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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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

		Dates Findings Submitted to:	
Date(s) of Audit	**Phase(s) Audited**	**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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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 (b) (4) 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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1. RESPONSIBLE PERSONNEL

1.1. Test Facility

Study Director (b) (6)

Test Facility Management (b) (6)

1.2. Individual Scientists (IS) at Test Facility

Ophthalmology (b) (6)
Charles River Laboratories Montreal ULC,
Senneville Site (CR MTL), Canada

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

Immunology
(α1-Acid Glycoprotein and α-2
Macroglobulin Analysis) (b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB), Canada

Biomarkers
(Cytokines Analysis
And interpretation) (b) (6)
Charles River Laboratories Montreal ULC
Sherbrooke Site (CR SHB), Canada

Pathology (b) (6)
Charles River Laboratories Montreal ULC,
Senneville Site (CR MTL), Canada

1.3. PIs at Sponsor-designated Test Site

Immunogenicity
(b) (4)

(b) (6)
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), (b) (4) 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 (b) (4)

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 (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4) 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 (b) (4) using a microneutralization assay qualified for the detection of (b) (4) in human serum-(Battelle (b) (4)

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 (b) (6) 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

	Statistical Method
Variables for Inferential Analysis	**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 (b) (4) 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

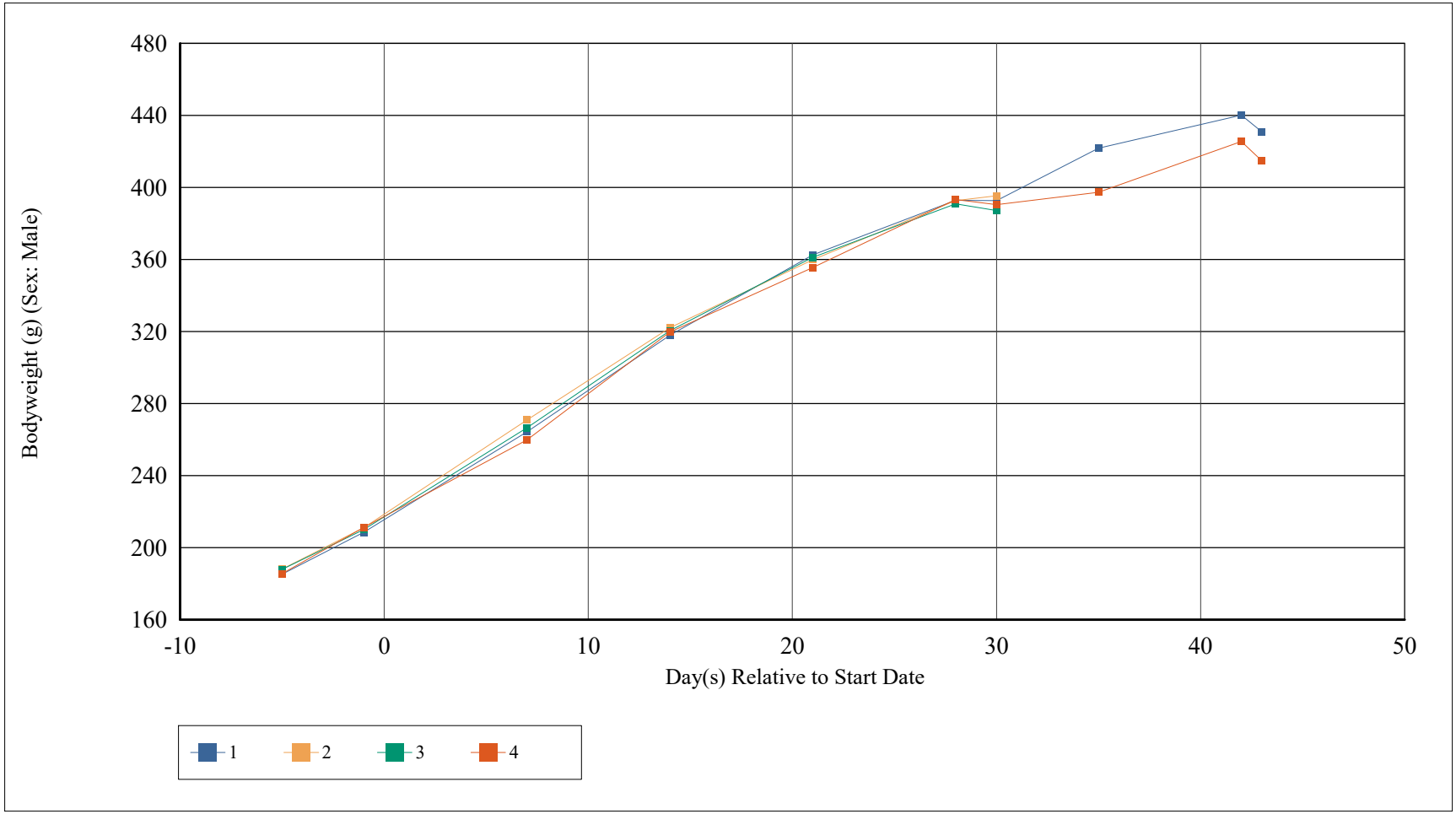

Figure 2
Summary of Body Weights

5002400

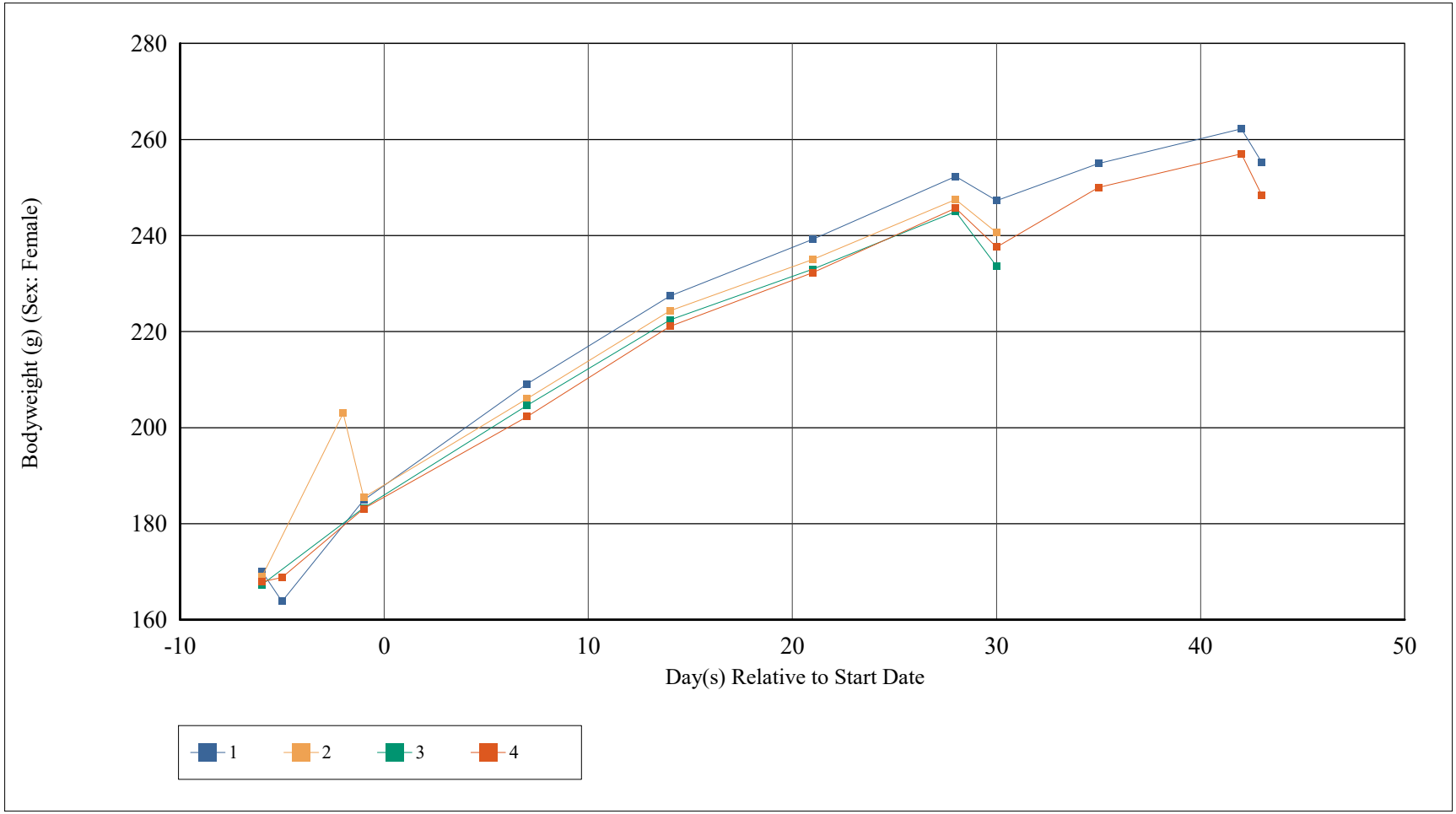

Table 1

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	Male				Female			
From Day -13 (Start Date) to 43 (Start Date)	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	Male				Female			
From Day -13 (Start Date) to 43 (Start Date)	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
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	Male				Female			
From Day -13 (Start Date) to 43 (Start Date)	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 ug/dose Group 1	Mean	7.673	14.18	44.01	57.48	18.50	32.23	12.26
	SD	0.392	0.32	0.90	2.23	0.67	0.35	0.42
	N	10	10	10	10	10	10	10
		-	-	-	-	-	-	-
10 ug/dose Group 2	Mean	7.566	13.89	43.20	57.13	18.36	32.15	12.50
	SD	0.229	0.45	1.57	2.01	0.59	0.34	0.49
	N	10	10	10	10	10	10	10
	tCtrl	0.99	0.98	0.98	0.99	0.99	1.00	1.02
30 ug/dose Group 3	Mean	7.562	13.62 *	42.89	56.77	18.02	31.78	13.40 **
	SD	0.316	0.43	1.27	2.29	0.58	0.50	0.40
	N	10	10	10	10	10	10	10
	tCtrl	0.99	0.96	0.97	0.99	0.97	0.99	1.09
96 ug/dose Group 4	Mean	7.740	14.03	44.00	56.85	18.14	31.90	14.24 **
	SD	0.244	0.44	1.38	1.93	0.59	0.66	0.36
	N	10	10	10	10	10	10	10
	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: * = $p \leq 0.05$
[G1] - Anova & Dunnett: * = $p \leq 0.05$

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	Mean	7.214	13.32	41.16	57.08	18.48	32.40	11.38
ug/dose	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	Mean	7.366	13.20	40.32	54.74 **	17.92 *	32.72	13.38 **
ug/dose	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 ug/dose Group 1	Mean	3.11	10.33	142.2	4.76	102.2	6.93
	SD	0.54	0.24	2.0	0.25	1.5	0.87
	N	10	10	10	10	10	10
		-	-	-	-	-	-
10 ug/dose Group 2	Mean	2.62	10.69 *	140.7	4.83	100.4	7.52
	SD	0.36	0.33	2.4	0.32	2.4	0.73
	N	10	10	10	10	10	10
	tCtrl	0.84	1.03	0.99	1.01	0.98	1.09
30 ug/dose Group 3	Mean	2.03 **	10.74 *	141.6	4.83	100.7	7.25
	SD	0.21	0.23	1.1	0.37	0.9	0.83
	N	10	10	10	10	10	10
	tCtrl	0.65	1.04	1.00	1.01	0.99	1.05
96 ug/dose Group 4	Mean	1.90 **	10.78 *	142.3	4.86	100.8	7.89
	SD	0.23	0.45	1.9	0.28	1.8	0.62
	N	10	10	10	10	10	10
	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 - $P \leq 0.05$ B - $P \leq 0.01$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ (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 - $P \leq 0.05$ B - $P \leq 0.01$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ (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 - $P \leq 0.05$ B - $P \leq 0.01$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ (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 - $P \leq 0.05$ B - $P \leq 0.01$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ (Dunn)

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FINAL STUDY PLAN

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

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1. OBJECTIVES

The objectives of this study are 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.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	mRNA

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date:	07 Nov 2018
Experimental Completion Date:	30 May 2019 (Last date data are collected from the study)
Animal Arrival:	07 Nov 2018
Initiation of Dosing:	19 Nov 2018 (Male) 20 Nov 2018 (Female)
Completion of In-life:	18 Dec 2018 (Main) 31 Jan 2019 (Recovery) (Last date of necropsy)
Unaudited Draft Report:	05 Mar 2019 (43days following completion of in-life)
Audited Draft Report	09 Apr 2019
Final Report:	16 Apr 2019 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- 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)*.

4. REGULATORY COMPLIANCE

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

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

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines will be 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

5. QUALITY ASSURANCE

5.1. Test Facility

The Test Facility Quality Assurance Program (QAP) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAP will review the Study Plan, amendment(s)

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conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

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

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

5.2. Test Facility-designated Subcontractor

The following study phase performed by Test Facility-designated subcontractor will be audited by the Test Facility QAP:

- Ophthalmology

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

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Management Contact

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

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

Individual Scientists (IS) at the Test Facility

Analytical Chemistry (Purity, Concentration and Particle size Analysis)	(b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Ophthalmology	(b) (6) (b) (6) 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Immunology (α1-Acid Glycoprotein α-2 Macroglobulin Analysis)	(b) (6) Address as cited for Test Facility Tel: (b) (6) Fax: (b) (6) E-mail: (b) (6)
Biomarkers (Cytokines Analysis and interpretation)	(b) (6) Address as cited for Test Facility Tel: (b) (6) Fax: (b) (6) E-mail: (b) (6)
Pathology	Will be added by amendment
Immunogenicity (Anti-Therapeutic Antibody Analysis And Interpretation)	Will be added by amendment

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

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

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1893
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	MTDP18195
Concentration:	0.5 mg/mL
Retest Date:	To be updated by amendment
Physical Description:	White to off-white lipid nanoparticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C

8.2. Reference Item

Identification: Phosphate-buffered Saline (PBS) pH 7.2

8.3. Test Item Characterization

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

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

8.4. End of Use Analysis of Test Item

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

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

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

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Concentration, Particle size and Purity analysis will be performed by IEX- HPLC, Differential Light Scattering (DLS) and IPRP-HPLC using validated or qualified analytical procedures.

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

8.5. Reserve Samples

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

8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned to the Sponsor (after completion of dosing) by an overnight express courier on gel packs (-20°C), with a temperature monitor.

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

9. SAFETY

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

10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

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

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

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

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10.2. Preparation of Test Item

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

The bulk Test Item will be removed from the freezer and allowed to thaw at room temperature for no more than 1 hour . The bulk Test Item will be diluted with phosphate buffered saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each day of dosing (i.e., Days 1, 15, and 29) and will be stored in a refrigerator set to maintain 4°C. Aliquots will be removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots can be maintained directly at room temperature for up to 4 hours . The formulations will not be vortexed or sonicated, but may be gently swirled. Stock vials will be used only once.

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

10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity[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 will be averaged and utilized as the concentration results.

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1802291).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis: Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On Day29, the formulation will only be sampled from the middle.

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Backup Samples:	Triplicate top, middle, and bottom samples (triplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On Day 29 the formulation will only be sampled from the middle.
Sampling Containers:	Appropriately-sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Sprague-Dawley Crl:CD(SD)
Source:	Charles River Canada Inc. St. Constant Quebec, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at the Initiation of Dosing:	6 to 8 weeks
Target Weight at the Initiation of Dosing:	126 to 150 g (males) 101 to 125 g (females)

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

11.1. Justification of Test System and Number of Animals

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

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

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

11.2. Animal Identification

Each animal will be identified using a subcutaneously implanted electronic identification chip. If required, animals may be temporarily identified using an approved identification method such as indelible ink.

11.3. Environmental Acclimation

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

11.4. Selection, Assignment, and Replacement of Animals

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

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

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

The alternate animals may be used as replacements on the study within 3 days.

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

12. HUSBANDRY

12.1. Housing

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

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

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12.2. Environmental Conditions

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

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

12.3. Food

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

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

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

12.4. Water

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

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

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

12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study*		Recovery Study*	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1893	10	200	0.05	10	10	-	-
3	mRNA-1893	30	200	0.15	10	10	-	-
4	mRNA-1893	100	200	0.5	10	10	5	5

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

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site will be alternated on each dosing occasion (Site 1 left thigh and Site 2 right thigh). The volume for each dose will be administered using a syringe/needle within the demarcated area. The first day of dosing will be designated as Day 1 (exception: alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

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

13.2. Justification of Route and Dosage 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 is possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound. Similarly formulated vaccine test items have been tested in GLP studies at the test site 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.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below including Laboratory Investigations listed in section below will be performed for all main study and recovery animals,

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

14.1. Mortality/Moribundity Checks

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

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

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: At least every two weeks during the predosing period and weekly during the dosing and recovery periods.

Procedure: Animals removed from the cage for examination.

14.2.2. Detailed Examination of the Injection Sites

Frequency: Once prestudy and on days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 29 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 30.

Procedure: All animals will have the dose injection site examined. Animals removed from the cage for examination. Existing clinical signs are verified and confirmed/closed at this examination and new clinical signs are recorded. The injection site region is observed for any scabs, lesions, discharges, colors and any visible abnormalities, and palpated for any swellings.

14.3. Body Weights

Frequency: At least every 2 weeks during the predosing period and weekly during the dosing and recovery periods.

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

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14.4. Food Consumption

Frequency:	Weekly, starting Day -1, throughout the dosing and recovery periods.
Procedure:	Food consumption will be quantitatively measured except for on the day of scheduled euthanasia.

14.5. Ophthalmic Examinations

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

14.6. Body Temperatures

Frequency:	On Day 1 and Day 29 at predose, 2, 6 and 24 hours post dose (end of each group). If body temperature is above or below normal range (36.0° C to 38.0° C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes measurements may be taken at the discretion of the Study Director.
Procedure:	Body temperature will be recorded via subcutaneous implanted transponder

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15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

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

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

Samples for Clinical Pathology Evaluation

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

X = Sample to be collected

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

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

15.1.2. Hematology

Target Volume: 0.5 mL

Anticoagulant: EDTA

Hematology Parameters

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

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15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 1.5 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Clinical Chemistry Parameters

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

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

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (ATTACHMENT A). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.1.6. Blood Markers (α1-acid glycoprotein and α2-macroglobulin)

Blood will be collected via the abdominal aorta following isoflurane anesthesia before scheduled and unscheduled euthanasia for all animals.

