.	.	.	.
10	Mean	26.06	27.74	28.74	28.89	28.60	.	.
ug/dose	SD	1.69	2.27	2.26	2.32	1.52	.	.
	N	10	10	10	10	10	.	.
Group 2	%Diff	-1.65	-2.74	-2.99	-2.26	1.06	.	.
30	Mean	25.27	28.26	28.93	29.87	30.10	.	.
ug/dose	SD	1.80	1.53	1.70	2.08	1.77	.	.
	N	10	10	10	10	10	.	.
Group 3	%Diff	-4.62	-0.93	-2.36	1.08	6.36	.	.
96	Mean	24.17	29.38	29.00	30.70	31.10	28.43	31.49
ug/dose	SD	1.34	0.60	1.03	1.67	0.58	3.13	3.27
	N	15	15	15	15	10	5	5
Group 4	%Diff	-8.77	3.01	-2.12	3.87	9.89	-3.49	6.47

Table 4
Summary of Food Consumption

5002400
Food Mean Daily Consumption (g/animal/day)

Sex: Female		Day(s) Relative to Start Date						
		-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29	21 → 29	29 → 35
0	Mean	20.10	20.24	20.93	20.70	20.00	20.58	20.67
ug/dose	SD	0.56	0.76	0.71	0.17	1.71	1.07	0.15
	N	15	15	15	10	10	5	5
Group 1		.	.	.	.	.	.	.
10	Mean	19.49	19.66	19.84	19.93	19.60	.	.
ug/dose	SD	0.55	11.39	3.23	6.80	7.73	.	.
	N	7	10	10	10	10	.	.
Group 2	%Diff	-3.01	-2.87	-5.21	-3.73	-2.00	.	.
30	Mean	24.16	19.50	20.11	19.93	20.30	.	.
ug/dose	SD	6.84	1.03	1.16	1.24	1.81	.	.
	N	10	10	10	10	10	.	.
Group 3	%Diff	20.21	-3.65	-3.91	-3.73	1.50	.	.
96	Mean	18.21	19.30	19.70	20.04	20.90	19.80	19.13
ug/dose	SD	1.38	1.22	1.41	1.46	1.44	0.79	0.50
	N	15	15	15	10	10	5	5
Group 4	%Diff	-9.38	-4.61	-5.87	-3.17	4.50	-3.77	-7.42

Table 4
Summary of Food Consumption

5002400
Food Mean Daily Consumption (g/animal/day)

Sex: Female		Day(s) Relative to Start Date
		35 → 42
0	Mean	20.97
ug/dose	SD	0.81
	N	5
Group 1		.
10	Mean	.
ug/dose	SD	.
	N	.
Group 2	%Diff	.
30	Mean	.
ug/dose	SD	.
	N	.
Group 3	%Diff	.
96	Mean	21.17
ug/dose	SD	1.26
	N	5
Group 4	%Diff	0.95

Table 5
Summary of Body Temperature Values

5002400
Body Temperature (oC)

Sex: Male		Day(s) Relative to Start Date						
		1 (PR) [G]	1 (2H) [G]	1 (6H) [G]	2 (24H) [G]	3 [G1]	29 (PR) [G]	29 (2H) [G]
0	Mean	38.33	37.49	37.77	37.51	-	37.41	36.85
ug/dose	SD	0.33	0.42	0.76	0.55	-	0.78	0.65
	N	15	15	15	15	-	15	15
Group 1		-	-	-	-	-	-	-
10	Mean	38.36	37.62	38.47*	37.09	38.20n	37.56	37.16
ug/dose	SD	0.39	0.53	0.47	0.37	0.57	0.51	0.55
	N	10	10	10	10	4	10	10
Group 2	%Diff	0.09	0.34	1.84	-1.13	-	0.39	0.85
30	Mean	38.46	38.01	38.72**	37.36	37.40n	37.22	37.70**
ug/dose	SD	0.19	0.64	0.47	0.39	-	0.80	0.53
	N	10	10	10	10	1	10	10
Group 3	%Diff	0.35	1.38	2.51	-0.41	-	-0.52	2.32
96	Mean	38.43	37.75	39.13**	38.31**	-	38.23**	37.43
ug/dose	SD	0.38	0.60	0.54	0.34	-	0.44	0.83
	N	15	15	15	15	-	15	15
Group 4	%Diff	0.28	0.68	3.58	2.13	-	2.17	1.57

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$
[G1] - Kruskal-Wallis & Dunn: n - Inappropriate for statistics

Table 5
Summary of Body Temperature Values

5002400
Body Temperature (oC)

Sex: Male		Day(s) Relative to Start Date						
		29 (6H) [G]	30 (24H) [G]	33 [G1]	34 [G1]	35 [G1]	37 [G1]	38 [G1]
0	Mean	37.30	36.90	36.20n	36.90n	36.80n	35.70n	36.00n
ug/dose	SD	0.66	0.75	0.44	0.78	0.57	-	-
	N	15	15	3	3	2	1	1
Group 1		-	-	-	-	-	-	-
10	Mean	37.47	37.19	-	-	-	-	-
ug/dose	SD	0.41	0.75	-	-	-	-	-
	N	10	10	-	-	-	-	-
Group 2	%Diff	0.46	0.79	-	-	-	-	-
30	Mean	37.82	36.80	-	-	-	-	-
ug/dose	SD	0.59	0.41	-	-	-	-	-
	N	10	10	-	-	-	-	-
Group 3	%Diff	1.39	-0.27	-	-	-	-	-
96	Mean	38.76**	37.65**	36.00n	36.70n	36.80n	36.50n	36.10n
ug/dose	SD	0.73	0.51	-	-	-	-	-
	N	15	15	1	1	1	1	1
Group 4	%Diff	3.91	2.04	-0.55	-0.54	0.00	2.24	0.28