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum; Samples will be mixed gently and will be allowed to clot at ambient conditions until centrifugation, which will be

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	carried out as soon as practical. The samples will be centrifuged as per standard procedures. Serum will be split into three aliquots (target of 75 µL in the first two aliquots, one per analyte, and the remaining amount of serum in the last aliquot).
Storage conditions:	Stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin will be conducted using a validated electrochemiluminescence (ECL) assay (Study No. 3600390). The procedure to be followed along with the assay acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.

Any residual/retained samples will be discarded prior to report finalization.

15.2. Laboratory Investigations (Cytokines Analysis)

Blood will be collected by jugular venipuncture from appropriate main study animals (5 animals/sex/group will be bled). Blood will also be collected from abdominal aorta following isoflurane anesthesia (when possible) from any unscheduled euthanized animals. After collection, blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

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Sample Collection Schedule

Target Blood Volume (mL)			0.5
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	0	5/5	X
	2	5/5	X
	6	5/5	X
15	0	5/5	X
	2	5/5	X
	6	5/5	X
29	0	5/5	X
	2	5/5	X
	6	5/5	X
43[a]	N/A	5/5	X
Matrix			Plasma
Volume per aliquot (µL)			100µL
Number of aliquot(s)			2x100µL and a leftover (if available)
Storage condition (set to maintain)			-80°C
Responsible Lab			CR SHB

N/A = Not applicable
[a] Samples will only be collected on recovery animals

The number of aliquots and volumes are targets that may be adjusted based on sample volume availability.
The samples will be analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1α and MCP-1 will be conducted using a scientifically acceptable multiplex Luminex method (non-GLP). The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in the appropriate analytical procedure. Samples will be analyzed in duplicate.
Following Study Director approval, any residual/retained samples will be discarded prior to report finalization.

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

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

Blood will be collected from animals by jugular venipuncture or from an appropriate peripheral vein.
Time Points: Prestudy, Day 30 (main animals only) and Day 43 (recovery animals).

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Target Volume: 0.5 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum: samples will be mixed gently and kept under ambient conditions until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4) at (b) (4) The resultant serum will be separated,transferred to uniquely labeled clear polypropylene tubes, and frozen immediately over dry ice and transferred to a freezer set to maintain -80°C until shipment. Samples will be shipped on dry ice to:

Shipping Contact: Will be added by amendment

The immunology department will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored in a freezer set to maintain -80°C.

Disposition: The samples will be analyzed for rat anti-ZIKA antibodies using an appropriately qualified method (Study number reference : Will be added by amendment). Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the AuditedDraft Report after which samples will be discarded.Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period.An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

Reporting: An Immunology Report for ATA analysis will be included as an appendix to the Final Report.

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	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

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

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

16.1. Unscheduled Deaths

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

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of laboratory evaluation will be obtained if possible as specified in Section 15. These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

16.2. Scheduled Euthanasia

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

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16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered formalin, except for tissues requiring alternate fixatives as defined by standard operating procedures. Additional tissue samples may be collected to elucidate abnormal findings.

17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. All the tissues listed in ATTACHMENT A will be evaluated for Groups 1 and 4 animals (including recovery) and potential target tissues identified will be communicated to the study Director. These target tissues will be evaluated for Group 2 and 3 and reported. In the event that a dose is

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not tolerated, the next lower group will also be considered as the High Dose Group and all tissues specified in Attachment A will be evaluated. Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by Study Plan amendment following discussion with the Study Director and in consultation with the Sponsor.

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

17.3. Pathology Peer Review

A pathology peer review will be conducted by:

(b) (6)
Moderna Therapeutics
200 Technology Square, 3rd Floor
Cambridge, MA 02139
Tel: (b) (6)
E-mail: (b) (6)

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

18. CONSTRUCTED VARIABLES

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

19. STATISTICAL ANALYSIS

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

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

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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 will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

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

20. COMPUTERIZED SYSTEMS

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

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

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Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation and purity analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
BioPlex Manager	Cytokines data collection
Softmax Pro GxP	α1-acid glycoprotein and α2-macroglobulin data collection
Watson LIMS	Regression analysis of α1-acid glycoprotein, α2-macroglobulin and cytokines data
Dynamics (Wyatt)	Data acquisition for particle size analysis of the Test Item using DLS

21. AMENDMENTS AND DEVIATIONS

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

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

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

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

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

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

23. REPORTING

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

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

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

24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

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TEST FACILITY APPROVAL

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

(b) (6) Date: 07 Nov 2018

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

(b) (6) Date: 07 Nov 2018

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SPONSOR APPROVAL

The Study Plan was approved by the Sponsor by email on 06 Nov 2018. The signature below confirms the approval of the Study Plan by the Sponsor Representative

_____(b) (6)_____Date:_____30Apr19_____
(b) (6)

Appendix 1

ATTACHMENT A

Tissue Collection and Preservation

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

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Tissue	Weigh	Collect	Histology	Microscopic Evaluation[ab]	Comment
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Iliac	-	X	X	X	Lymph node draining the last administration site used (unilateral examination)
Lymph node, Inguinal	-	X	X	X	Lymph node draining the last administration site used (unilateral examination)
Lymph node, Popliteal	-	X	X	X	Lymph node draining the last administration site used (unilateral examination)
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Both
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

[b] Efforts will be made to evaluate all study plan-required tissues microscopically; however, it is not always feasible for every study plan-required tissue to be present on every slide. Study plan-required tissues that are not examined will be documented in the histopathology data and the impact of these missing tissues on the study will be documented in the pathology report.

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STUDY PLAN AMENDMENT 17

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

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SUMMARY OF CHANGES AND JUSTIFICATIONS

Study Plan effective date: 07 Nov 2018

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

Item or Section(s)	Justification
Amendment 1	**Date: 14-Nov-2018**
2.PROPOSED STUDY SCHEDULED	To update/correct the initiation of dosing dates, the completion of in-life dates and the experimental completion date and report dates
4.REGULATORY COMPLIANCE	To delete compliance for US site, as no US test site associated to this study
5.2 Test Facility-designated Subcontractor	To delete last section, as not applicable (there are currently no test facility designated subcontractor that will be audited by a subcontractor QAP
8.1 Test Item	To correct the concentration as per Summary of Analysis
8.3 Test Item Characterization	To delete reference item characterization, as not applicable. The reference item will not be provided by the sponsor and is commercially available
8.4 End of Use Analysis of Test Item	To correct the condition of shipping, as the Test Item is stored at -20°C To correct the acronym definition
10.1 Preparation of Reference Item	To provide an altenative disposition of the reference item
13.2 Justification of Route and Dosage Levels	To correct typo
14.4 Food Consumption	To clarify the food consumption measurement
14.6 Body Temperature	To clarify and update the method and to change the range of the body temperature readings To correct the text format used
15.2 Laboratory Investigations (Cytokines Analysis)	To delete main animals, due to blood collection will also be taken from recovery animals To remove the time point predose, due to blood volume limitations based on body weight data
15.3 Anti-therapeutic Antibody (ATA) Sample Collection, Processing and Analysis	To correct the optional blood collection site to abdominal aorta, as this is the only other optional vein for rats To clarify the qualified method used
19. STATISTICAL ANALYSIS	To clarify the parameters involved for this statistical method.
19.1 Parametric/Non-Parametric	To clarify the parameters involved for this statistical method.
23 REPORTING	To delete the handwritten signature requirement, as sponsor usually uses docusign for signature of reports and phase reports
Amendment 2	**Date: 16-Nov-2018**
13. EXPERIMENTAL DESIGN	To adjust the dose level and the concentration to the new Test Item concentration, as per the Summary of Analysis
15.3 Anti-therapeutic Antibody (ATA) Sample Collection, Processing and	To adjust the speed of centrifuge to the right speed

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Item or Section(s)	Justification
Analysis	
Amendment 3	**Date: 29-Nov-2018**
15.2 Laboratory Investigations (Cytokines Analysis)	To rectify the table and re-add the Days of collect
ATTACHMENT A	To clarify tissue collection as per sponsor recommendation
Amendment 4	**Date: 13-Dec-2018**
15.1.6 Blood Markers (α1-acid glycoprotein and α2-macroglobulin)	To reflect the method used To add the analytical procedure used
15.2 Laboratory Investigations (Cytokines Analysis)	To reflect the method used To add the analytical procedure used
Amendment 5	**Date: 20-Dec-2018**
8.6 Test and Reference Item Inventory and Disposition	To change the disposition of the unused Sponsor-supplied bulk Test Item
Amendment 6	**Date: 21-Dec-2018**
7. RESPONSIBLE PERSONNEL	To assign an IS to the pathology phase
Amendment 7	**Date: 07-Jan-2019**
4. REGULATORY COMPLIANCE	To add the anti-therapeutic antibody analysis to the GLP exeptions
7. RESPONSIBLE PERSONNEL	To assign an PI to the Immunogenicity phase
15.3 Anti-therapeutic Antibody (ATA) Sample Collection, Processing and Analysis	To add the shipping contact for the shipment of samples To clarify the assay description
20. COMPUTERIZED SYSTEMS	To update the critical computerized systems table due to a change in the method of analysis for the blood markers samples
Amendment 8	**Date: 07-Feb-2019**
4.REGULATORY COMPLIANCE	To add the regulatory compliance for method conduct in the USA, as the ATA analysis is conduct in the USA
15.3 Anti-therapeutic Antibody (ATA) Sample Collection, Processing and Analysis	To change the method of analysis used, as the method previously wrote was not right To add reference number for the ATA analysis
Amendment 9	**Date: 07-Feb-2019**
SUMMARY OF CHANGES AND JUSTIFICATIONS	To correct minor typo
4.REGULATORY COMPLIANCE	To remove the regulatory compliance for ATA analysis as it is conduct as an exception to the GLP
Amendment 10	**Date: 11-Feb-2019**
4.REGULATORY COMPLIANCE	To reflect more appropriately the analyses that will be performed by Battelle
7.RESPONSIBLE PERSONNEL	To reflect more appropriately the analyses that will be performed by Battelle
(b) (4)	To reflect more appropriately the analyses that will be performed by Battelle To reflect the settings on the freezers at Battelle Facility To correct minor typo in shipping contact information

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Item or Section(s)	Justification
Amendment 11	**Date: 17-Apr-2019**
8.1 Test Item	To add clarification on administration form of dosing, for SEND compliance
12.3 Food	To change the name of the food given, to be consistend with SEND compliance
23.1. Send Datasets (new section)	To add SEND information into the Study Plan for clarity of expectations related to SEND deliverables.
Amendment 12	**Date: 26-Apr-2019**
5.1 Test Facility	To change the QAP contact following reassignment
7. RESPONSIBLE PERSONNEL	To reassign the Immunology and Biomarkers portions of the study following workload reassignment.
Amendment 13	**Date: 10-May-2019**
22 RETENTION OF RECORDS, SAMPLES, AND SPECIMENS	To clarify that sponsor will be contacted to determine the disposition of materials associated with the study, at least one year after the issue of the final report, instead of the draft report.
Amendment 14	**Date: 10-Sep-2019**
8.1 Test Item	To update the administration dose form in order to be aligned with SEND nomenclature for injection studies as suspension is only to be used for oral gavage studies. To update the restest date as per Summary of Analysis document
Amendment 15	**Date: 12-Sep-2019**
8.1 Test Item	To correct minor typo To change administration form of dosing, for SEND compliance
Amendment 16	**Date: 13-Sep-2019**
8.1 Test Item	To change administration form of dosing, for SEND compliance
Amendment 17	**Date: 16-Sep-2019**
8.6 Test and Reference Item Inventory and Disposition	To correct the disposition of unused Sponsor-supplied bulk Test Item

Appendix 1

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Appendix 1

1. OBJECTIVES

The objectives of this study are 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.

1.1. Study Classification

Study Category:	TOX
Study Type:	Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	mRNA

2. PROPOSED STUDY SCHEDULE

Proposed study dates are listed below. Actual applicable dates will be included in the Final Report.

Experimental Start Date:	07 Nov 2018
Experimental Completion Date:	15 Apr 2019 (Last date data are collected from the study)
Animal Arrival:	07 Nov 2018
Initiation of Dosing:	19 Nov 2018 (Main Male + Recovery) 20 Nov 2018 (Main Female)
Completion of In-life:	19 Dec 2018 (Main) 31 Dec 2018 (Recovery) (Last date of necropsy)
Unaudited Draft Report:	04 Mar 2019 (43days following completion of in-life)
Audited Draft Report	08 Apr 2019
Final Report:	15 Apr 2019 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

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- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99corr.
- ICH Harmonised Tripartite Guideline M3 (R2). *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.
- 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)*.

4. REGULATORY COMPLIANCE

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

Exceptions to GLPs include the following study elements:

- Characterization of the Test Item will be performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses will not be conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines and (b) (4) will be 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

5. QUALITY ASSURANCE

5.1. Test Facility

The Test Facility Quality Assurance Program (QAP) will monitor the study to assure the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with Good Laboratory Practice regulations. The QAP will review the Study Plan, amendment(s) conduct inspections at intervals adequate to assure the integrity of the study, and audit the Final Report to assure that it accurately describes the methods and standard operating procedures and that the reported results accurately reflect the raw data of the study.

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

Appendix 1

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

5.2. Test Facility-designated Subcontractor

The following study phase performed by Test Facility-designated subcontractor will be audited by the Test Facility QAP:

- Ophthalmology

6. SPONSOR

Sponsor Representative

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

7. RESPONSIBLE PERSONNEL

Study Director

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

Management Contact

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

Individual Scientists (IS) at the Test Facility

Analytical Chemistry (Purity, Concentration and Particle size Analysis)	(b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada

Appendix 1

	Tel: (b) (6) E-mail: (b) (6)
Ophthalmology	(b) (6) 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)
Immunology (α1-Acid Glycoprotein α-2 Macroglobulin Analysis)	(b) (6) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Biomarkers (Cytokines Analysis and interpretation)	(b) (6) Address as cited for Test Facility Tel: (b) (6) E-mail: (b) (6)
Pathology	(b) (6) Charles River Laboratories Montreal ULC 22022 Transcanadienne Senneville, QC H9X 3R3 Canada Tel: (b) (6) E-mail: (b) (6)

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

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

Principal Investigators (PI) at Sponsor or Sponsor-designated Test Site

Immunogenicity
(b) (4)

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(b) (4)

(b) (6)
Battelle Biomedical Research Center (BBRC)
Clinical and Nonclinical Research, Healt Business Unit
1425 Plain City Georgesville Road, JM-7
West Jefferson, OH 43162
Tel: (b) (6)
E-mail: (b) (6)

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

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

8. TEST AND REFERENCE ITEMS

8.1. Test Item

Identification:	mRNA-1893
Supplier:	Moderna Therapeutics, Inc.
Batch (Lot) Number:	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
Administration Dose Form:	Injection, Suspension, Liposomal

8.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2

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8.3. Test Item Characterization

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

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

8.4. End of Use Analysis of Test Item

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

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

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

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

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

8.5. Reserve Samples

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

8.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, storage, and disposition of Test and Reference Items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item will be returned to the Sponsor ~~**(before issue of the Final Report)**~~ by an overnight express courier on gel packs (-20°C), with a temperature monitor.

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

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9. SAFETY

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

10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Reference Item

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

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

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

10.2. Preparation of Test Item

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

The bulk Test Item will be removed from the freezer and allowed to thaw at room temperature for no more than 1 hour . The bulk Test Item will be diluted with phosphate buffered saline, pH 7.2, as necessary for administration. The dosing formulations will be prepared on each day of dosing (i.e., Days 1, 15, and 29) and will be stored in a refrigerator set to maintain 4°C. Aliquots will be removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes prior to dosing. Alternatively, the aliquots can be maintained directly at room temperature for up to 4 hours . The formulations will not be vortexed or sonicated, but may be gently swirled. Stock vials will be used only once.

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

10.3. Sample Collection and Analysis

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

Dose Formulation Sample Collection Schedule

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

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N/A = Not applicable.

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

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

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

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

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

10.3.1. Analytical Method

Analyses described below will be performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No. 1802291).

10.3.1.1. Concentration and Homogeneity Analysis

Samples for Analysis:	Duplicate top, middle, and bottom samples (duplicate middle only from Group 1); sent for analysis as noted in Section 10.3. On Day29, the formulation will only be sampled from the middle.
Backup Samples:	Triplicate top, middle, and bottom samples (triplicate middle only from Group 1); maintained at the Test Facility. Backup samples may be analyzed at the discretion of the Study Director. On Day 29 the formulation will only be sampled from the middle.
Sampling Containers:	Appropriately-sized glass containers.
Sample Volume:	0.5 mL for analysis and backup samples.
Storage Conditions:	Kept in a refrigerator set to maintain 4°C.
Acceptance Criteria:	For concentration, the criteria for acceptability will be mean sample concentration results within or equal to ± 15% of theoretical concentration. Each individual sample concentration result within or equal to ± 20%. For homogeneity, the criteria for acceptability will be a relative standard deviation (RSD) of concentrations of ≤ 5% for each group.

10.3.1.2. Stability Analysis

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

11. TEST SYSTEM

Species:	Rat
Strain:	Sprague-Dawley Crl:CD(SD)

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Source:	Charles River Canada Inc. St. Constant Quebec, Canada
Number of Males Ordered:	60
Number of Females Ordered:	60
Target Age at the Initiation of Dosing:	6 to 8 weeks
Target Weight at the Initiation of Dosing:	126 to 150 g (males) 101 to 125 g (females)

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

11.1. Justification of Test System and Number of Animals

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

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

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

11.2. Animal Identification

Each animal will be identified using a subcutaneously implanted electronic identification chip. If required, animals may be temporarily identified using an approved identification method such as indelible ink.

11.3. Environmental Acclimation

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

11.4. Selection, Assignment, and Replacement of Animals

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

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

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

The alternate animals may be used as replacements on the study within 3 days.

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

12. HUSBANDRY

12.1. Housing

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

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

12.2. Environmental Conditions

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

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

12.3. Food

Lab Diet Certified CR Rodent Diet 5CR4 will be provided ad libitum throughout the study, except during designated procedures. The same diet in meal form may be provided to individual animals as warranted by clinical signs (e.g., broken/damaged incisors or other health changes).

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

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

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12.4. Water

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

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

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

12.5. Animal Enrichment

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

12.6. Veterinary Care

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

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

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Test Material	Dose Level (µg/dose)	Dose Volume (µL/dose)	Dose Concentration (mg/mL)	No. of Animals			
					Main Study*		Recovery Study*	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-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 will be necropsied 1 day following the last dose, the remaining 5/sex/Groups 1 and 4 (recovery),will be necropsied 2 weeks following the last dose.

13.1. Administration of Test and Reference Items

The Test and Reference Items will be administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15 and 29, the injection site will be alternated on each dosing occasion (Site 1 left thigh and Site 2 right thigh). The volume for each dose will be administered using a syringe/needle within the demarcated area. The first day of dosing will be designated as Day 1 (exception: alternate animals used for replacement after Day 1 will assume the day of the animal being replaced).

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

13.2. Justification of Route and Dosage 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 is possible mild to moderate injection site reaction (redness, swelling) and potentially elevation of systemic cytokine/acute phase markers may be observed. The mid- and low-dose were selected to evaluate the dose-dependent effect of this compound. 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.

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below including Laboratory Investigations listed in section below will be performed for all main study and recovery animals,

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

14.1. Mortality/Moribundity Checks

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

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

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

Frequency: At least every two weeks during the predosing period and weekly during the dosing and recovery periods.

Procedure: Animals removed from the cage for examination.

14.2.2. Detailed Examination of the Injection Sites

Frequency: Once prestudy and on days of dosing; at least 24 and 72 hours post-dose (end of each group). Weekly when there is no dosing and during the recovery period. Following Day 29 dosing, no assessment will be performed on main animals at 72 hours postdose as animals will be sent to necropsy on Day 30.

Procedure: All animals will have the dose injection site examined. Animals removed from the cage for examination. Existing clinical signs are verified and confirmed/closed at this examination and new clinical signs are recorded. The injection site region is observed for any scabs, lesions, discharges, colors and any visible abnormalities, and palpated for any swellings.

14.3. Body Weights

Frequency: At least every 2 weeks during the predosing period and weekly during the dosing and recovery periods.

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

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14.4. Food Consumption

Frequency:	Weekly, starting Day -1, throughout the dosing and recovery periods.
Procedure:	Food consumption (cage measurement) will be quantitatively measured except for on the day of scheduled euthanasia.

14.5. Ophthalmic Examinations

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

14.6. Body Temperatures

Frequency:	On Day 1 and Day 29 at predose, 2, 6 and 24 hours post dose (end of each group). If body temperature is significantly outside normal range (37.0°C to 39.5°C) the temperature will be monitored daily till return to normal. If clinical observations indicate a possible body temperature changes measurements may be taken at the discretion of the Study Director.
Procedure:	Body temperature will be recorded via subcutaneous implanted transponder. Anytime throughout the study, the rectal body temperature can be recorded if needed.

15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

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

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

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Samples for Clinical Pathology Evaluation

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

X = Sample to be collected

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

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

15.1.2. Hematology

Target Volume: 0.5 mL

Anticoagulant: EDTA

Hematology Parameters

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

15.1.3. Coagulation

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

Anticoagulant: Citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 1.5 mL

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Anticoagulant: None, collected in serum separator tubes

Processing: To serum

Clinical Chemistry Parameters

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

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

15.1.5. Bone Marrow Smear Evaluation (Optional)

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (ATTACHMENT A). Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.1.6. Blood Markers (α1-acid glycoprotein and α2-macroglobulin)

Blood will be collected via the abdominal aorta following isoflurane anesthesia before scheduled and unscheduled euthanasia for all animals.

Target Volume: 0.7 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum; Samples will be mixed gently and will be allowed to clot at ambient conditions until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged as per standard procedures. Serum will be split into three aliquots (target of 75 µL in the first two aliquots, and the remaining amount of serum in the last aliquot).

Storage conditions: Stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin will be conducted using a validated electrochemiluminescence (ECL) assay (Study No. 3600390). The procedure to be followed along with the assay acceptance criteria will be detailed in CR SHB analytical procedure AP.5002400.rtsAPP.xx (where 'xx' denotes the version number). Samples will be analyzed in duplicate.

Any residual/retained samples will be discarded prior to report finalization.

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15.2. Laboratory Investigations (Cytokines Analysis)

Blood will be collected by jugular venipuncture from appropriate animals (5 animals/sex/group will be bled). Blood will also be collected from abdominal aorta following isoflurane anesthesia (when possible) from any unscheduled euthanized animals. After collection, blood samples for plasma will be transferred on wet ice to the appropriate laboratory for processing.

Sample Collection Schedule

Target Blood Volume (mL)			0.5
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)			100µL
Number of aliquot(s)			2x100µL and a leftover (if available)
Storage condition (set to maintain)			-80°C
Responsible Lab			CR SHB

N/A = Not applicable

[a] Samples will only be collected on recovery animals

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

The samples will be analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1α and MCP-1 will be conducted using a scientifically acceptable multiplex Luminex method (non-GLP). The procedures to be followed during the course of this study along with the assays acceptance criteria will be detailed in CR SHB analytical procedure AP.5002400.Cyt.xx (where 'xx' denotes the version number). Samples will be analyzed in duplicate.

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

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

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15.3. (b) (4)

Blood will be collected from animals by jugular venipuncture and from the abdominal aorta, when the samples are collected at termination, or a unscheduled euthanasia, if possible.

Time Points: Prestudy, Day 30 (main animals only) and Day 43 (recovery animals).

Target Volume: 0.5 mL

Anticoagulant: None, collected in serum separator tubes

Processing: To serum: samples will be mixed gently and kept under ambient conditions until centrifugation, which will be carried out as soon as practical. The samples will be centrifuged for (b) (4) in a refrigerated centrifuge (set to maintain (b) (4)) at (b) (4). The resultant serum will be separated,transferred to uniquely labeled clear polypropylene tubes, and frozen immediately over dry ice and transferred to a freezer set to maintain -80°C until shipment. Samples will be shipped on dry ice to:

Shipping Contact: (b) (6)
Battelle Biomedical Research Center (BBRC)
Clinical and Nonclinical Research, Health Business Unit
1425 Plain City Georgesville Road, JM-7
West Jefferson, OH 43162
Tel: (b) (6)
E-mail: (b) (6)

The immunology department will be notified before shipment of the samples. Upon receipt at the immunology laboratory, the samples will be stored in a freezer set to maintain ≤-70°C.

Disposition: The samples will be analyzed for (b) (4) (b) (4) Any residual/retained samples will be maintained for a minimum of 6 months following issuance of the AuditedDraft Report after which samples will be discarded.Alternatively, residual/retained samples will be discarded prior to the 6 month period should the issuance of the Final Report occur prior to the end of the 6 month retention period.An earlier discard of these residual/retained samples may also be requested and authorized by the Study Director.

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Reporting: (b) (4)

16. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Terminal Procedures for Main Study and Recovery Animals

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

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

16.1. Unscheduled Deaths

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

Main or recovery animals may be euthanized for humane reasons as per Test Facility SOPs. The samples for evaluation of laboratory evaluation will be obtained if possible as specified in Section 15. These animals will undergo exsanguination by incision from the abdominal aorta following isoflurane anesthesia unless deemed inappropriate by the Study Director and/or the clinical veterinarian and will undergo complete necropsy examination, and specified tissues will be retained. If necessary, the animal will be refrigerated (set to maintain 4°C) to minimize autolysis.

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

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will be retained (as per Tissue Collection and Preservation section), and any data generated will not be included in the report unless deemed appropriate by the Study Director.

16.2. Scheduled Euthanasia

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

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table in ATTACHMENT A will be collected from all animals and preserved in 10% neutral buffered formalin, except for tissues requiring alternate fixatives as defined by standard operating procedures. Additional tissue samples may be collected to elucidate abnormal findings.

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17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist. All the tissues listed in ATTACHMENT A will be evaluated for Groups 1 and 4 animals (including recovery) and potential target tissues identified will be communicated to the study Director. These target tissues will be evaluated for Group 2 and 3 and reported. In the event that a dose is not tolerated, the next lower group will also be considered as the High Dose Group and all tissues specified in Attachment A will be evaluated. Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by Study Plan amendment following discussion with the Study Director and in consultation with the Sponsor.

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

17.3. Pathology Peer Review

A pathology peer review will be conducted by:

(b) (6)
Moderna Therapeutics
200 Technology Square, 3rd Floor
Cambridge, MA 02139
Tel: (b) (6)
E-mail: (b) (6)

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

18. CONSTRUCTED VARIABLES

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

Appendix 1

19. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
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 will be made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

19.1. Parametric/Non-Parametric

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

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

Appendix 1

20. COMPUTERIZED SYSTEMS

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

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

Critical Computerized Systems

System Name	Description of Data Collected and/or Analyzed
Provantis	In-life; clinical pathology; postmortem
Dispense	Test Material receipt, accountability and/or formulation activities
SRS (CR-MTL in-house application built with SAS) and SAS system for Windows and/or In-house reporting software Nevis 2012 (using SAS)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Data acquisition for dose formulation and purity analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
BioPlex Manager	Cytokines data collection
MSD Discovery Workbench	Data capture for α1-acid glycoprotein and α2-macroglobulin
Watson LIMS	Regression analysis of α1-acid glycoprotein, α2-macroglobulin and cytokines data
Dynamics (Wyatt)	Data acquisition for particle size analysis of the Test Item using DLS

21. AMENDMENTS AND DEVIATIONS

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

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

Appendix 1

22. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

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

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

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

23. REPORTING

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

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

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

Appendix 1

23.1. Send Datasets

At the request of the Sponsor, SEND datasets will be generated and provided outside the context of the Final GLP Report. Since SEND data sets are not subject to audit or Study Director evaluation, the timing of their issuance, relative to the Final Study Report, will be established and agreed with the Sponsor.

24. ANIMAL WELFARE

24.1. Institutional Animal Care and Use Committee Approval

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

Appendix 1

AMENDMENT APPROVAL

DocuSigned by:
(b) (6)
Signer Name: (b) (6)
Signing Reason: I approve this document
Signing Time: 16-Sep-2019 | 16:00:34 EDT
101CC5D946F24517957E68CB580E7480

(b) (6)

Appendix 1

SPONSOR APPROVAL

The Study Plan Amendment was approved by the Sponsor by email on 16 Sep 2019.

Appendix 1

ATTACHMENT A

Tissue Collection and Preservation

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

Appendix 1

Tissue	Weigh	Collect	Histology	Microscopic Evaluation[ab]	Comment
Lung	X	X	X	X	-
Lymph node, mandibular	-	X	X	X	-
Lymph node, mesenteric	-	X	X	X	-
Lymph node, Iliac	-	X	X	X	Lymph node drainage will be collected bilateral, only the drainage lymph node of the last administration site used will be evaluated
Lymph node, Inguinal	-	X	X	X	Lymph node drainage will be collected bilateral, only the drainage lymph node of the last administration site used will be evaluated
Lymph node, Popliteal	-	X	X	X	Lymph node drainage will be collected bilateral, only the drainage lymph node of the last administration site used will be evaluated
Muscle, skeletal	-	X	X	X	Quadriceps
Nerve, optic	-	X	X	X	-
Nerve, sciatic	-	X	X	X	-
Ovary	X	X	X	X	-
Pancreas	-	X	X	X	-
Site, Injection	-	X	X	X	Both sites collected. Only the last administration site used will be evaluated
Skin	-	X	X	X	-
Small intestine, duodenum	-	X	X	X	-
Small intestine, ileum	-	X	X	X	-
Small intestine, jejunum	-	X	X	X	-
Spinal cord	-	X	X	X	-
Spleen	X	X	X	X	-
Stomach	-	X	X	X	-
Testis	X	X	X	X	-
Thymus	X	X	X	X	-
Tongue	-	X	X	X	-
Trachea	-	X	X	X	-
Urinary bladder	-	X	X	X	-
Uterus	X	X	X	X	-
Vagina	-	X	X	X	-

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

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

[b] Efforts will be made to evaluate all study plan-required tissues microscopically; however, it is not always feasible for every study plan-required tissue to be present on every slide. Study plan-required tissues that are not examined will be documented in the histopathology data and the impact of these missing tissues on the study will be documented in the pathology report.

Appendix 1

DEVIATIONS

All deviations that occurred during the study have been authorized/acknowledged by the Study Director, assessed for impact, and documented in the study records. All study plan deviations that could have impacted the quality or integrity of the study are listed below. Minor SOP deviations that did not impact the quality or integrity of the study have not been included.

None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

In-life Observations, Measurements, and Evaluations

- On a few occasions on Days 31, 32, and 36, even if body temperatures were significantly outside of normal range the body temperature, they were not measured for few males, due to technical oversight. As only on few animals on only few occasions, these deviations were considered to have no adverse impact on the study outcome.
- On Day 1 (females), the 6-hour postdose body temperature was evaluated up to 47 minutes earlier at 10 µg/dose. These time excursions had no impact on the study outcome as it only occurred once and since the time excursions were considered minimal.
- As per study plan, recovery ophthalmic examination was only to be performed if Test Item related findings were observed in Week 4. As per Week 4 evaluation form, no Test Item related findings was observed and recovery examination was not required however, recovery examinations was performed to allowing time for an most investigative evaluation between examination. This deviations was considered to have no impact on study results and outcome as considered as extra monitoring.

Appendix 2

moderna

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

Summary of Analysis

Date of Document Generation	25 September 2018
Revision	001
Product name	**mRNA-1893 non-GMP Drug Product**
Product description	mRNA-1893 LNP in 100mm Tris, 7% propylene glycol, 1mM DTPA, pH 7.5
Lot No.	**MTDP18195**
Drug Substance (API)	MTDS18011
Date of Manufacture	19 July 2018
Time Point	Release
Storage	-20°C
Retest Period	TBD

Test	Method	Testing Reference	Target Attributes	Results
ID	RT Sanger Sequencing (b) (4)	Eurofins Lancaster Analysis #9051277	Sequence matches reference standard	Sequence matches reference standard
mRNA Content	1-P-QM-WI-9045525 Rev 3	2008, Preps, Client 041771, 2018-07 (Jul)-0058	Report Results	(b) (4)
Endotoxin	USP <85> (b) (4)	Associates of Cape Cod COA 0718-094	(b) (4)	Location: Beginning, Middle, End; Endotoxin Concentration (b) (4)
Bioburden	USP <61>	2004, MLT MF 2018-08 (Aug)-0007	Type: Total Viable Count, TAMC, TYMC; CFU Count (b) (4)	Type: Total Viable Count, TAMC, TYMC

Appendix 2

moderna

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Revision History:

Revision	Change Detail	Effective Date	Author
1.0	New document	Date of Last Signature	(b) (6)

Document Approval:

	Date
* (b) (6)	26 Sep 2018
*	26 Sep 2018

Appendix 3

FINAL REPORT

Study Phase: Analytical Chemistry

Test Facility Study No. 5002400

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

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Appendix 3

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Appendix 3

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Appendix 3

1. SUMMARY

Dose formulation samples have been analyzed by Ion Exchange High Performance Liquid Chromatography (IEX-HPLC) for the determination of mRNA-1893.

In addition, at the end of the study dosing phase, the bulk test item was analyzed by Ion Exchange High Performance Liquid Chromatography (IEX-HPLC) for concentration analysis, by Ion Pairing Reversed Phase High Performance Liquid Chromatography (IPRP-HPLC) for purity analysis, and by Dynamic Light Scattering (DLS) for particle size analysis.

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

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

2. INTRODUCTION

This report describes the analytical evaluation of mRNA-1893 in dose formulations (Phosphate-buffered Saline (PBS) pH 7.2) and in the bulk test item from Study 5002400.

For the work detailed in this report, the analytical phase experimental start date was 21 Nov 2018, and the analytical phase experimental completion date was 23 Feb 2019.

3. EXPERIMENTAL DESIGN

3.1. Dose Formulation Analysis

Analysis of dose formulations was carried out with regard to concentration and homogeneity.

On Day 1 of the study, for both replicates, duplicate samples were collected from the top, middle and bottom strata of Group 2 to 4 for concentration and homogeneity verification and duplicate samples were collected from the middle strata of Group 1. On Day 29 of the study, for both replicates, duplicate samples were collected from the middle strata of Group 1 to 4 for concentration verification. The samples were shipped on ice packs, and if required stored refrigerated until analysis within the established stability.

3.2. Bulk Test Item Analysis

Analysis of the bulk test item was carried out with regard to concentration, purity, and particle size analysis.

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

Appendix 3

4. MATERIALS AND METHODS

4.1. Materials

4.1.1. Reference Standard

Identification:	CX-005809
Physical Description:	Clear, colorless solution, essentially no visible particulates
Batch/Lot No.:	MTDS18011
Concentration:	1.71 mg/mL
Retest Date:	Jun 2019
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

4.1.2. Reference Material (Bulk Test Item)

Identification:	mRNA-1893 Drug Product
Physical Description:	White to off-white dispersion. May contain visible, white or translucent product-related particulates
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)
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

4.1.3. Characterization of Reference Standard and Reference Material

The Sponsor provided the documentation for the identity, strength, purity, composition, and stability for the reference standard and reference material. Copies of the supplied Summary of Analysis (SoA) or equivalent documentation are presented in Appendix 2.

4.1.4. Inventory and Disposition of Reference Standard and Reference Material

Records of the receipt, distribution, and storage of the reference standard and reference material were maintained. All unused Sponsor-supplied reference standard and reference material were retained for use on subsequent studies for the Sponsor.

Appendix 3

4.2. Methods

4.2.1. Analytical Procedures

The method for concentration analysis is documented in Analytical Procedure AP.5002400.SP.02 (Appendix 1) and was previously validated under Study No. 1802291. Concentration stability data were generated by the department of Analytical Chemistry, Charles River, CR MTL for 1 day for formulation samples stored at ambient temperature and for 8 days for formulation samples stored in a refrigerator set to maintain 4°C and in a freezer set to maintain -20°C, over the concentration range of 0.00960 – 0.480 mg/mL, under Study No. 1802291.

The method for particle size analysis is documented in Analytical Procedure AP.5002400.DLS.01 (Appendix 1).

The method for purity analysis is documented in Analytical Procedure AP.5002400.PU.02 (Appendix 1).

4.3. Computerized Systems

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

Text Table 1
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Empower 3 (Waters Corporation)	Build 3471 SR1	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
Dynamics (Wyatt)	7.1.9.3	Data acquisition for particle size analysis for the test item using DLS
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

Appendix 3

5. RESULTS AND DISCUSSIONS

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

5.1. Dose Formulation Analysis

All study samples analyzed had mean concentrations within or equal to the acceptance criteria of ± 15% (individual values within or equal to ± 20%) of their theoretical concentrations. Results are presented in Table 1.