[G] - Anova & Dunnett: ** = $p \leq 0.01$
[G1] - Kruskal-Wallis & Dunn: n - Inappropriate for statistics

Table 5
Summary of Body Temperature Values

5002400
Body Temperature (oC)

Sex: Male		Day(s) Relative to Start Date				
		39	40	41	42	43
0	Mean	36.50n	36.80n	35.90n	36.70n	37.70n
ug/dose	SD	-	-	-	-	-
	N	1	1	1	1	1
Group 1		-	-	-	-	-
10	Mean	-	-	-	-	-
ug/dose	SD	-	-	-	-	-
	N	-	-	-	-	-
Group 2	%Diff	-	-	-	-	-
30	Mean	-	-	-	-	-
ug/dose	SD	-	-	-	-	-
	N	-	-	-	-	-
Group 3	%Diff	-	-	-	-	-
96	Mean	38.40n	-	-	-	-
ug/dose	SD	-	-	-	-	-
	N	1	-	-	-	-
Group 4	%Diff	5.21	-	-	-	-

Kruskal-Wallis & Dunn: n - Inappropriate for statistics

Table 5
Summary of Body Temperature Values

5002400
Body Temperature (oC)

Sex: Female		Day(s) Relative to Start Date						
		-1 (PR) [G1]	1 (PR) [G]	1 (2H) [G]	1 (6H) [G]	2 (24H) [G]	3 [G1]	29 (PR) [G]
0	Mean	-	38.17	38.12	37.49	38.35	38.30n	38.28
ug/dose	SD	-	0.55	0.67	0.46	0.66	-	0.83
	N	-	15	15	15	15	1	15
Group 1		-	-	-	-	-	-	-
10	Mean	38.50n	38.44	37.74	37.63	37.82	38.30n	38.64
ug/dose	SD	-	0.65	0.91	0.55	0.71	-	0.76
	N	1	10	10	10	10	1	10
Group 2	%Diff	-	0.70	-1.00	0.36	-1.39	0.00	0.94
30	Mean	-	38.63	37.92	37.93	38.40	-	38.85
ug/dose	SD	-	0.48	0.72	0.71	0.40	-	0.31
	N	-	10	10	10	10	-	10
Group 3	%Diff	-	1.20	-0.52	1.16	0.12	-	1.49
96	Mean	-	38.39	37.79	38.77**	39.09**	38.10n	38.49
ug/dose	SD	-	0.55	0.67	0.65	0.54	0.42	0.80
	N	-	15	15	15	15	2	15
Group 4	%Diff	-	0.56	-0.87	3.40	1.91	-0.52	0.56

[G] - Anova & Dunnett: ** = $p \leq 0.01$
[G1] - Kruskal-Wallis & Dunn: n - Inappropriate for statistics

Table 5
Summary of Body Temperature Values

5002400
Body Temperature (oC)

Sex: Female		Day(s) Relative to Start Date		
		29 (2H) [G]	29 (6H) [G1]	30 (24H) [G]
0	Mean	37.68	38.47	38.53
ug/dose	SD	0.92	0.81	0.63
	N	15	15	15
Group 1		-	-	-
10	Mean	38.20	37.83	38.76
ug/dose	SD	0.54	0.97	0.37
	N	10	10	10
Group 2	%Diff	1.38	-1.67	0.59
30	Mean	38.44	37.76	39.23*
ug/dose	SD	0.48	0.72	0.40
	N	10	10	10
Group 3	%Diff	2.02	-1.85	1.81
96	Mean	38.06	38.89	39.09*
ug/dose	SD	0.97	0.68	0.81
	N	15	15	15
Group 4	%Diff	1.01	1.09	1.44

[G] - Kruskal-Wallis & Dunn: * = $p \leq 0.05$
[G1] - Anova & Dunnett

Table 6
Summary of Hematology Values

5002400
Day: 30 Relative to Start Date

Sex: Male		Reporting Hematology						
		WBC (10^3/uL) [G]	NEUT (10^3/uL) [G1]	LYMPH (10^3/uL) [G1]	MONO (10^3/uL) [G]	EOS (10^3/uL) [G1]	BASO (10^3/uL) [G]	LUC (10^3/uL) [G]
0	Mean	7.276	0.917	6.142	0.097	0.055	0.004	0.058
ug/dose	SD	2.742	0.237	2.463	0.046	0.022	0.005	0.050
	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
10	Mean	8.150	2.333	5.422	0.142	0.113 *	0.007	0.134 *
ug/dose	SD	2.243	0.924	1.563	0.043	0.042	0.007	0.067
	N	10	10	10	10	10	10	10
Group 2	tCtrl	1.12	2.54	0.88	1.46	2.05	1.75	2.31
30	Mean	12.894 **	6.557 **	5.859	0.189 *	0.167 **	0.006	0.115
ug/dose	SD	1.705	1.709	0.846	0.094	0.068	0.005	0.068
	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.77	7.15	0.95	1.95	3.04	1.50	1.98
96	Mean	16.045 **	10.648 **	4.888	0.233 **	0.172 **	0.011	0.097
ug/dose	SD	2.136	1.660	1.095	0.075	0.066	0.007	0.045
	N	10	10	10	10	10	10	10
Group 4	tCtrl	2.21	11.61	0.80	2.40	3.13	2.75	1.67