For homogeneity, the RSD of concentrations for all samples in each group tested was within the acceptance criteria of ≤ 5%. Results are presented in Table 2.

5.2. Bulk Test Item Analysis

The concentration, purity, and particle size of the bulk test item were measured after completion of dosing. Concentration, purity, and particle size results were consistent (and within the target attributes) with the initial Summary of Analysis provided by the Sponsor.

Results are presented in Table 3, Table 4, and Table 5.

A representative purity analysis chromatogram is presented in Figure 1.

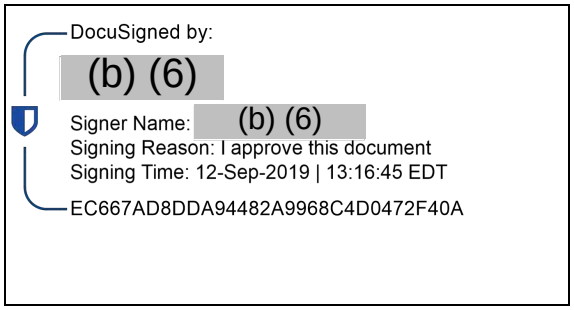
6. CONCLUSION

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

The bulk Test Item analysis demonstrated that the test item was suitable for use during the study period.

Appendix 3

7. REPORT APPROVAL



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Appendix 3

Table 1 Study Samples - Concentration and Homogeneity

Occasion (Sampling Date)	Group	Theoretical Concentration (mg/mL)	Sampling Location	Measured Concentration (mg/mL)	Percent of Theoretical	RSD (%)
Day 1, (19 Nov 2018)	1	(b) (4)	Middle	ND	-	-
				ND	-	
			Mean	-	-	
	2		Top	(b) (4)		
			Middle			
			Bottom			
			Mean			
	3		Top			
			Middle			
			Bottom			
			Mean			
	4		Top			
			Middle			
			Bottom			
			Mean			

ND = None detected.

Appendix 3

Table 2 Study Samples - Concentration

Occasion (Sampling Date)	Group	Theoretical Concentration (mg/mL)	Sampling Location	Measured Concentration (mg/mL)	Percent of Theoretical	RSD (%)
Day 29, (18 Dec 2018)	1	(b) (4)	Middle	ND	-	-
				ND	-	
			Mean	-	-	
	2		Middle	(b) (4)		-
			Mean			
	3		Middle			-
			Mean			
	4		Middle			-
			Mean			

ND = None detected.

Appendix 3

Table 3 Bulk Test Item - Concentration

Occasion (Analysis Date)	Theoretical Concentration (mg/mL)	Measured Concentration (mg/mL)	Percent of Theoretical	Mean Measured Concentration (mg/mL)
End of study (21 Dec 2018)	(b) (4)			

Table 4 Bulk Test Item - Particle Size Analysis

Occasion (Analysis Date)	Theoretical Diameter (nm)	Measured Diameter (nm)	PD Index	% Difference Between Duplicate	Mean Measured Diameter (nm)
End of study (21 Dec 2018)	(b) (4)				

Appendix 3

Table 5 Bulk Test Item - Purity Analysis

Occasion (Analysis Date)	Theoretical Purity (% Peak Area) [a]		Measured Purity (% Peak Area)			
	Main	78	Main (total)	IG 1	IG 2	IG 3
End of study (22 Feb 2019)	(b) (4)					

IG = Impurity Group.
a = As per initial (T=0) Summary of Analysis (SoA), revision 001.

Appendix 3

Figure 1 Representative Purity Analysis Chromatogram (Zoomed to Scale)

(b) (4)

Appendix 3

Appendix 1
Analytical Procedures

Appendix 3

Analytical Procedure (AP.5002400.SP.02)

Determination of mRNA-1893 in Dose Formulations by Ion Exchange High Performance Chromatography Using Ultraviolet/Visible Detection

Reference Standard, Reference Material and Vehicle

Reference Standard	CX-005809
Lot number	MTDS18011
Concentration (actual)	1.71 mg/mL
Reference Material/Test Item	mRNA-1893 Drug Product
Lot number	MTDP18195
Concentration	0.48 mg/mL
Vehicle	Phosphate-buffered Saline (PBS) pH 7.2

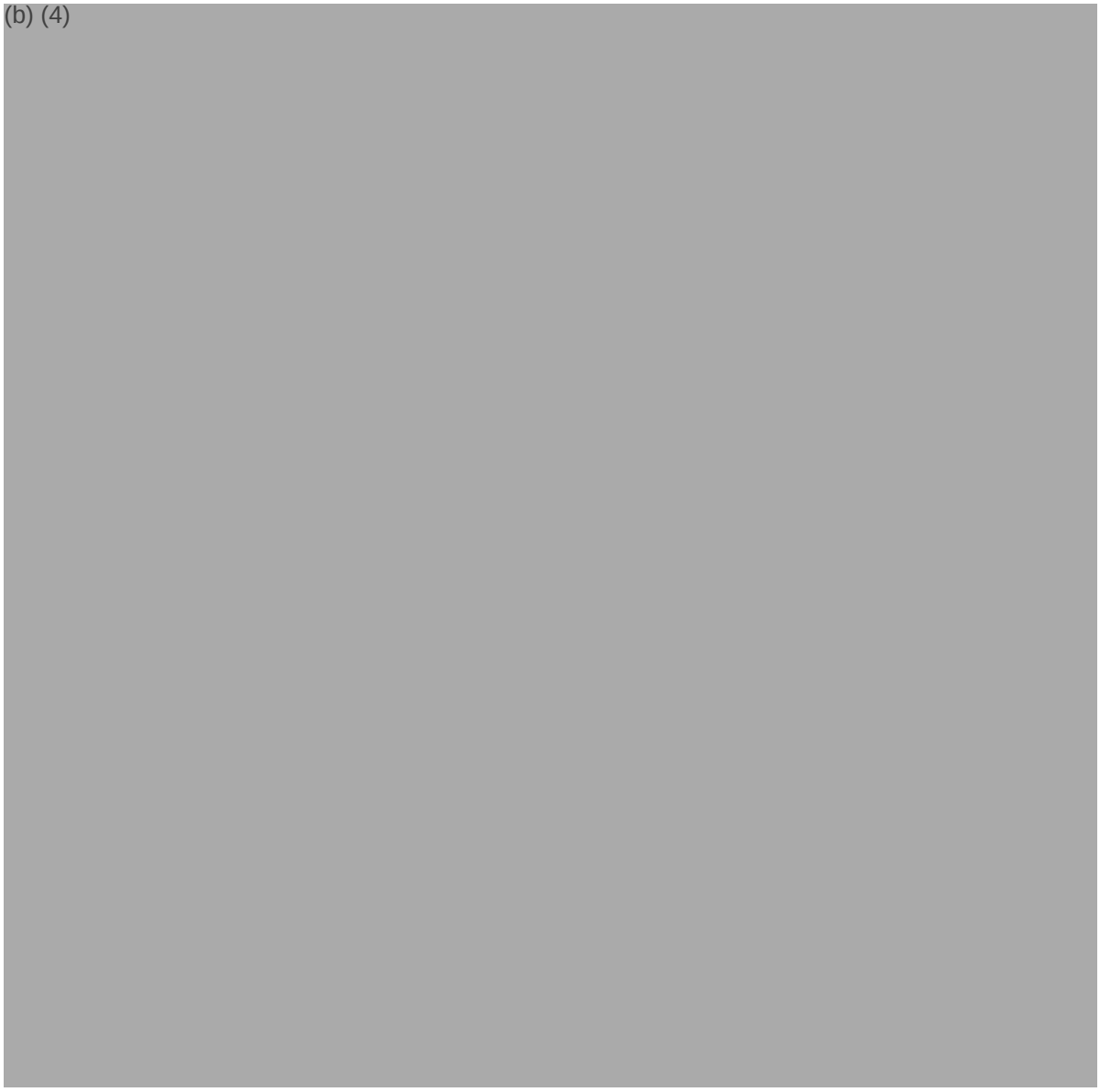
For storage conditions reference standard and reference material supplied by the Sponsor, refer to the corresponding log sheets.

NOTES:

- ❑ Modifications may be made to the chromatographic conditions in order to optimize the chromatography.
- ❑ Solution volumes throughout this AP (including reagent solutions, blanks, standard stocks, standards and spiked samples) may be scaled up or down as long as the final concentration remains the same as specified in the procedure.
- ❑ Any changes made are to be documented in the raw data of the run.
- ❑ Unless otherwise indicated, information relating to the time of mixing/stirring, temperature or mixing method used in the preparation of solutions, diluents, mobile phases and vehicle will be considered non-critical. If a step is deemed critical, it will be noted within the procedure, and a positive entry will be made in the raw data
- ❑ **The compound is a mRNA, benchwork and handling should be performed under clean conditions to limit RNase contamination. When possible use RNase free tubes, pipette and repeater tips for reference standard/test item dilutions. DO NOT VORTEX, mix manually by inversion.**
- ❑ The analytical method was previously validated under study No. 1802291.

Appendix 3

(b) (4)



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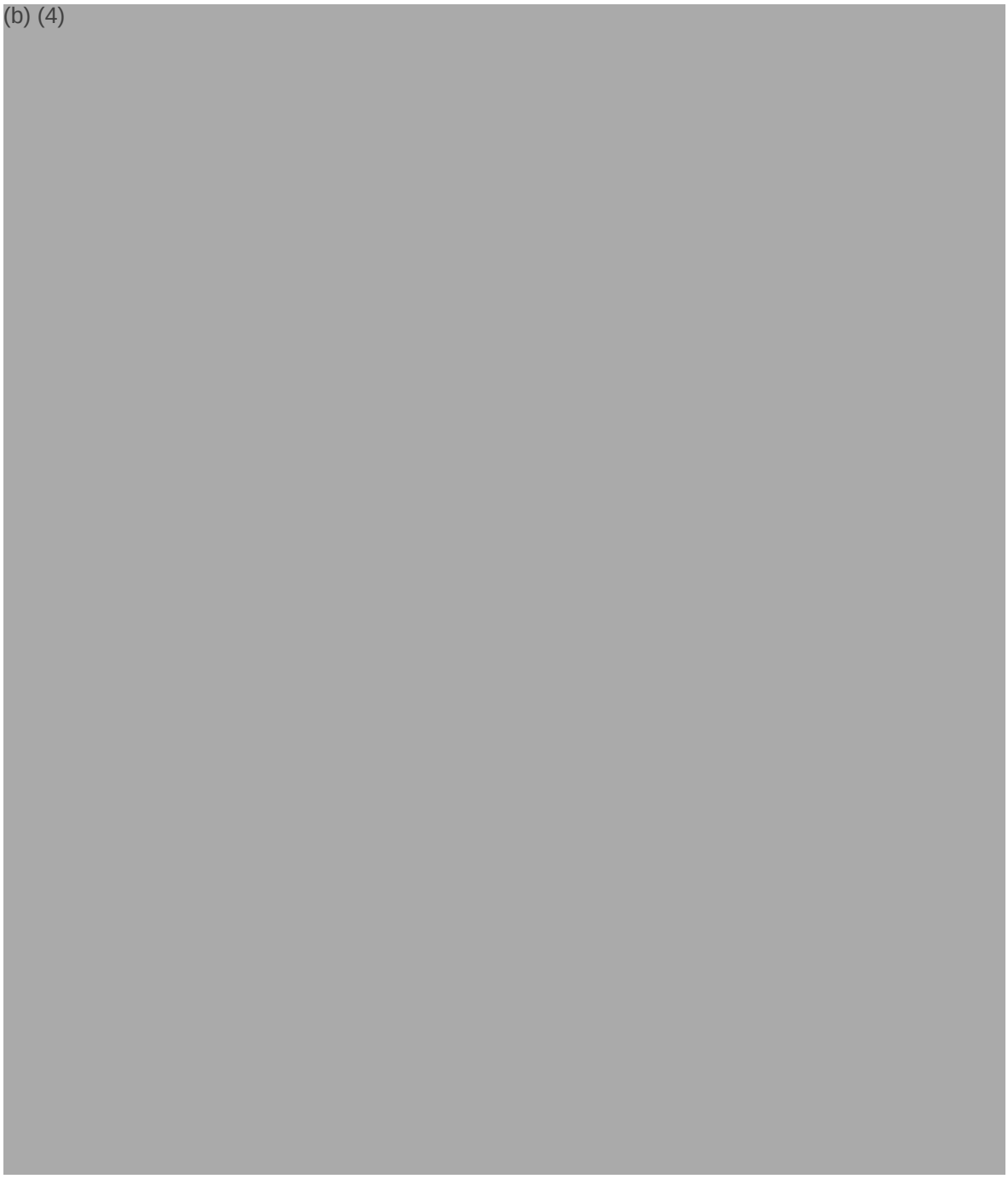
Appendix 3

(b) (4)



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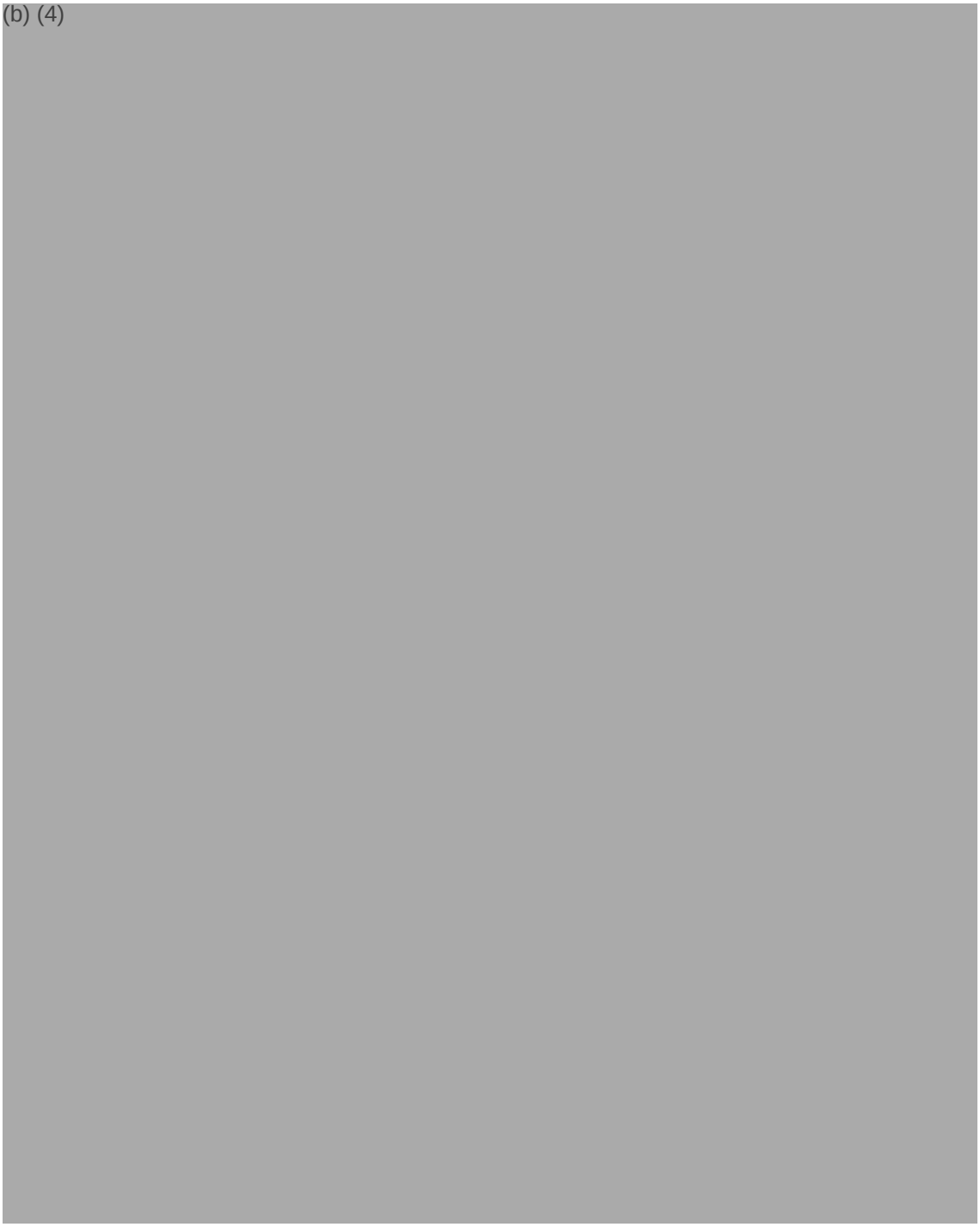
(b) (4)



Appendix 3

(b) (4)

Acceptance criteria

Unless specified in the following or in the Study Plan, refer to SOP CAD-001 and SOP CAD-002 for acceptance criteria.

(b) (4)

Appendix 3

Analytical Procedure (AP.5002400.SP.02)

Page 8 of 8

AP Version Control

First update (supersedes AP.5002400.SP.01) for the following reason:

- Included missing expiry periods throughout the procedure.

Verified by (b) (6) Date 26 Feb 2019

Approved by (b) (6) Date 26 Feb 2019

Authorized by (b) (6) Date 26 Feb 2019

Scientific Director ☑

Appendix 3

Analytical Procedure (AP.5002400.DLS.01)

Determination of the Particle Size Distribution of mRNA-1893 Drug Product by Dynamic Light Scattering (DLS) using Wyatt DynaPro NanoStar.

Bulk Test Item

Identity	mRNA-1893 Drug Product
Description	White to off-white lipid nanoparticle dispersion.
Lot number	MTDP18195
Concentration (actual)	0.48 mg/mL

For storage conditions for test item supplied by the Sponsor, refer to the corresponding log sheets.

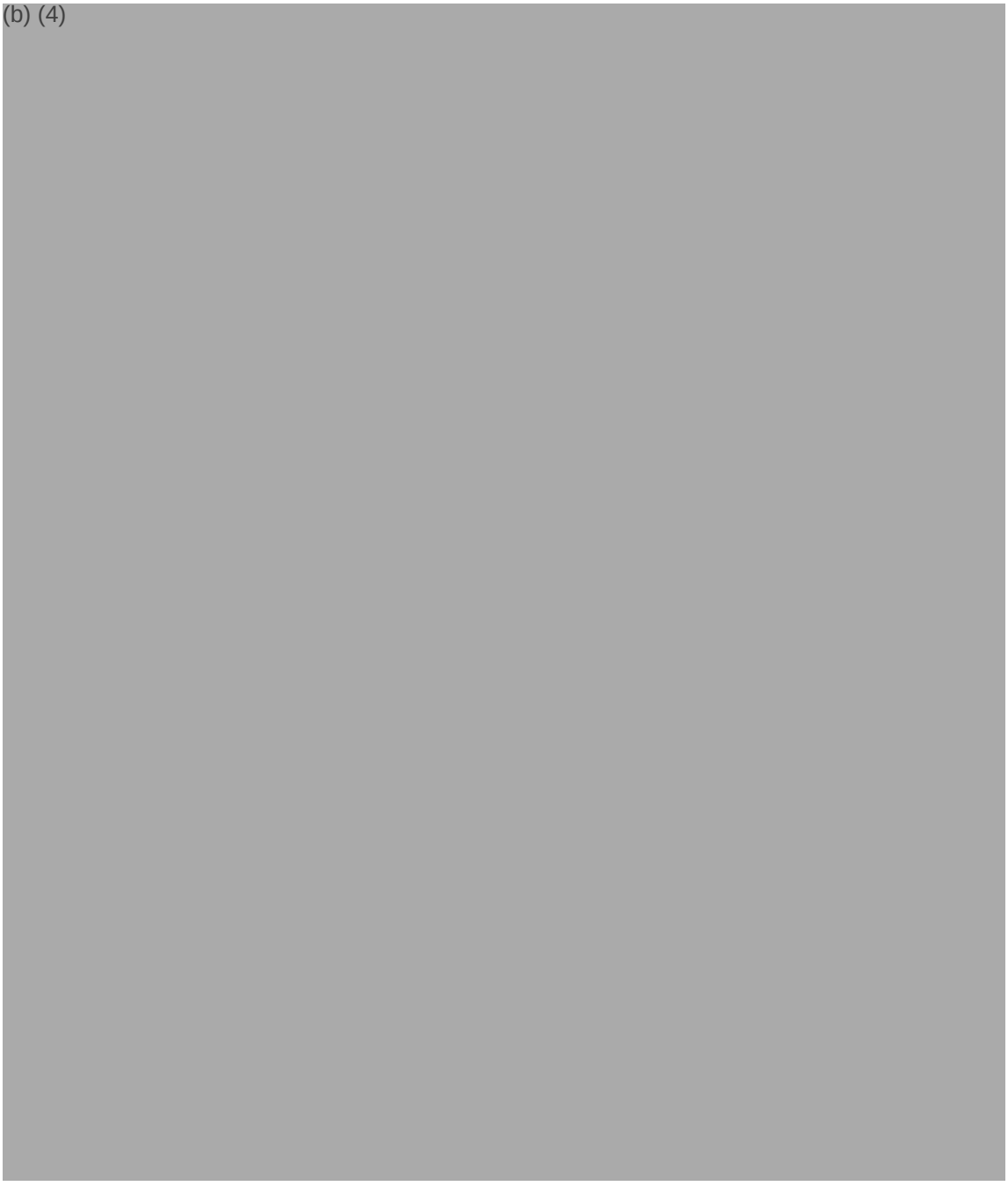
NOTES:

- ❑ Solution volumes throughout this AP may be scaled up or down as long as the final concentration remains the same as specified in the procedure.
- ❑ Any changes made are to be documented in the raw data of the run.
- ❑ Unless otherwise indicated, information relating to the time of mixing/stirring, temperature or mixing method used in the preparation of solutions will be considered non-critical. If a step is deemed critical, it will be noted within the procedure, and a positive entry will be made in the raw data
- ❑ **The compound is a mRNA, benchwork and handling should be performed under clean conditions to limit RNase contamination. When possible use RNase free tubes, pipette and repeater tips for test item dilutions. DO NOT VORTEX, mix manually by inversion.**
- ❑ Refer to SOP CAE-238 for operation of the Dynapro Nanostar DLS instrument with Dynamics software.

(b) (4)

Appendix 3

(b) (4)



Appendix 3

Analytical Procedure (AP.5002400.DLS.01)

(b) (4)

Instrument Parameters for Sample Reading

Save all settings as a preset on location D:\Dynamics\Projects\5002400.

(b) (4)

Appendix 3

(b) (4)

AP Version Control

Initial version.

Verified by (b) (6) Date 18 Dec 2018

Approved by (b) (6) Date 18 Dec 2018

Authorized by (b) (6) Date 07 Mar. 2019

Scientific Director ☑

Appendix 3

Analytical Procedure (AP.5002400.PU.02)

Determination of the Purity of mRNA-1893 Drug Product by Ion Pairing Reversed Phase High Performance Chromatography Using Ultraviolet/Visible Detection

Reference Standard, Test Item and Placebo

Reference Standard (RS)	CX-005809
Lot number	MTDS18011
Concentration (total mRNA)	1.71 mg/mL
Bulk Test Item	mRNA-1893 Drug Product
Lot number	MTDP18195
Concentration (actual)	0.48 mg/mL (to be used for calculations)
Main Peak Purity (as per initial SoA)	78%

(b) (4)

For storage conditions for reference standard, test item and placebo supplied by the Sponsor, refer to the corresponding log sheets.

HPLC Conditions

(b) (4)

Appendix 3

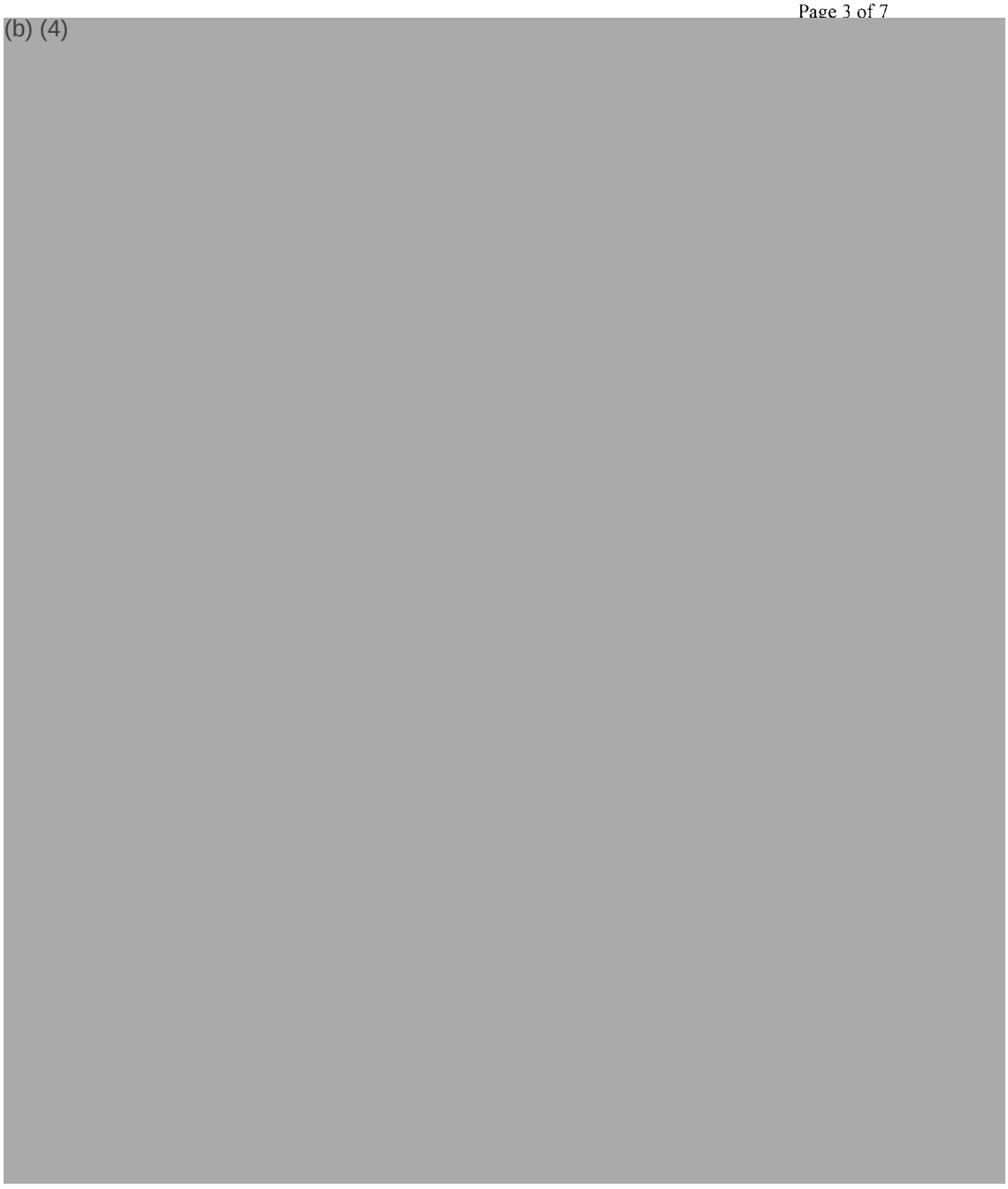
(b) (4)

NOTES:

- Modifications may be made to the chromatographic conditions in order to optimize the chromatography.
- Solution volumes throughout this AP (including reagent solutions, blanks, standard stocks, standards and spiked samples) may be scaled up or down as long as the final concentration remains the same as specified in the procedure.
- Any changes made are to be documented in the raw data of the run.
- Unless otherwise indicated, information relating to the time of mixing/stirring, temperature or mixing method used in the preparation of solutions, diluents, mobile phases and vehicle will be considered non-critical. If a step is deemed critical, it will be noted within the procedure, and a positive entry will be made in the raw data
- **The compound is a mRNA, benchwork and handling should be performed under clean conditions to limit RNase contamination. When possible use RNase free tubes, pipette and repeater tips for reference standard/test item dilutions. DO NOT VORTEX, mix manually by inversion.**
- The purity method was previously validated under 1803056.

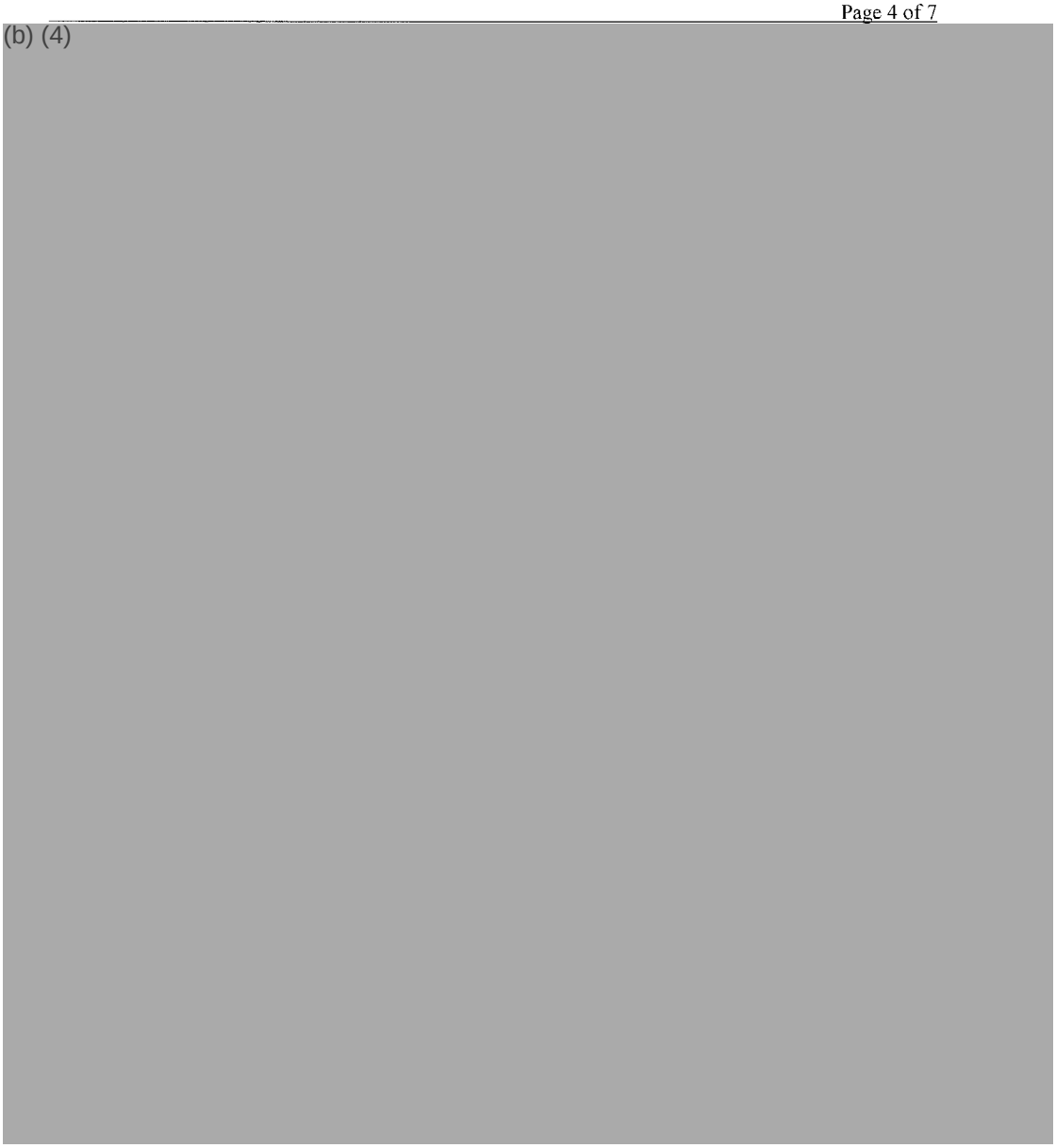
Appendix 3

(b) (4)



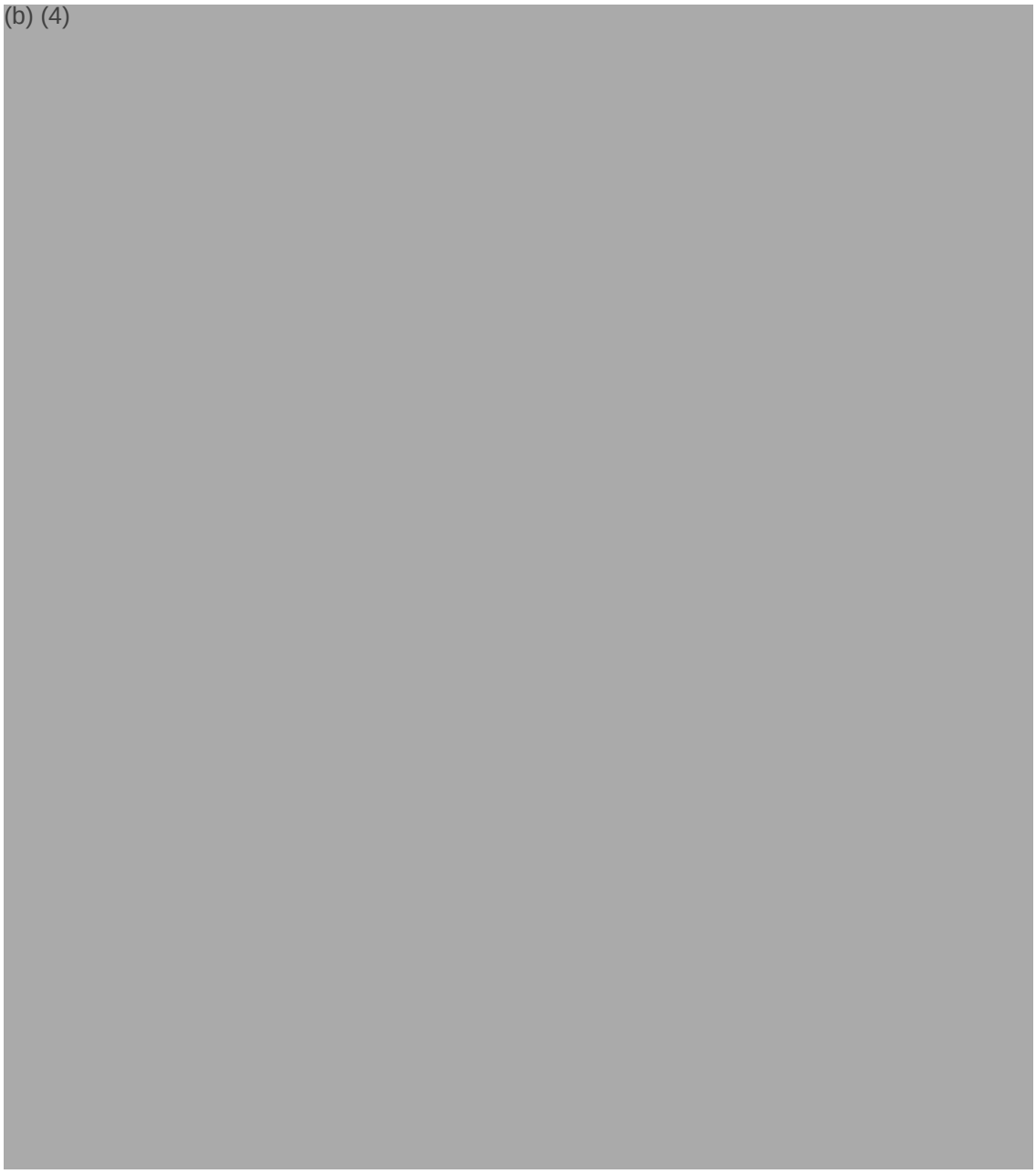
Appendix 3

(b) (4)