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$
[G1] - Kruskal-Wallis & Dunn: * = $p \leq 0.05$; ** = $p \leq 0.01$

Table 6
Summary of Hematology Values

5002400
Day: 30 Relative to Start Date

Sex: Male		Reporting Hematology						
		RBC (10^6/uL) [G]	HGB (g/dL) [G]	HCT (%) [G]	MCV (fL) [G]	MCH (pg) [G]	MCHC (g/dL) [G1]	RDW (%) [G]
0	Mean	7.673	14.18	44.01	57.48	18.50	32.23	12.26
ug/dose	SD	0.392	0.32	0.90	2.23	0.67	0.35	0.42
	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
10	Mean	7.566	13.89	43.20	57.13	18.36	32.15	12.50
ug/dose	SD	0.229	0.45	1.57	2.01	0.59	0.34	0.49
	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.99	0.98	0.98	0.99	0.99	1.00	1.02
30	Mean	7.562	13.62 *	42.89	56.77	18.02	31.78	13.40 **
ug/dose	SD	0.316	0.43	1.27	2.29	0.58	0.50	0.40
	N	10	10	10	10	10	10	10
Group 3	tCtrl	0.99	0.96	0.97	0.99	0.97	0.99	1.09
96	Mean	7.740	14.03	44.00	56.85	18.14	31.90	14.24 **
ug/dose	SD	0.244	0.44	1.38	1.93	0.59	0.66	0.36
	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.01	0.99	1.00	0.99	0.98	0.99	1.16

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$
[G1] - Kruskal-Wallis & Dunn

Table 6
Summary of Hematology Values

5002400
Day: 30 Relative to Start Date

Sex: Male		Reporting Hematology	
		PLT (10^3/uL) [G]	RETIC (10^9/L) [G]
0 ug/dose Group 1	Mean	1298.1	263.81
	SD	128.4	48.45
	N	10	10
		-	-
10 ug/dose Group 2	Mean	1228.6	253.95
	SD	99.1	40.29
	N	10	10
	tCtrl	0.95	0.96
30 ug/dose Group 3	Mean	1285.6	233.41
	SD	157.6	44.78
	N	10	10
	tCtrl	0.99	0.88
96 ug/dose Group 4	Mean	1257.5	203.67 *
	SD	158.4	49.47
	N	10	10
	tCtrl	0.97	0.77

[G] - Anova & Dunnett: * = $p \leq 0.05$

Table 6
Summary of Hematology Values

5002400
Day: 30 Relative to Start Date

Sex: Female		Reporting Hematology						
		WBC (10^3/uL) [G]	NEUT (10^3/uL) [G]	LYMPH (10^3/uL) [G]	MONO (10^3/uL) [G]	EOS (10^3/uL) [G]	BASO (10^3/uL) [G]	LUC (10^3/uL) [G]
0	Mean	6.404	0.868	5.302	0.098	0.069	0.007	0.064
ug/dose	SD	1.979	0.734	1.572	0.079	0.024	0.005	0.046
	N	9	9	9	9	9	9	9
Group 1		-	-	-	-	-	-	-
10	Mean	8.152	2.901 **	4.825	0.129	0.188 **	0.003	0.103
ug/dose	SD	2.278	0.888	1.405	0.047	0.066	0.005	0.046
	N	10	10	10	10	10	10	10
Group 2	tCtrl	1.27	3.34	0.91	1.32	2.73	0.45	1.60
30	Mean	11.196 **	6.531 **	4.193	0.161 *	0.213 **	0.005	0.090
ug/dose	SD	2.030	1.235	1.246	0.056	0.058	0.005	0.036
	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.75	7.53	0.79	1.65	3.09	0.75	1.40
96	Mean	8.582	5.500 **	2.725 **	0.098	0.174 **	0.003	0.082
ug/dose	SD	1.923	1.091	1.027	0.024	0.052	0.005	0.049
	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.34	6.34	0.51	1.00	2.53	0.45	1.27

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Table 6
Summary of Hematology Values