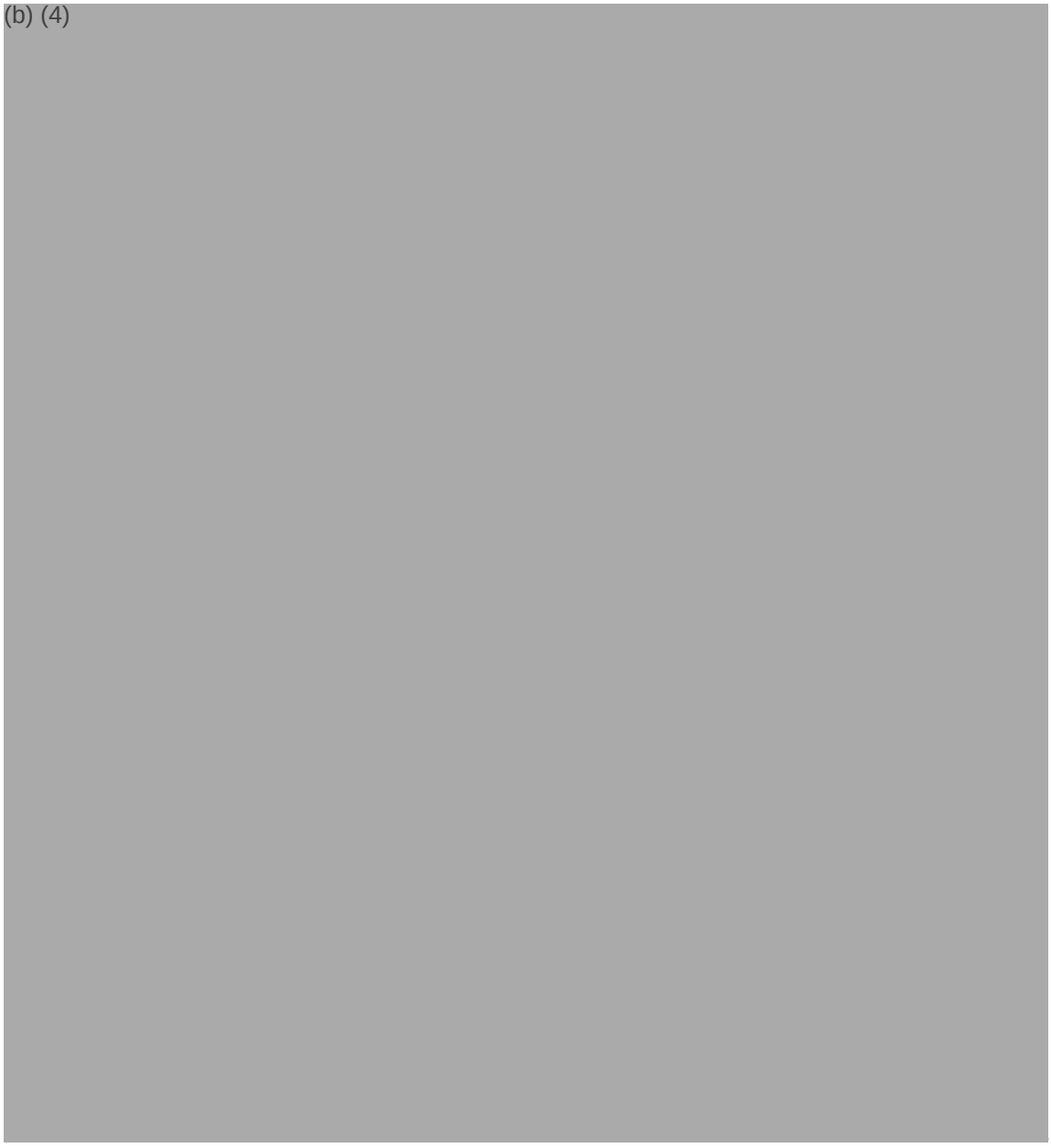
Appendix 3

(b) (4)



Appendix 3

(b) (4)



Appendix 3

(b) (4)

[redacted]

AP Version Control

First update (supersedes AP.5002400.PU.01) for the following reason:

- Included the expiry period of the test item samples in the injection medium.

Verified by (b) (6) Date 26 Feb 2019

Approved by (b) (6) Date 26 Feb 2019

Authorized by (b) (6) Date 26 Feb. 2019

Scientific Director

Appendix 3

Appendix 2
Certificates of Analysis

Appendix 3

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SUMMARY OF ANALYSIS

Sample Description:	**CX-005809** (GLP Tox-enabling batch)
SCC:	34.27 µg/mL
Plasmid ID:	PL-016985
Chemistry:	G5
Lot Number:	**MTDS18011**
Diluent:	2 mM Sodium Citrate, pH 6.5
Manufacturing Site:	Moderna Therapeutics (Cambridge site)
Date of Manufacture:	May 2018
Date of Analysis:	June 2018
Storage:	Shipping Temperature: - 20°C ± 5°C Storage Temperature: - 20°C ± 5°C
Retest Date:	June 2019

TEST	TEST METHOD	TARGET CRITERIA	RESULT	REFERENCE
Appearance	1-P-QM-WI-9045479 Revision 2	Clear, colorless solution, essentially free of visible particulates	Clear, colorless solution, essentially free of visible particulates	2018, Preps, Client 041771, 2018-06 (Jun)-0004
Identity	I-P-QM-WI-9051277	Sequence matches 100% description of coding region	Sequence matches 100% description of coding region	Report distribution 399651
Total RNA content	1-P-QM-WI-9045490 Revision 3	(b) (4)		2008, Preps, Client 041771, 2018-06 (Jun)-0003
Purity	1-P-QM-WI-9045492 Revision 3			2008, Preps, Client 041771, 2018-06 (Jun)-0022
Product related impurities	1-P-QM-WI-9045492 Revision 3			2008, Preps, Client 041771, 2018-06 (Jun)-0022
pH	1-P-QM-WI-9045482 Revision 2			2008, pH Measurement, 2018-06 (Jun)-0002
Residual DNA template	1-P-QM-WI-9045475 Revision 3			276872/10-26,28
Residual total protein	1-P-QM-WI-9045476 Revision 3			277122/1-6

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Residual solvents		(b) (4)	
TEA	1-P-QM-WI-9045484 Revision 3		2008, Preps, Client 041771, 2018-06 (Jun)-0016
IPA	1-P-QM-WI-9045488 Revision 3		2008, Preps, Client 041771, 2018-06 (Jun)-0015
Ethanol	1-P-QM-WI-9045488 Revision 3		2008, Preps, Client 041771, 2018-06 (Jun)-0015
Hexylene glycol	1-P-QM-WI-9045489 Revision 3		2008, Preps, Client 041771, 2018-06 (Jun)-0020
% Poly A tailed RNA (% Tailless RNA)	1-P-QM-WI-9045491 Revision 4		2008, Preps, Client 041771, 2018-06 (Jun)-0009
% 5' Capped	1-P-QM-WI-9045521 Revision 4		2008, Preps, Client 041771, 2018-06 (Jun)-0012
Bacterial Endotoxins	LL Test Method 7802 (EDR# 1-P-QM-WI-9014312)		275588
Bioburden	LL Test Method 0493 (EDR# 1-P-QM-WI-9011695), USP <61>, EP 2.6.12, JP 4.05 I		2004, MLT MF, 2018-06 (Jun)-0020

Revision #	Change Details	Author
1.0	SoA of release	(b) (6)
2.0	Corrected typo where sample description in headed was listed as "CX-005908" instead of "CX-005809"	(b) (6)

Si (b) (6)

(b) (6) ed by: (b) (6)

(b) (6)

Revie (b) (6)

22 Feb 2019
Date:

22 Feb 2019
Date:

CX-005809 Page 2 of 2 version 02

Appendix 3

Number: DPAD-00219 Version: 1.0 Approved Date: 11 Feb 2019
SoA for mRNA-1893, Lot MTDP18195

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Summary of Analysis

Document number	**Veeva Doc # DPAD-00219**
Product:	**RNA-1893, Drug Product**
Drug Product Lot #:	**MTDP18195**
Product Description:	mRNA-1893, in 100mM Tris, 7% PG, 1mM DTPA, pH 7.5
Container Closure:	2R Glass Vial, 13mm Flurotec Stopper, Blue Flip Cap
Fill Volume:	0.5 mL
Drug Substance Lot #:	**CX-005809, Lot MTDS18011**
Manufacturer Name:	MODERNA
Date of Manufacture:	July 2018
Storage	-20 °C
Retest Period	July 2019

Test	Method	Target Attributes		Results
Appearance	Visual Lancaster 1-P-QM-WI-9045522	White to off-white dispersion. May contain visible, white or translucent product-related particulates		White to off-white dispersion. May contain visible particulates, white or translucent product -related particles
Identity	RT/Sanger Sequencing Lancaster 1-P-QM-WI-9051277	Sequence matches description of the coding region		Conforms
mRNA Content	(b) (4) Lancaster 1-P-QM-WI-9045525	(b) (4)		
mRNA Purity	RP - HPLC Lancaster 1-P-QM-WI-9063774			(b) (4)
Product-related impurities		Report % Area for each imp. group:	Impurity Group 1 (pre-main peak area) Impurity Group 2 (post-main peak area) Impurity Group 3 (mRNA-adduct Species)	
% RNA Encapsulation	Fluorescence (b) (4) : Lancaster 1-P-QM-WI-9045478	(b) (4)		
pH	USP <791> Lancaster 1-P-QM-WI-9045523			

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Appendix 3

Number: DPAD-00219 Version: 1.0 Approved Date: 11 Feb 2019
SoA for mRNA-1893, Lot MTDP18195

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Osmolality	USP <785> Lancaster 1-P-QM-WI-9063917	Report Results (mOsm/kg)	(b) (4)
Filtered Mean Particle Size	Dynamic Light Scattering Lancaster 1-P-QM-WI-9063778	(b) (4)	
Filtered Polydispersity Index		Report Result	(b) (4)
Product Related Particles	(b) (4) Lancaster 1-P-QM-WI-9063825	Report Result	
Lipid Identification:			
SM-102	UPLC-CAD Lancaster 1-P-QM-WI-9063776	Matches Retention time of Reference	Conforms
Cholesterol		Matches Retention time of Reference	Conforms
DSPC		Matches Retention time of Reference	Conforms
PEG2000-DMG		Matches Retention time of Reference	Conforms
Lipid Content (mg/mL)			
SM-102	UPLC-CAD Lancaster 1-P-QM-WI-9063776	(b) (4)	
Cholesterol			
DSPC			
PEG2000-DMG			
Lipid Impurities		Report % area and RRT of individual impurities	RRT / % Area Blank (b) (4) Peak 1 (b) (4)
		Report % area of total impurities	(b) (4)
Bacterial Endotoxin	USP <85> Associates of Cape Cod	(b) (4)	
Bioburden	SOP-0378		
Particulate Matter	USP <788>, Method 2 Lancaster 1-P-QM-WI-9014657		
Residual Solvents Ethanol	Lancaster 1-P-QM-WI-9011695		

Appendix 3

Number: DPAD-00219 Version: 1.0 Approved Date: 11 Feb 2019
SoA for mRNA-1893, Lot MTDP18195

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Reference:
Lancaster Certificate of Analysis: Report 408093 (Sample ID NS-09717996)
Lancaster Certificate of Analysis: Report 401172 (Sample ID NS-09717992)
Lancaster Certificate of Analysis: Report 419376 (Lipid 3M -20ºC sample NS-09894301)
Bioburden: Lancaster Report 402640
Bacterial Endotoxin: ACCI Study 0718-094

Revision History:

Revision	Change Detail	Effective Date	Author
1.0	Summarized T0 Release data in single document with Moderna target attributes (Based off Doc. SPC-599) Default 1-year expiration date	Date of Approval in Veeva	(b) (6)

Document Approval:

Function	Name	Signature	Date
Sr. Scientist, Drug Product-Analytical Development	(b) (6)	N/A	Date of Approval in Veeva

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Summary of Analysis

Date of Document Generation	25 September 2018
Revision	001
Product name	**mRNA-1893 non-GMP Drug Product**
Product description	mRNA-1893 LNP in 100mm Tris, 7% propylene glycol, 1mM DTPA, pH 7.5
Lot No.	**MTDP18195**
Drug Substance (API)	MTDS18011
Date of Manufacture	19 July 2018
Time Point	Release
Storage	-20°C
Retest Period	TBD

Test	Method	Testing Reference	Target Attributes	Results
ID	RT Sanger Sequencing (b) (4)	Eurofins Lancaster Analysis #9051277	Sequence matches reference standard	Sequence matches reference standard
mRNA Content	1-P-QM-WI-9045525 Rev 3	2008, Preps, Client 041771, 2018-07 (Jul)-0058	Report Results	(b) (4)
Endotoxin	USP <85> (b) (4)	Associates of Cape Cod COA 0718-094	(b) (4)	Location: Beginning, Middle, End; Endotoxin Concentration (b) (4)
Bioburden	USP <61>	2004, MLT MF 2018-08 (Aug)-0007	Type: Total Viable Count, TAMC, TYMC; CFU Count (b) (4)	Type: Total Viable Count, TAMC, TYMC

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Revision History:

Revision	Change Detail	Effective Date	Author
1.0	New document	Date of Last Signature	(b) (6)

Document Approval:

	Date
* (b) (6)	26 Sep 2018
*	26 Sep 2018

Page 2 of 2

Appendix 4

Individual Mortality Explanation Page

Abbreviation	Description	Abbreviation	Description
AD or ACCD	Accidental death	PM SIR	Signs of ill health or reaction to treatment check in the afternoon
AM SIR	Signs of ill health or reaction to treatment check in the morning	REC	Recovery euthanasia
FD	Found dead	REL	Released
INTM	Interim	TE or TERM	Terminal euthanasia
NR	Not recorded	UE or UNSC	Unscheduled euthanasia

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Removal Time represents the time the removal was entered into the Provantis system and may not be representative of the time of death.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 4

Individual Mortality

5002400

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
1	0 ug/dose	Male	1001	1001	30	5	18DEC2018	15:42	.	.	TERM
			1002	1001	30	5	18DEC2018	15:50	.	.	TERM
			1003	1001	30	5	18DEC2018	17:01	.	.	TERM
			1004	1004	30	5	18DEC2018	17:02	.	.	TERM
			1005	1004	30	5	18DEC2018	18:17	.	.	TERM
			1006	1004	30	5	18DEC2018	18:07	.	.	TERM
			1007	1007	30	5	18DEC2018	20:38	.	.	TERM
			1008	1007	30	5	18DEC2018	20:20	.	.	TERM
			1009	1009	30	5	18DEC2018	21:51	.	.	TERM
			1010	1009	30	5	18DEC2018	21:30	.	.	TERM
			1011	1011	43	7	31DEC2018	9:15	.	.	REC
			1012	1011	43	7	31DEC2018	10:17	.	.	REC
			1013	1011	43	7	31DEC2018	11:12	.	.	REC
			1014	1014	43	7	31DEC2018	9:14	.	.	REC
			1015	1014	43	7	31DEC2018	10:04	.	.	REC
1	0 ug/dose	Female	1501	1501	30	5	19DEC2018	14:24	.	.	TERM
			1502	1501	30	5	19DEC2018	14:28	.	.	TERM
			1503	1501	30	5	19DEC2018	15:32	.	.	TERM
			1504	1504	30	5	19DEC2018	15:30	.	.	TERM
			1505	1504	30	5	19DEC2018	16:44	.	.	TERM
			1506	1504	30	5	19DEC2018	16:24	.	.	TERM
			1507	1507	30	5	19DEC2018	18:52	.	.	TERM
			1508	1507	30	5	19DEC2018	17:26	.	.	TERM
			1509	1509	30	5	19DEC2018	20:04	.	.	TERM
			1510	1509	30	5	19DEC2018	18:19	.	.	TERM
			1511	1511	43	7	31DEC2018	10:49	.	.	REC
			1512	1511	43	7	31DEC2018	11:33	.	.	REC
			1513	1511	43	7	31DEC2018	12:04	.	.	REC
			1514	1514	43	7	31DEC2018	13:52	.	.	REC
			1515	1514	43	7	31DEC2018	12:19	.	.	REC
2	10 ug/dose	Male	2001	2001	30	5	18DEC2018	16:42	.	.	TERM
			2002	2001	30	5	18DEC2018	16:46	.	.	TERM
			2003	2001	30	5	18DEC2018	17:59	.	.	TERM
			2004	2004	30	5	18DEC2018	17:51	.	.	TERM
			2005	2004	30	5	18DEC2018	20:20	.	.	TERM

Appendix 4

Individual Mortality

5002400

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
2	10 ug/dose	Male	2006	2004	30	5	18DEC2018	20:04	.	.	TERM
			2007	2007	30	5	18DEC2018	21:34	.	.	TERM
			2008	2007	30	5	18DEC2018	21:14	.	.	TERM
			2009	2009	30	5	18DEC2018	16:24	.	.	TERM
			2010	2009	30	5	18DEC2018	16:51	.	.	TERM
2	10 ug/dose	Female	2501	2501	30	5	19DEC2018	15:16	.	.	TERM
			2502	2501	30	5	19DEC2018	15:18	.	.	TERM
			2503	2501	30	5	19DEC2018	16:28	.	.	TERM
			2604	2604	30	5	19DEC2018	16:12	.	.	TERM
			2505	2604	30	5	19DEC2018	18:33	.	.	TERM
			2506	2604	30	5	19DEC2018	17:06	.	.	TERM
			2507	2507	30	5	19DEC2018	19:45	.	.	TERM
			2508	2507	30	5	19DEC2018	18:05	.	.	TERM
			2509	2509	30	5	19DEC2018	15:50	.	.	TERM
			2510	2509	30	5	19DEC2018	16:07	.	.	TERM
3	30 ug/dose	Male	3001	3001	30	5	18DEC2018	16:22	.	.	TERM
			3002	3001	30	5	18DEC2018	16:29	.	.	TERM
			3003	3001	30	5	18DEC2018	17:41	.	.	TERM
			3004	3004	30	5	18DEC2018	17:34	.	.	TERM
			3005	3004	30	5	18DEC2018	20:00	.	.	TERM
			3006	3004	30	5	18DEC2018	18:37	.	.	TERM
			3007	3007	30	5	18DEC2018	21:14	.	.	TERM
			3008	3007	30	5	18DEC2018	20:54	.	.	TERM
			3009	3009	30	5	18DEC2018	22:29	.	.	TERM
			3010	3009	30	5	18DEC2018	22:06	.	.	TERM
3	30 ug/dose	Female	3501	3501	30	5	19DEC2018	14:59	.	.	TERM
			3502	3501	30	5	19DEC2018	15:03	.	.	TERM
			3503	3501	30	5	19DEC2018	16:09	.	.	TERM
			3504	3504	30	5	19DEC2018	15:57	.	.	TERM
			3505	3504	30	5	19DEC2018	17:16	.	.	TERM
			3506	3504	30	5	19DEC2018	16:52	.	.	TERM
			3507	3507	30	5	19DEC2018	19:28	.	.	TERM
			3508	3507	30	5	19DEC2018	17:53	.	.	TERM
			3509	3509	30	5	19DEC2018	15:31	.	.	TERM