5002400
Day: 30 Relative to Start Date

Sex: Female		Reporting Hematology						
		RBC (10^6/uL) [G]	HGB (g/dL) [G]	HCT (%) [G]	MCV (fL) [G]	MCH (pg) [G]	MCHC (g/dL) [G]	RDW (%) [G]
0	Mean	7.397	13.88	41.92	56.68	18.77	33.12	10.87
ug/dose	SD	0.422	0.67	1.98	1.48	0.45	0.68	0.25
	N	9	9	9	9	9	9	9
Group 1		-	-	-	-	-	-	-
10	Mean	7.313	13.49	40.88	55.89	18.44	33.00	11.12
ug/dose	SD	0.189	0.38	0.86	1.24	0.47	0.27	0.24
	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.99	0.97	0.98	0.99	0.98	1.00	1.02
30	Mean	7.347	13.50	40.68	55.41	18.40	33.18	11.88 **
ug/dose	SD	0.354	0.59	1.83	1.22	0.44	0.27	0.33
	N	10	10	10	10	10	10	10
Group 3	tCtrl	0.99	0.97	0.97	0.98	0.98	1.00	1.09
96	Mean	7.523	13.82	41.67	55.42	18.38	33.19	12.60 **
ug/dose	SD	0.344	0.40	1.19	1.53	0.60	0.43	0.50
	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.02	1.00	0.99	0.98	0.98	1.00	1.16

[G] - Anova & Dunnett: ** = $p \leq 0.01$

Table 6
Summary of Hematology Values

5002400
Day: 30 Relative to Start Date

Sex: Female		Reporting Hematology	
		PLT (10^3/uL) [G]	RETIC (10^9/L) [G]
0 ug/dose Group 1	Mean	1219.6	204.79
	SD	138.0	33.97
	N	9	9
		-	-
10 ug/dose Group 2	Mean	1187.7	197.88
	SD	173.0	22.77
	N	10	10
	tCtrl	0.97	0.97
30 ug/dose Group 3	Mean	1155.1	204.12
	SD	131.1	36.03
	N	10	10
	tCtrl	0.95	1.00
96 ug/dose Group 4	Mean	1073.1	192.62
	SD	260.2	35.03
	N	10	10
	tCtrl	0.88	0.94

[G] - Anova & Dunnett

Table 6
Summary of Hematology Values

5002400
Day: 43 Relative to Start Date

Sex: Male		Reporting Hematology						
		WBC (10^3/uL) [G]	NEUT (10^3/uL) [G]	LYMPH (10^3/uL) [G]	MONO (10^3/uL) [G]	EOS (10^3/uL) [G]	BASO (10^3/uL) [G]	LUC (10^3/uL) [G]
0	Mean	7.184	1.068	5.852	0.122	0.066	0.002	0.076
ug/dose	SD	1.782	0.195	1.589	0.035	0.038	0.004	0.022
	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
96	Mean	9.848	1.892 *	7.506	0.220 *	0.100	0.010	0.124
ug/dose	SD	2.668	0.654	2.523	0.072	0.046	0.007	0.080
	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.37	1.77	1.28	1.80	1.52	5.00	1.63

[G] - Anova & Dunnett: * = $p \leq 0.05$

Table 6
Summary of Hematology Values

5002400
Day: 43 Relative to Start Date

Sex: Male		Reporting Hematology						
		RBC (10^6/uL) [G]	HGB (g/dL) [G1]	HCT (%) [G1]	MCV (fL) [G1]	MCH (pg) [G1]	MCHC (g/dL) [G1]	RDW (%) [G1]
0 ug/dose Group 1	Mean	7.594	13.74	42.96	56.58	18.10	32.00	12.74
	SD	0.395	0.70	2.15	1.36	0.35	0.51	1.08
	N	5	5	5	5	5	5	5
		-	-	-	-	-	-	-
96 ug/dose Group 4	Mean	7.730	13.82	43.34	56.06	17.84	31.82	14.34 *
	SD	0.074	0.49	1.53	1.54	0.53	0.64	0.44
	N	5	5	5	5	5	5	5
	tCtrl	1.02	1.01	1.01	0.99	0.99	0.99	1.13

[G] - Kruskal-Wallis & Dunn
[G1] - Anova & Dunnett: * = $p \leq 0.05$

Table 6
Summary of Hematology Values

5002400
Day: 43 Relative to Start Date

Sex: Male		Reporting Hematology	
		PLT (10^3/uL) [G]	RETIC (10^9/L) [G]
0 ug/dose Group 1	Mean	1226.0	223.86
	SD	146.9	31.96
	N	5	5
		-	-
96 ug/dose Group 4	Mean	1331.8	242.98
	SD	184.7	29.31
	N	5	5
	tCtrl	1.09	1.09

[G] - Anova & Dunnett

Table 6
Summary of Hematology Values

5002400
Day: 43 Relative to Start Date

Sex: Female		Reporting Hematology						
		WBC (10^3/uL) [G]	NEUT (10^3/uL) [G1]	LYMPH (10^3/uL) [G]	MONO (10^3/uL) [G1]	EOS (10^3/uL) [G]	BASO (10^3/uL) [G1]	LUC (10^3/uL) [G1]
0	Mean	5.124	0.780	4.146	0.098	0.034	0.002	0.062
ug/dose	SD	0.630	0.256	0.669	0.018	0.009	0.004	0.027
	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
96	Mean	7.994 *	1.644 *	5.970	0.172 *	0.096 *	0.006	0.104
ug/dose	SD	1.696	0.529	1.594	0.061	0.031	0.005	0.079
	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.56	2.11	1.44	1.76	2.82	3.00	1.68