Appendix 4

Individual Mortality

5002400

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
3	30 ug/dose	Female	3510	3509	30	5	19DEC2018	18:47	.	.	TERM
4	96 ug/dose	Male	4001	4001	30	5	18DEC2018	16:02	.	.	TERM
			4002	4001	30	5	18DEC2018	16:11	.	.	TERM
			4003	4001	30	5	18DEC2018	17:20	.	.	TERM
			4004	4004	30	5	18DEC2018	17:17	.	.	TERM
			4005	4004	30	5	18DEC2018	18:36	.	.	TERM
			4006	4004	30	5	18DEC2018	18:22	.	.	TERM
			4007	4007	30	5	18DEC2018	20:55	.	.	TERM
			4008	4007	30	5	18DEC2018	20:37	.	.	TERM
			4009	4009	30	5	18DEC2018	22:09	.	.	TERM
			4010	4009	30	5	18DEC2018	21:45	.	.	TERM
			4011	4011	43	7	31DEC2018	9:48	.	.	REC
			4012	4011	43	7	31DEC2018	10:45	.	.	REC
			4013	4011	43	7	31DEC2018	11:37	.	.	REC
			4014	4014	43	7	31DEC2018	9:42	.	.	REC
			4015	4014	43	7	31DEC2018	10:24	.	.	REC
4	96 ug/dose	Female	4501	4501	30	5	19DEC2018	14:42	.	.	TERM
			4502	4501	30	5	19DEC2018	14:49	.	.	TERM
			4503	4501	30	5	19DEC2018	15:48	.	.	TERM
			4504	4504	30	5	19DEC2018	15:43	.	.	TERM
			4505	4504	30	5	19DEC2018	16:58	.	.	TERM
			4506	4504	30	5	19DEC2018	16:38	.	.	TERM
			4507	4507	30	5	19DEC2018	19:09	.	.	TERM
			4508	4507	30	5	19DEC2018	17:39	.	.	TERM
			4509	4509	30	5	19DEC2018	16:27	.	.	TERM
			4510	4509	30	5	19DEC2018	18:33	.	.	TERM
			4511	4511	43	7	31DEC2018	11:11	.	.	REC
			4512	4511	43	7	31DEC2018	11:54	.	.	REC
			4513	4511	43	7	31DEC2018	13:22	.	.	REC
			4514	4514	43	7	31DEC2018	14:15	.	.	REC
			4515	4514	43	7	31DEC2018	12:40	.	.	REC

Appendix 5

Individual Clinical Observations Explanation Page

Abbreviation	Description	Abbreviation	Description
.	Not scheduled to be performed / Not seen / Dead	Fev	Food evaluation
AM_S	Signs of ill health or reaction to treatment check in the morning	OTHR	Other
CAM	Cage side observation in the morning	p #	Observation post dose
Cp #	Cage side observation post dose	PM_S	Signs of ill health or reaction to treatment check in the afternoon
Cpr	Cage side observation predose	pr #	Observation predose
CSO	Cage side observation	SIRT	Signs of ill health or reaction to treatment
DE/D	Detailed examination	U #/Up #	Unscheduled examination post dose
Dp1	Detailed examination of injection site 24 hours post dose	UDu	Unscheduled examination during dosing
Dp2	Detailed examination of injection site 72 hours post dose	Un #/Unsc #	Unscheduled examination
Dpr1	Detailed examination of injection site Day -1	Upr	Unscheduled observation predose
DuRx	Observation during dosing	Vet	Anything observed by Vet Aid
DW	Detailed examination weekly of injection site	#	Number to avoid using the same timeslot/animal/day

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Only animals with findings are presented in this appendix.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 5

Individual Clinical Observations

5002400

0 ug/dose Group 1 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		7 DE	14 DE	16 Dp1	18 Dp2	42 DE	43 DE	
1003	Skin, Scab, Hindlimb, Left	.	X	.	.	.	.	
	Skin, Scab, Lumbar	.	X	.	.	.	.	
	Skin, Scab, Treatment Site No.02	X	.	.	.	.	.	
1007	Skin, Scab, Pinna, Left	.	X	.	.	.	.	
1009	Skin, Scab, Treatment Site No.01	.	.	X	X	.	.	
1012	Fur, Thin Cover, Forepaw, Left	.	.	.	.	X	X	
	Fur, Thin Cover, Forepaw, Right	.	.	.	.	X	X	

X=Present

Appendix 5

Individual Clinical Observations

5002400

10 ug/dose Group 2 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-3 Unsc	-1 DE	2 Dp1	4 Dp2	7 DE	30 Dp1	
2001	Skin, Scab, Treatment Site No.02	.	.	X	X	.	.	
2003	Skin, Scab, Hindlimb, Left	.	X	.	.	.	.	
2009	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	X	.	
	Skin, Scab, Dorsal Cervical	.	X	.	.	X	.	
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	X	
2010	Muscle Tone, Forelimb, Left, Decreased	X	.	.	.	.	.	
	Muscle Tone, Forelimb, Right, Decreased	X	.	.	.	.	.	
	Muscle Tone, Hindlimb, Left, Decreased	X	.	.	.	.	.	
	Muscle Tone, Hindlimb, Right, Decreased	X	.	.	.	.	.	
	Breathing, Shallow	X	.	.	.	.	.	
	Skin, Pallor	X	.	.	.	.	.	
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	X	.	.	
	Skin, Scab, Treatment Site No.02	.	.	.	.	X	.	
	Eyeball, Abnormal Color, Left, Pale	X	.	.	.	.	.	
	Eyeball, Abnormal Color, Right, Pale	X	.	.	.	.	.	
	Weak	X	.	.	.	.	.	
	Activity Decreased	X	.	.	.	.	.	

X=Present

Appendix 5

Individual Clinical Observations

5002400

30 ug/dose Group 3 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 DE	2 DW	7 DE	14 DE	16 Dp1	16 DW	30 DE
3001	Fur, Staining, Cranium, Red	.	.	X	.	.	.	.
	Skin, Scab, Pinna, Right	.	.	.	X	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
3002	Skin, Scab, Dorsal Cervical	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
3004	Skin, Scab, Treatment Site No.02	.	.	.	X	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	.	X
3005	Skin, Scab, Treatment Site No.01	.	X	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	.	X
3007	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
3008	Skin, Scab, Treatment Site No.01	.	.	.	.	X	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	.	X
3009	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

30 ug/dose Group 3 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		30 Dp1						
3001	Fur, Staining, Cranium, Red	.						
	Skin, Scab, Pinna, Right	.						
	Swollen, Treatment Site No.02, Slight, Firm	X						
3002	Skin, Scab, Dorsal Cervical	.						
	Swollen, Treatment Site No.02, Slight, Firm	X						
3004	Skin, Scab, Treatment Site No.02	.						
	Swollen, Treatment Site No.02, Slight, Firm	X						
	Swollen, Treatment Site No.02, Slight, Soft	.						
3005	Skin, Scab, Treatment Site No.01	.						
	Swollen, Treatment Site No.02, Slight, Soft	.						
3007	Swollen, Treatment Site No.02, Moderate, Firm	X						
3008	Skin, Scab, Treatment Site No.01	.						
	Swollen, Treatment Site No.02, Slight, Soft	X						
3009	Swollen, Treatment Site No.02, Slight, Firm	X						

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 Dpr1	-1 DE	2 Dp1	4 Dp2	7 DE	30 DE	30 Dp1
4001	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	X	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	X	X
4002	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	X	.	.	.	.	.	.
	Skin, Scab, Hindlimb, Right	.	X	.	.	.	.	.
	Skin, Scab, Treatment Site No.02	.	.	X	X	X	.	.
	Swollen, Treatment Site No.02, Moderate, Soft	.	.	.	.	.	X	.
4003	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Soft	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	X
4004	Vocalization, Increased	.	.	X	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	X	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	X	.
4005	Vocalization, Increased	.	.	X	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	X	.
4006	Vocalization, Increased	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Moderate, Soft	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	X	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 Dpr1	-1 DE	2 Dp1	4 Dp2	7 DE	30 DE	30 Dp1
4007	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	X	.
	Abnormal Gait	.	.	.	.	.	.	X
4008	Vocalization, Increased	.	.	.	.	.	.	X
	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	X
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	X	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	X	.
4009	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	X	.
4010	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.
4011	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Skin, Scab, Hindlimb, Right	.	X	.	.	.	.	.
	Skin, Scab, Treatment Site No.02	.	.	X	X	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	X
4012	Vocalization, Increased	.	.	X	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 Dpr1	-1 DE	2 Dp1	4 Dp2	7 DE	30 DE	30 Dp1
4013	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Skin, Discolored, Hindpaw, Left, Red	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	X
	Skin, Scab, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.
4014	Vocalization, Increased	.	.	X	.	.	.	.
	Fur, Staining, Cranium, Red	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.
4015	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		35 DE	43 DE					
4001	Skin Thickening, Treatment Site No.02	.	.					
	Skin, Discolored, Treatment Site No.02, Red	.	.					
	Swollen, Treatment Site No.02, Moderate, Firm	.	.					
4002	Skin Thickening, Treatment Site No.02	.	.					
	Skin, Discolored, Treatment Site No.02, Red	.	.					
	Skin, Scab, Hindlimb, Right	.	.					
	Skin, Scab, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Moderate, Soft	.	.					
4003	Skin Thickening, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Moderate, Soft	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
4004	Vocalization, Increased	.	.					
	Skin Thickening, Treatment Site No.02	.	.					
	Skin, Discolored, Treatment Site No.02, Red	.	.					
	Swollen, Treatment Site No.02, Moderate, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Soft	.	.					
4005	Vocalization, Increased	.	.					
	Skin Thickening, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
4006	Vocalization, Increased	.	.					
	Swollen, Treatment Site No.02, Moderate, Firm	.	.					
	Swollen, Treatment Site No.02, Moderate, Soft	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Soft	.	.					

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		35 DE	43 DE					
4007	Skin Thickening, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Severe, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
	Abnormal Gait	.	.					
4008	Vocalization, Increased	.	.					
	Skin Thickening, Treatment Site No.02	.	.					
	Skin, Discolored, Treatment Site No.02, Pink	.	.					
	Skin, Discolored, Treatment Site No.02, Red	.	.					
	Swollen, Treatment Site No.02, Moderate, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
4009	Skin Thickening, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Moderate, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
4010	Skin Thickening, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Moderate, Firm	.	.					
	Swollen, Treatment Site No.02, Severe, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
4011	Skin Thickening, Treatment Site No.02	.	.					
	Skin, Scab, Hindlimb, Right	X	.					
	Skin, Scab, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
4012	Vocalization, Increased	.	.					
	Skin Thickening, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Severe, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date						
		35 DE	43 DE					
4013	Skin Thickening, Treatment Site No.02	.	.					
	Skin, Discolored, Hindpaw, Left, Red	.	X					
	Skin, Discolored, Treatment Site No.02, Pink	.	.					
	Skin, Scab, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Severe, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
4014	Vocalization, Increased	.	.					
	Fur, Staining, Cranium, Red	.	X					
	Skin Thickening, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Severe, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					
4015	Skin Thickening, Treatment Site No.02	.	.					
	Swollen, Treatment Site No.02, Severe, Firm	.	.					
	Swollen, Treatment Site No.02, Slight, Firm	.	.					

X=Present

Appendix 5

Individual Clinical Observations

5002400

0 ug/dose Group 1 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-12 Vet	-1 DE	2 Dp1	2 DW	4 Dp2	7 DE	9 DW
1504	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	.	.	.
1505	Fur, Thin Cover, Cranium	.	.	.	.	.	.	.
	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	.	.	.
	Skin, Scab, Treatment Site No.02	.	.	.	.	.	.	.
1509	Pinna, Missing (PT), Right, Partly	X	.	.	.	.	.	.
1511	Fur, Thin Cover, Forepaw, Left	.	.	.	.	.	.	.
	Fur, Thin Cover, Forepaw, Right	.	.	.	.	.	.	.
	Skin, Lesion w/ Discharge, Tail, Slight	.	.	.	.	.	.	.
	Skin, Scab, Treatment Site No.02	.	.	.	.	.	X	.
1512	Skin, Scab, Pinna, Right	.	X	.	.	.	.	.
	Pinna, Missing (PT), Left, Partly	.	X	X	X	X	X	X
	Pinna, Missing (PT), Right, Partly	.	.	.	.	.	.	.
1515	Fur, Thin Cover, Forelimb, Left	.	.	.	.	.	.	.
	Fur, Thin Cover, Forelimb, Right	.	.	.	.	.	.	.
	Fur, Thin Cover, Forepaw, Left	.	.	.	.	.	.	.
	Fur, Thin Cover, Forepaw, Right	.	.	.	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

0 ug/dose Group 1 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		14 DE	15 Unsc	16 Dp1	16 DW	18 Dp2	21 DE	23 DW
1504	Fur, Thin Cover, Dorsal Cervical	X	.	.	.	.	.	.
1505	Fur, Thin Cover, Cranium	X	.	.	.	.	.	.
	Fur, Thin Cover, Dorsal Cervical	X	.	.	.	.	.	.
	Skin, Scab, Treatment Site No.02	.	.	.	.	.	.	.
1509	Pinna, Missing (PT), Right, Partly	.	.	.	.	.	.	.
1511	Fur, Thin Cover, Forepaw, Left	.	.	.	.	.	.	.
	Fur, Thin Cover, Forepaw, Right	.	.	.	.	.	.	.
	Skin, Lesion w/ Discharge, Tail, Slight	.	X	.	.	.	.	.
	Skin, Scab, Treatment Site No.02	.	.	.	.	.	.	.
1512	Skin, Scab, Pinna, Right	.	.	.	.	.	.	.
	Pinna, Missing (PT), Left, Partly	X	.	X	X	X	X	X
	Pinna, Missing (PT), Right, Partly	.	.	.	.	.	.	.
1515	Fur, Thin Cover, Forelimb, Left	.	.	.	.	.	.	.
	Fur, Thin Cover, Forelimb, Right	.	.	.	.	.	.	.
	Fur, Thin Cover, Forepaw, Left	.	.	.	.	.	.	.
	Fur, Thin Cover, Forepaw, Right	.	.	.	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

0 ug/dose Group 1 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		28 DE	30 DE	30 Dp1	30 DW	32 Dp2	35 DE	37 DW
1504	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	.	.	.
1505	Fur, Thin Cover, Cranium	.	.	.	.	.	.	.
	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	.	.	.
	Skin, Scab, Treatment Site No.02	X	X	.	.	.	.	.
1509	Pinna, Missing (PT), Right, Partly	.	.	.	.	.	.	.
1511	Fur, Thin Cover, Forepaw, Left	.	.	.	.	.	.	.
	Fur, Thin Cover, Forepaw, Right	.	.	.	.	.	.	.
	Skin, Lesion w/ Discharge, Tail, Slight	.	.	.	.	.	.	.
	Skin, Scab, Treatment Site No.02	.	.	.	.	.	.	.
1512	Skin, Scab, Pinna, Right	.	.	.	.	.	.	.
	Pinna, Missing (PT), Left, Partly	X	.	X	X	X	X	X
	Pinna, Missing (PT), Right, Partly	.	.	.	.	.	.	.
1515	Fur, Thin Cover, Forelimb, Left	.	.	.	.	.	.	.
	Fur, Thin Cover, Forelimb, Right	.	.	.	.	.	.	.
	Fur, Thin Cover, Forepaw, Left	.	.	.	.	.	X	.
	Fur, Thin Cover, Forepaw, Right	.	.	.	.	.	X	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

0 ug/dose Group 1 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		42 DE	43 DE					
1504	Fur, Thin Cover, Dorsal Cervical	.	.					
1505	Fur, Thin Cover, Cranium	.	.					
	Fur, Thin Cover, Dorsal Cervical	.	.					
	Skin, Scab, Treatment Site No.02	.	.					
1509	Pinna, Missing (PT), Right, Partly	.	.					
1511	Fur, Thin Cover, Forepaw, Left	.	X					
	Fur, Thin Cover, Forepaw, Right	X	X					
	Skin, Lesion w/ Discharge, Tail, Slight	.	.					
	Skin, Scab, Treatment Site No.02	.	.					
1512	Skin, Scab, Pinna, Right	.	.					
	Pinna, Missing (PT), Left, Partly	X	X					
	Pinna, Missing (PT), Right, Partly	X	X					
1515	Fur, Thin Cover, Forelimb, Left	X	X					
	Fur, Thin Cover, Forelimb, Right	X	X					
	Fur, Thin Cover, Forepaw, Left	.	.					
	Fur, Thin Cover, Forepaw, Right	.	.					