[G] - Kruskal-Wallis & Dunn: * = p ≤ 0.05
[G1] - Anova & Dunnett: * = p ≤ 0.05

Table 6
Summary of Hematology Values

5002400
Day: 43 Relative to Start Date

Sex: Female		Reporting Hematology						
		RBC (10^6/uL) [G]	HGB (g/dL) [G]	HCT (%) [G]	MCV (fL) [G]	MCH (pg) [G]	MCHC (g/dL) [G]	RDW (%) [G]
0 ug/dose	Mean	7.214	13.32	41.16	57.08	18.48	32.40	11.38
	SD	0.187	0.45	1.03	0.54	0.31	0.30	0.46
	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
96 ug/dose	Mean	7.366	13.20	40.32	54.74 **	17.92 *	32.72	13.38 **
	SD	0.205	0.39	1.12	0.78	0.33	0.23	0.29
	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.02	0.99	0.98	0.96	0.97	1.01	1.18

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Table 6
Summary of Hematology Values

5002400
Day: 43 Relative to Start Date

Sex: Female		Reporting Hematology	
		PLT (10^3/uL) [G]	RETIC (10^9/L) [G]
0 ug/dose Group 1	Mean	1192.8	203.90
	SD	79.7	29.46
	N	5	5
		-	-
96 ug/dose Group 4	Mean	1460.4 **	210.88
	SD	112.2	22.63
	N	5	5
	tCtrl	1.22	1.03

[G] - Anova & Dunnett: ** = $p \leq 0.01$

Table 7
Summary of Coagulation Values

5002400
Day: 30 Relative to Start Date

Sex: Male		Reporting Coagulation		
		PT (sec) [G]	APTT (sec) [G1]	FIB (mg/dL) [G]
0 ug/dose Group 1	Mean	16.72	15.79	310.7
	SD	0.57	0.69	29.2
	N	10	10	10
		-	-	-
10 ug/dose Group 2	Mean	16.17	16.11	543.8 **
	SD	0.68	0.68	69.7
	N	10	10	10
	tCtrl	0.97	1.02	1.75
30 ug/dose Group 3	Mean	15.96 *	17.35 *	734.1 **
	SD	0.39	0.62	103.4
	N	10	10	10
	tCtrl	0.95	1.10	2.36
96 ug/dose Group 4	Mean	16.20	20.19 **	873.2 **
	SD	0.56	1.72	104.5
	N	10	10	10
	tCtrl	0.97	1.28	2.81

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$
[G1] - Kruskal-Wallis & Dunn: * = $p \leq 0.05$; ** = $p \leq 0.01$

Table 7
Summary of Coagulation Values

5002400
Day: 30 Relative to Start Date

Sex: Female		Reporting Coagulation		
		PT (sec) [G]	APTT (sec) [G]	FIB (mg/dL) [G1]
0 ug/dose Group 1	Mean	16.87	15.32	219.7
	SD	0.52	0.59	28.4
	N	9	9	9
		-	-	-
10 ug/dose Group 2	Mean	16.57	16.58 *	362.4
	SD	0.61	1.11	84.9
	N	10	10	10
	tCtrl	0.98	1.08	1.65
30 ug/dose Group 3	Mean	16.69	18.32 **	616.8 **
	SD	0.94	1.29	64.9
	N	10	10	10
	tCtrl	0.99	1.20	2.81
96 ug/dose Group 4	Mean	16.70	19.68 **	712.6 **
	SD	0.83	0.68	40.4
	N	10	10	10
	tCtrl	0.99	1.28	3.24

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$
[G1] - Kruskal-Wallis & Dunn: ** = $p \leq 0.01$

Table 7
Summary of Coagulation Values

5002400
Day: 43 Relative to Start Date

Sex: Male		Reporting Coagulation		
		PT (sec) [G]	APTT (sec) [G1]	FIB (mg/dL) [G]
0 ug/dose Group 1	Mean	15.80	15.06	293.8
	SD	0.24	0.36	31.7
	N	5	5	5
		-	-	-
96 ug/dose Group 4	Mean	16.08	15.40	283.6
	SD	0.54	1.12	45.3
	N	5	5	5
	tCtrl	1.02	1.02	0.97

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Table 7
Summary of Coagulation Values

5002400
Day: 43 Relative to Start Date

Sex: Female		Reporting Coagulation		
		PT (sec) [G]	APTT (sec) [G]	FIB (mg/dL) [G]
0 ug/dose Group 1	Mean	15.66	15.90	203.0
	SD	1.23	0.83	15.6
	N	5	4	5
		-	-	-
96 ug/dose Group 4	Mean	15.85	16.50	200.7
	SD	0.33	0.59	6.8
	N	4	4	4
	tCtrl	1.01	1.04	0.99

[G] - Anova & Dunnett

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 30 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		AST (U/L) [G]	ALT (U/L) [G]	ALP (U/L) [G1]	GGT (U/L) [G1]	CK (U/L) [G1]	TBIL (mg/dL) [G]	UREAN (mg/dL) [G]
0	Mean	74.0	40.1	162.0	1.5	421.5	0.040	15.7
ug/dose	SD	22.4	5.8	39.3	0.0	342.5	0.027	2.2
	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
10	Mean	74.3	41.3	152.9	1.5	400.2	0.026	15.8
ug/dose	SD	20.0	6.1	31.6	0.0	296.0	0.024	2.1
	N	10	10	10	10	10	10	10
Group 2	tCtrl	1.00	1.03	0.94	1.00	0.95	0.65	1.01
30	Mean	78.5	39.0	151.9	1.5	553.2	0.038	17.0
ug/dose	SD	30.1	9.0	20.4	0.0	560.2	0.023	2.5
	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.06	0.97	0.94	1.00	1.31	0.95	1.08
96	Mean	104.7	35.9	151.3	1.5	841.1	0.056	16.0
ug/dose	SD	38.9	3.5	20.9	0.0	651.9	0.024	2.4
	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.41	0.90	0.93	1.00	2.00	1.40	1.02

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 30 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		CREAT (mg/dL) [G]	GLUC (mg/dL) [G]	CHOL (mg/dL) [G]	TRIG (mg/dL) [G]	TPROT (g/dL) [G]	ALB (g/dL) [G]	GLOB (g/dL) [G]
0	Mean	0.30	201.9	65.9	59.5	5.42	3.77	1.65
ug/dose	SD	0.07	40.3	12.3	25.5	0.31	0.23	0.13
	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
10	Mean	0.31	188.2	70.6	52.4	5.48	3.60	1.88 *
ug/dose	SD	0.03	18.6	15.0	24.0	0.33	0.27	0.19
	N	10	10	10	10	10	10	10
Group 2	tCtrl	1.03	0.93	1.07	0.88	1.01	0.95	1.14
30	Mean	0.33	198.1	73.7	52.5	5.63	3.43 **	2.20 **
ug/dose	SD	0.05	44.7	13.1	21.4	0.25	0.08	0.25
	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.10	0.98	1.12	0.88	1.04	0.91	1.33
96	Mean	0.33	165.9	67.4	53.7	5.89 **	3.40 **	2.49 **
ug/dose	SD	0.05	36.1	15.3	18.1	0.31	0.17	0.22
	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.10	0.82	1.02	0.90	1.09	0.90	1.51

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 30 Relative to Start Date

Sex: Male		Reporting Biochemistry					
		A/G (ratio) [G]	CA (mg/dL) [G]	NA (mmol/L) [G]	K (mmol/L) [G]	CL (mmol/L) [G]	PHOS (mg/dL) [G]
0	Mean	2.30	9.91	137.9	5.02	98.7	7.71
ug/dose	SD	0.18	0.31	2.6	0.41	2.8	0.75
	N	10	10	10	10	10	10
Group 1		-	-	-	-	-	-
10	Mean	1.92 **	10.03	136.1	5.12	96.9	7.76
ug/dose	SD	0.25	0.44	3.0	0.25	2.0	0.66
	N	10	10	10	10	10	10
Group 2	tCtrl	0.83	1.01	0.99	1.02	0.98	1.01
30	Mean	1.57 **	10.34 *	138.4	5.46 *	98.0	8.18
ug/dose	SD	0.19	0.28	2.3	0.41	1.8	0.89
	N	10	10	10	10	10	10
Group 3	tCtrl	0.68	1.04	1.00	1.09	0.99	1.06
96	Mean	1.37 **	10.55 **	139.2	5.65 **	98.1	8.69 *
ug/dose	SD	0.14	0.31	1.6	0.41	2.1	0.73
	N	10	10	10	10	10	10
Group 4	tCtrl	0.60	1.06	1.01	1.13	0.99	1.13

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 30 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		AST (U/L) [G]	ALT (U/L) [G1]	ALP (U/L) [G1]	GGT (U/L) [G]	CK (U/L) [G1]	TBIL (mg/dL) [G1]	UREAN (mg/dL) [G1]
0	Mean	91.9	41.1	99.7	1.5	406.4	0.046	16.0
ug/dose	SD	32.9	9.0	14.1	0.0	269.9	0.022	3.6
	N	10	10	10	10	9	10	10
Group 1		-	-	-	-	-	-	-
10	Mean	72.3	40.9	101.7	1.5	215.7	0.054	15.1
ug/dose	SD	11.7	6.3	23.8	0.0	120.9	0.014	2.1
	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.79	1.00	1.02	1.00	0.53	1.17	0.94
30	Mean	92.8	47.7	82.8	1.5	364.4	0.051	17.3
ug/dose	SD	38.0	42.1	14.7	0.0	259.5	0.022	2.9
	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.01	1.16	0.83	1.00	0.90	1.11	1.08
96	Mean	108.9	42.0	90.6	1.5	579.6	0.076 **	12.9 *
ug/dose	SD	41.0	14.2	14.6	0.0	471.8	0.023	2.0
	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.18	1.02	0.91	1.00	1.43	1.65	0.81

[G] - Kruskal-Wallis & Dunn
[G1] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 30 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		CREAT (mg/dL) [G]	GLUC (mg/dL) [G]	CHOL (mg/dL) [G]	TRIG (mg/dL) [G]	TPROT (g/dL) [G]	ALB (g/dL) [G]	GLOB (g/dL) [G]
0	Mean	0.40	192.2	72.3	41.5	6.20	4.67	1.53
ug/dose	SD	0.07	28.1	14.3	15.2	0.40	0.32	0.22
	N	10	10	10	10	10	10	10
Group 1		-	-	-	-	-	-	-
10	Mean	0.36	193.1	81.9	39.5	6.11	4.41	1.70
ug/dose	SD	0.05	19.2	9.5	9.4	0.46	0.41	0.17
	N	10	10	10	10	10	10	10
Group 2	tCtrl	0.90	1.00	1.13	0.95	0.99	0.94	1.11
30	Mean	0.43	164.5 *	78.3	38.8	6.30	4.22 *	2.08 **
ug/dose	SD	0.05	29.0	11.3	14.5	0.34	0.30	0.17
	N	10	10	10	10	10	10	10
Group 3	tCtrl	1.08	0.86	1.08	0.93	1.02	0.90	1.36
96	Mean	0.40	145.9 **	76.1	42.4	6.36	4.16 **	2.20 **
ug/dose	SD	0.05	21.4	14.5	10.6	0.35	0.33	0.17
	N	10	10	10	10	10	10	10
Group 4	tCtrl	1.00	0.76	1.05	1.02	1.03	0.89	1.44

[G] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 30 Relative to Start Date

Sex: Female		Reporting Biochemistry					
		A/G (ratio) [G]	CA (mg/dL) [G1]	NA (mmol/L) [G1]	K (mmol/L) [G1]	CL (mmol/L) [G1]	PHOS (mg/dL) [G1]
0	Mean	3.11	10.33	142.2	4.76	102.2	6.93
ug/dose	SD	0.54	0.24	2.0	0.25	1.5	0.87
	N	10	10	10	10	10	10
Group 1		-	-	-	-	-	-
10	Mean	2.62	10.69 *	140.7	4.83	100.4	7.52
ug/dose	SD	0.36	0.33	2.4	0.32	2.4	0.73
	N	10	10	10	10	10	10
Group 2	tCtrl	0.84	1.03	0.99	1.01	0.98	1.09
30	Mean	2.03 **	10.74 *	141.6	4.83	100.7	7.25
ug/dose	SD	0.21	0.23	1.1	0.37	0.9	0.83
	N	10	10	10	10	10	10
Group 3	tCtrl	0.65	1.04	1.00	1.01	0.99	1.05
96	Mean	1.90 **	10.78 *	142.3	4.86	100.8	7.89
ug/dose	SD	0.23	0.45	1.9	0.28	1.8	0.62
	N	10	10	10	10	10	10
Group 4	tCtrl	0.61	1.04	1.00	1.02	0.99	1.14

[G] - Kruskal-Wallis & Dunn: ** = $p \leq 0.01$
[G1] - Anova & Dunnett: * = $p \leq 0.05$

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 43 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		AST (U/L) [G]	ALT (U/L) [G]	ALP (U/L) [G]	GGT (U/L) [G1]	CK (U/L) [G]	TBIL (mg/dL) [G]	UREAN (mg/dL) [G]
0	Mean	104.6	47.6	148.6	1.5	681.8	0.078	16.4
ug/dose	SD	23.7	8.0	14.1	0.0	316.3	0.027	0.5
	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
96	Mean	90.0	45.8	145.4	1.5	380.0	0.076	15.6
ug/dose	SD	12.9	3.8	12.8	0.0	196.2	0.017	0.9
	N	5	5	5	5	5	5	5
Group 4	tCtrl	0.86	0.96	0.98	1.00	0.56	0.97	0.95

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 43 Relative to Start Date

Sex: Male		Reporting Biochemistry						
		CREAT (mg/dL) [G]	GLUC (mg/dL) [G]	CHOL (mg/dL) [G1]	TRIG (mg/dL) [G]	TPROT (g/dL) [G]	ALB (g/dL) [G]	GLOB (g/dL) [G]
0	Mean	0.32	216.0	70.2	58.6	5.58	3.92	1.66
ug/dose	SD	0.04	30.7	6.5	18.2	0.28	0.22	0.24
	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
96	Mean	0.32	196.8	66.6	43.6	5.78	4.00	1.78
ug/dose	SD	0.04	42.1	12.3	9.6	0.24	0.16	0.15
	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.00	0.91	0.95	0.74	1.04	1.02	1.07

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 43 Relative to Start Date

Sex: Male		Reporting Biochemistry					
		A/G (ratio) [G]	CA (mg/dL) [G]	NA (mmol/L) [G]	K (mmol/L) [G]	CL (mmol/L) [G]	PHOS (mg/dL) [G]
0	Mean	2.40	9.86	139.8	5.22	102.0	7.54
ug/dose	SD	0.40	0.15	0.8	0.19	1.0	0.71
	N	5	5	5	5	5	5
Group 1		-	-	-	-	-	-
96	Mean	2.24	10.10	140.8	4.96	102.6	8.18
ug/dose	SD	0.21	0.20	0.8	0.19	1.1	0.98
	N	5	5	5	5	5	5
Group 4	tCtrl	0.93	1.02	1.01	0.95	1.01	1.08

[G] - Anova & Dunnett

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 43 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		AST (U/L) [G]	ALT (U/L) [G]	ALP (U/L) [G]	GGT (U/L) [G1]	CK (U/L) [G]	TBIL (mg/dL) [G]	UREAN (mg/dL) [G]
0	Mean	79.4	42.0	74.4	1.5	233.2	0.058	18.4
ug/dose	SD	15.0	14.5	15.4	0.0	153.9	0.022	3.4
	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
96	Mean	102.4	40.2	81.2	1.5	584.2	0.056	17.6
ug/dose	SD	28.3	8.8	12.0	0.0	558.5	0.022	2.6
	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.29	0.96	1.09	1.00	2.51	0.97	0.96

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 43 Relative to Start Date

Sex: Female		Reporting Biochemistry						
		CREAT (mg/dL) [G]	GLUC (mg/dL) [G]	CHOL (mg/dL) [G]	TRIG (mg/dL) [G]	TPROT (g/dL) [G]	ALB (g/dL) [G]	GLOB (g/dL) [G]
0	Mean	0.38	184.2	69.6	40.2	6.46	4.84	1.62
ug/dose	SD	0.04	35.3	10.6	11.3	0.33	0.29	0.19
	N	5	5	5	5	5	5	5
Group 1		-	-	-	-	-	-	-
96	Mean	0.38	147.6	73.4	40.4	6.66	4.82	1.84
ug/dose	SD	0.04	10.9	8.7	10.9	0.57	0.36	0.23
	N	5	5	5	5	5	5	5
Group 4	tCtrl	1.00	0.80	1.05	1.00	1.03	1.00	1.14

[G] - Anova & Dunnett

Table 8
Summary of Clinical Chemistry Values

5002400
Day: 43 Relative to Start Date

Sex: Female		Reporting Biochemistry					
		A/G (ratio) [G]	CA (mg/dL) [G]	NA (mmol/L) [G]	K (mmol/L) [G]	CL (mmol/L) [G]	PHOS (mg/dL) [G]
0	Mean	3.02	10.40	139.4	4.56	102.6	8.64
ug/dose	SD	0.41	0.22	2.6	0.21	2.1	0.96
	N	5	5	5	5	5	5
Group 1		-	-	-	-	-	-
96	Mean	2.64	10.28	139.0	4.68	102.8	7.14 *
ug/dose	SD	0.18	0.19	1.7	0.20	1.6	0.85
	N	5	5	5	5	5	5
Group 4	tCtrl	0.87	0.99	1.00	1.03	1.00	0.83

[G] - Anova & Dunnett: * = $p \leq 0.05$

Table 9

Summary of Blood Marker (α1-acid Glycoprotein and α2-macroglobulin) Values

Scheduled Euthanasia - Day 30
Males

Group 1 - Reference Item
Group 2 - mRNA-1893 10 µg/dose
Group 3 - mRNA-1893 30 µg/dose
Group 4 - mRNA-1893 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
1	Mean	33308.095	15123.563
	SD	10181.870	4483.838
	N	10	10
2	Mean	164871.115	81552.517
	SD	124693.087	114898.307
	N	10	10
	% Diff (G1)	395	439
3	Mean	384683.154 E	280453.324 E
	SD	134845.449	142627.831
	N	10	10
	% Diff (G1)	1055	1754
4	Mean	690352.583 E	1222406.563 E
	SD	208044.802	782610.970
	N	10	10
	% Diff (G1)	1973	7983

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 (Dunn)

Table 9

Summary of Blood Marker (α1-acid Glycoprotein and α2-macroglobulin) Values

Scheduled Euthanasia - Day 30
Females

Group 1 - Reference Item
Group 2 - mRNA-1893 10 µg/dose
Group 3 - mRNA-1893 30 µg/dose
Group 4 - mRNA-1893 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
1	Mean	25825.490	8803.271
	SD	6529.223	1657.317
	N	10	10
2	Mean	67156.156	10511.909
	SD	28759.054	5193.398
	N	10	10
	% Diff (G1)	160	19
3	Mean	302753.384 E	70097.595 E
	SD	115371.219	91633.164
	N	10	10
	% Diff (G1)	1072	696
4	Mean	649982.890 E	496666.713 E
	SD	173145.951	396701.376
	N	10	10
	% Diff (G1)	2417	5542

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 (Dunn)

Table 9

Summary of Blood Marker (α1-acid Glycoprotein and α2-macroglobulin) Values

Scheduled Euthanasia - Day 43
Males

Group 1 - Reference Item

Group 4 - mRNA-1893 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
1	Mean	34976.510	8305.714
	SD	12312.134	1962.642
	N	5	5
4	Mean	31990.776	23133.352 A
	SD	7918.541	10435.952
	N	5	5
	% Diff (G1)	-9	179

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 (Dunn)

Table 9

Summary of Blood Marker (α1-acid Glycoprotein and α2-macroglobulin) Values

Scheduled Euthanasia - Day 43
Females

Group 1 - Reference Item

Group 4 - mRNA-1893 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
1	Mean	22092.828	7422.756
	SD	8675.914	3391.330
	N	5	5
4	Mean	20828.976	12457.842
	SD	7226.976	6592.394
	N	5	5
	% Diff (G1)	-6	68

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 (Dunn)