X=Present

Appendix 5

Individual Clinical Observations

5002400

10 ug/dose Group 2 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 DE	2 Dp1	2 DW	16 Dp1	21 DE	30 DE	30 Dp1
2501	Skin, Scab, Cranium	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
2502	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
2503	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
2604	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	X	.	.	.
2505	Skin, Discolored, Treatment Site No.01, Red	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
2506	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
2507	Skin, Discolored, Treatment Site No.01, Red	.	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	X
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	.	X	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	X	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
2508	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	X	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	X	X
	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
2509	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	X	.	.
	Skin, Discolored, Treatment Site No.01, Red	.	.	.	X	.	.	.
	Skin, Scab, Dorsal Cervical	.	.	.	.	X	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	X	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

10 ug/dose Group 2 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 DE	2 Dp1	2 DW	16 Dp1	21 DE	30 DE	30 Dp1
2509	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
2510	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	X	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	X	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

30 ug/dose Group 3 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 DE	2 Dp1	2 DW	4 Dp2	7 DE	14 DE	16 Dp1
3501	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	.	.	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
3502	Skin, Scab, Treatment Site No.01	.	.	X	.	.	.	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Moderate, Soft	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	X	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	.	.
3503	Skin, Scab, Cranium	X	.	.	.	.	.	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
3504	Swollen, Treatment Site No.01, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Moderate, Firm	.	X	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
3505	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	.
	Skin, Scab, Pinna, Left	.	.	.	.	X	.	.
	Skin, Scab, Pinna, Right	.	.	.	.	X	.	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	X	.	.	.	.	.
3506	Fur, Thin Cover, Cranium	.	.	.	.	.	.	.
	Skin, Scab, Cranium	.	.	.	.	.	.	.
	Skin, Scab, Pinna, Left	.	.	.	.	X	X	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

30 ug/dose Group 3 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 DE	2 Dp1	2 DW	4 Dp2	7 DE	14 DE	16 Dp1
3506	Skin, Scab, Pinna, Right	.	.	.	.	X	X	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	X	.	.	.	.	.
	Pinna, Missing (PT), Right, Partly	.	.	.	.	.	X	X
3507	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	X	.	.	.	.	.
3508	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	X	.	.	.	.	.
3509	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	.	.	.
	Skin, Scab, Treatment Site No.01	.	.	X	.	.	.	.
	Swollen, Treatment Site No.01, Slight, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	X	.	.	.	.	.
3510	Skin, Scab, Treatment Site No.02	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	X	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	X	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

30 ug/dose Group 3 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		16 DW	18 Dp2	21 DE	23 DW	28 DE	30 DE	30 Dp1
3501	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	.	X	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	X	.
3502	Skin, Scab, Treatment Site No.01	.	.	.	.	.	.	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Soft	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	X	.
3503	Skin, Scab, Cranium	.	.	.	.	.	.	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	X	X
3504	Swollen, Treatment Site No.01, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	X	.
3505	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	X
	Skin, Scab, Pinna, Left	.	.	.	.	.	X	.
	Skin, Scab, Pinna, Right	.	.	.	.	.	X	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	.	.
3506	Fur, Thin Cover, Cranium	.	.	.	.	X	X	.
	Skin, Scab, Cranium	.	.	.	.	X	X	.
	Skin, Scab, Pinna, Left	.	.	.	.	X	X	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

30 ug/dose Group 3 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		16 DW	18 Dp2	21 DE	23 DW	28 DE	30 DE	30 Dp1
3506	Skin, Scab, Pinna, Right	.	.	.	.	X	X	.
	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	X
	Pinna, Missing (PT), Right, Partly	X	X	X	X	X	X	X
3507	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	X	.
3508	Swollen, Treatment Site No.01, Slight, Soft	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	X
3509	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	.	X	.
	Skin, Scab, Treatment Site No.01	.	.	.	.	.	.	.
	Swollen, Treatment Site No.01, Slight, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	X	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
3510	Skin, Scab, Treatment Site No.02	.	.	.	.	X	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	X
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

30 ug/dose Group 3 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		30 DW						
3501	Skin, Discolored, Treatment Site No.02, Red	.						
	Swollen, Treatment Site No.01, Slight, Soft	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
3502	Skin, Scab, Treatment Site No.01	.						
	Swollen, Treatment Site No.01, Slight, Soft	.						
	Swollen, Treatment Site No.02, Moderate, Soft	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
	Swollen, Treatment Site No.02, Slight, Soft	.						
3503	Skin, Scab, Cranium	.						
	Swollen, Treatment Site No.01, Slight, Soft	.						
	Swollen, Treatment Site No.02, Slight, Soft	.						
3504	Swollen, Treatment Site No.01, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
3505	Skin, Discolored, Treatment Site No.02, Pink	.						
	Skin, Scab, Pinna, Left	.						
	Skin, Scab, Pinna, Right	.						
	Swollen, Treatment Site No.01, Slight, Soft	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
	Swollen, Treatment Site No.02, Slight, Soft	.						
3506	Fur, Thin Cover, Cranium	.						
	Skin, Scab, Cranium	.						
	Skin, Scab, Pinna, Left	.						

Appendix 5

Individual Clinical Observations

5002400

30 ug/dose Group 3 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		30 DW						
3506	Skin, Scab, Pinna, Right	.						
	Swollen, Treatment Site No.01, Slight, Soft	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
	Pinna, Missing (PT), Right, Partly	X						
3507	Skin, Discolored, Treatment Site No.02, Red	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
3508	Swollen, Treatment Site No.01, Slight, Soft	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
3509	Skin, Discolored, Treatment Site No.02, Red	.						
	Skin, Scab, Treatment Site No.01	.						
	Swollen, Treatment Site No.01, Slight, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
3510	Skin, Scab, Treatment Site No.02	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
	Swollen, Treatment Site No.02, Slight, Soft	.						

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 Dpr1	-1 DE	2 Dp1	2 DW	4 Dp2	7 DE	14 DE
4501	Vocalization, Increased	.	.	.	.	.	.	.
	Limited Usage, Hindlimb, Left, Slight	.	.	.	.	.	.	.
	Skin, Dry, Treatment Site No.02	.	.	.	.	X	X	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	X	X	.
	Skin, Discolored, Treatment Site No.01, Red	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	.
	Swollen, Treatment Site No.01, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	X	.	.
4502	Fur, Thin Cover, Cranium	.	.	.	.	.	.	.
	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.01, Red	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	X	.	.	.	.
	Skin, Scab, Dorsal Cervical	.	.	.	.	.	.	.
	Skin, Scab, Pinna, Left	.	.	.	.	.	.	.
	Skin, Scab, Pinna, Right	.	.	.	.	.	.	.
	Swollen, Treatment Site No.01, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
4503	Fur, Thin Cover, Dorsal Cervical	.	.	.	.	.	.	X
	Skin, Discolored, Treatment Site No.01, Red	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	X	.	.	.	.
	Skin, Scab, Dorsal Cervical	.	.	.	.	.	.	.
	Skin, Scab, Treatment Site No.01	.	.	.	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 Dpr1	-1 DE	2 Dp1	2 DW	4 Dp2	7 DE	14 DE
4503	Swollen, Treatment Site No.01, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
4504	Skin, Dry, Treatment Site No.02	.	.	.	.	X	X	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	X	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	X	.
	Swollen, Treatment Site No.01, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
4505	Skin, Discolored, Treatment Site No.01, Red	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	X	.	.	.	.
	Swollen, Treatment Site No.01, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	X	X	.
	Abnormal Gait	.	.	.	.	.	.	.
4506	Fur, Staining, Dorsal Cervical, Red	.	.	.	.	.	.	.
	Skin, Dry, Treatment Site No.02	.	.	.	.	X	X	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	X	X	.
	Skin, Discolored, Treatment Site No.01, Red	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	X	.	X	X	.
	Swollen, Treatment Site No.01, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 Dpr1	-1 DE	2 Dp1	2 DW	4 Dp2	7 DE	14 DE
4506	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	X	.	.	.	.
4507	Skin, Dry, Treatment Site No.02	.	.	.	.	X	X	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	X	X	.
	Skin, Discolored, Treatment Site No.01, Red	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	X	.	X	.	.
	Swollen, Treatment Site No.01, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
4508	Skin Thickening, Treatment Site No.02	.	.	X	.	X	X	.
	Skin, Discolored, Treatment Site No.01, Red	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	X	.	X	.	.
	Swollen, Treatment Site No.01, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	X	X	.
4509	Skin, Discolored, Treatment Site No.01, Red	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	X	.	.	.	.
	Skin, Scab, Pinna, Right	.	.	.	.	.	X	.
	Swollen, Hindlimb, Right, Slight, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.01, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
4510 !	Skin, Discolored, Treatment Site No.01, Red	.	.	.	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 Dpr1	-1 DE	2 Dp1	2 DW	4 Dp2	7 DE	14 DE
4510 !	Skin, Discolored, Treatment Site No.02, Red	.	.	X	.	X	.	.
	Skin, Scab, Treatment Site No.01	X	X	.	X	.	.	.
	Skin, Scab, Treatment Site No.02	X	X	X	.	.	.	.
	Swollen, Treatment Site No.01, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	X	X	.
	Abnormal Gait	.	.	.	.	.	.	.
4511	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.
4512	Vocalization, Increased	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.
4513	Fur, Staining, Dorsal Cervical, Red	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.
4514	Fur, Staining, Dorsal Cervical, Red	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.

!=Result comment recorded against 1 or more clinical observations. X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		-1 Dpr1	-1 DE	2 Dp1	2 DW	4 Dp2	7 DE	14 DE
4514	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.
4515	Skin Thickening, Treatment Site No.02	.	.	X	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	X	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		16 Dp1	16 Unsc	18 Dp2	28 DE	30 DE	30 Dp1	32 Dp2
4501	Vocalization, Increased	.	X	.	.	.	.	.
	Limited Usage, Hindlimb, Left, Slight	X	X	.	.	.	.	.
	Skin, Dry, Treatment Site No.02	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.01, Red	X	X	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	X	.
	Swollen, Treatment Site No.01, Severe, Firm	X	X	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	X	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
4502	Fur, Thin Cover, Cranium	.	.	.	X	.	.	.
	Fur, Thin Cover, Dorsal Cervical	.	.	.	X	X	.	.
	Skin, Discolored, Treatment Site No.01, Red	X	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Skin, Scab, Dorsal Cervical	.	.	.	X	X	.	.
	Skin, Scab, Pinna, Left	.	.	.	.	X	.	.
	Skin, Scab, Pinna, Right	.	.	.	X	X	.	.
	Swollen, Treatment Site No.01, Moderate, Firm	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	X	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	X	.
4503	Fur, Thin Cover, Dorsal Cervical	.	.	.	X	X	.	.
	Skin, Discolored, Treatment Site No.01, Red	X	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Skin, Scab, Dorsal Cervical	.	.	.	X	X	.	.
	Skin, Scab, Treatment Site No.01	.	.	.	X	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		16 Dp1	16 Unsc	18 Dp2	28 DE	30 DE	30 Dp1	32 Dp2
4503	Swollen, Treatment Site No.01, Moderate, Firm	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	X	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	X	.
4504	Skin, Dry, Treatment Site No.02	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	X	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Swollen, Treatment Site No.01, Moderate, Firm	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	X	X	.
4505	Skin, Discolored, Treatment Site No.01, Red	X	.	X	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Swollen, Treatment Site No.01, Moderate, Firm	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	X	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
	Abnormal Gait	.	.	.	.	.	X	.
4506	Fur, Staining, Dorsal Cervical, Red	.	.	.	.	X	.	.
	Skin, Dry, Treatment Site No.02	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.01, Red	X	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	X	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Swollen, Treatment Site No.01, Moderate, Firm	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	X	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		16 Dp1	16 Unsc	18 Dp2	28 DE	30 DE	30 Dp1	32 Dp2
4506	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Soft	.	.	.	.	.	.	.
4507	Skin, Dry, Treatment Site No.02	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.01, Red	X	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	X	.
	Swollen, Treatment Site No.01, Severe, Firm	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	X	X	.
4508	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.01, Red	X	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	X	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Swollen, Treatment Site No.01, Moderate, Firm	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	X	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
4509	Skin, Discolored, Treatment Site No.01, Red	X	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Skin, Scab, Pinna, Right	.	.	.	.	.	.	.
	Swollen, Hindlimb, Right, Slight, Firm	.	.	.	.	.	.	.
	Swollen, Treatment Site No.01, Moderate, Firm	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	X	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	X	.
4510	Skin, Discolored, Treatment Site No.01, Red	X	.	.	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		16 Dp1	16 Unsc	18 Dp2	28 DE	30 DE	30 Dp1	32 Dp2
4510	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	X	.	.
	Skin, Scab, Treatment Site No.01	.	.	.	.	.	.	.
	Skin, Scab, Treatment Site No.02	.	.	.	.	.	.	.
	Swollen, Treatment Site No.01, Severe, Firm	X	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	X	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
	Abnormal Gait	.	.	.	.	.	X	.
4511	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	X
4512	Vocalization, Increased	.	.	.	.	.	X	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	X	.
	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.
4513	Fur, Staining, Dorsal Cervical, Red	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.
	Skin, Discolored, Treatment Site No.02, Pink	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	X
4514	Fur, Staining, Dorsal Cervical, Red	.	.	.	.	.	.	.
	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		16 Dp1	16 Unsc	18 Dp2	28 DE	30 DE	30 Dp1	32 Dp2
4514	Skin, Discolored, Treatment Site No.02, Red	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Severe, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	X
4515	Skin Thickening, Treatment Site No.02	.	.	.	.	.	.	.
	Swollen, Treatment Site No.02, Moderate, Firm	.	.	.	.	.	X	.
	Swollen, Treatment Site No.02, Slight, Firm	.	.	.	.	.	.	.

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		43 DE						
4501	Vocalization, Increased	.						
	Limited Usage, Hindlimb, Left, Slight	.						
	Skin, Dry, Treatment Site No.02	.						
	Skin Thickening, Treatment Site No.02	.						
	Skin, Discolored, Treatment Site No.01, Red	.						
	Skin, Discolored, Treatment Site No.02, Pink	.						
	Swollen, Treatment Site No.01, Severe, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
4502	Fur, Thin Cover, Cranium	.						
	Fur, Thin Cover, Dorsal Cervical	.						
	Skin, Discolored, Treatment Site No.01, Red	.						
	Skin, Discolored, Treatment Site No.02, Red	.						
	Skin, Scab, Dorsal Cervical	.						
	Skin, Scab, Pinna, Left	.						
	Skin, Scab, Pinna, Right	.						
	Swollen, Treatment Site No.01, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
4503	Fur, Thin Cover, Dorsal Cervical	.						
	Skin, Discolored, Treatment Site No.01, Red	.						
	Skin, Discolored, Treatment Site No.02, Red	.						
	Skin, Scab, Dorsal Cervical	.						
	Skin, Scab, Treatment Site No.01	.						

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		43 DE						
4503	Swollen, Treatment Site No.01, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
4504	Skin, Dry, Treatment Site No.02	.						
	Skin Thickening, Treatment Site No.02	.						
	Skin, Discolored, Treatment Site No.02, Pink	.						
	Skin, Discolored, Treatment Site No.02, Red	.						
	Swollen, Treatment Site No.01, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
4505	Skin, Discolored, Treatment Site No.01, Red	.						
	Skin, Discolored, Treatment Site No.02, Red	.						
	Swollen, Treatment Site No.01, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
	Abnormal Gait	.						
4506	Fur, Staining, Dorsal Cervical, Red	.						
	Skin, Dry, Treatment Site No.02	.						
	Skin Thickening, Treatment Site No.02	.						
	Skin, Discolored, Treatment Site No.01, Red	.						
	Skin, Discolored, Treatment Site No.02, Pink	.						
	Skin, Discolored, Treatment Site No.02, Red	.						
	Swollen, Treatment Site No.01, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		43 DE						
4506	Swollen, Treatment Site No.02, Severe, Firm	.						
	Swollen, Treatment Site No.02, Slight, Soft	.						
4507	Skin, Dry, Treatment Site No.02	.						
	Skin Thickening, Treatment Site No.02	.						
	Skin, Discolored, Treatment Site No.01, Red	.						
	Skin, Discolored, Treatment Site No.02, Red	.						
	Swollen, Treatment Site No.01, Severe, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
4508	Skin Thickening, Treatment Site No.02	.						
	Skin, Discolored, Treatment Site No.01, Red	.						
	Skin, Discolored, Treatment Site No.02, Pink	.						
	Skin, Discolored, Treatment Site No.02, Red	.						
	Swollen, Treatment Site No.01, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
4509	Skin, Discolored, Treatment Site No.01, Red	.						
	Skin, Discolored, Treatment Site No.02, Red	.						
	Skin, Scab, Pinna, Right	.						
	Swollen, Hindlimb, Right, Slight, Firm	.						
	Swollen, Treatment Site No.01, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
4510	Skin, Discolored, Treatment Site No.01, Red	.						

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		43 DE						
4510	Skin, Discolored, Treatment Site No.02, Red	.						
	Skin, Scab, Treatment Site No.01	.						
	Skin, Scab, Treatment Site No.02	.						
	Swollen, Treatment Site No.01, Severe, Firm	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
	Abnormal Gait	.						
4511	Skin Thickening, Treatment Site No.02	.						
	Skin, Discolored, Treatment Site No.02, Pink	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
4512	Vocalization, Increased	.						
	Skin Thickening, Treatment Site No.02	.						
	Skin, Discolored, Treatment Site No.02, Pink	.						
	Skin, Discolored, Treatment Site No.02, Red	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
4513	Fur, Staining, Dorsal Cervical, Red	X						
	Skin Thickening, Treatment Site No.02	.						
	Skin, Discolored, Treatment Site No.02, Pink	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
4514	Fur, Staining, Dorsal Cervical, Red	X						
	Skin Thickening, Treatment Site No.02	.						

X=Present

Appendix 5

Individual Clinical Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date						
		43 DE						
4514	Skin, Discolored, Treatment Site No.02, Red	.						
	Swollen, Treatment Site No.02, Severe, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						
4515	Skin Thickening, Treatment Site No.02	.						
	Swollen, Treatment Site No.02, Moderate, Firm	.						
	Swollen, Treatment Site No.02, Slight, Firm	.						

Appendix 5

Individual Clinical Observations

5002400

Comment Information

Group	Sex	Animal	Day	Observation Type	Comment
4	Female	4510	-1 (Dpr1)	All Types	SKIN SCAB PROBABLY DUE TO SHAVING, SITE 1 AND 2
4	Female	4510	-1 (DE)	All Types	SKIN SCAB PROBABLY DUE TO SHAVING, SITE 1 AND 2
4	Female	4510	2 (DW)	All Types	SKIN SCAB PROBABLY DUE TO SHAVING, SITE 1
4	Female	4510	2 (Dp1)	All Types	SKIN SCAB PROBABLY DUE TO SHAVING, SITE 2
4	Female	4510	4 (Dp2)	All Types	SKIN SCAB PROBABLY DUE TO SHAVING, SITE 2
4	Female	4510	7 (DE)	All Types	SKIN SCAB PROBABLY DUE TO SHAVING, SITE 2

Appendix 6

Individual Body Weights Explanation Page

Abbreviation	Description	Abbreviation	Description
./-	Not scheduled to be performed/dead	RC	Result comment
< or >	Out of range	TERR	Technical error
NT	Not taken	UPTD	Unable to perform due to technical difficulty
OA	Omitted activity		

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 6
Individual Body Weights

5002400
Sex: Male Bodyweight (g)

0 ug/dose	Day(s) Relative to Start Date						
Group 1	-5	-1	7	14	21	28	30
1001	167	185	240 [a]	290	333	362	357
1002	207	231	288 [a]	341	385	417	416
1003	198	224	267	311	351	376	370
1004	196	220	267 [a]	309	339	364	360
1005	177	197	244	293	334	370	370
1006	160	184	236	291	332	358	360
1007	166	189	249	305	354	385	393
1008	185	207	269	330	380	421	427
1009	200	224	287	345	391	419	415
1010	207	236	301	366	423	458	460
1011	189	210	271	322	361	399	-
1012	175	201	265	320	374	407	-
1013	192	207	242	277	304	318	-
1014	169	196	255	312	359	392	-
1015	192	217	285	356	419	448	-
Mean	185.3	208.5	264.4	317.9	362.6	392.9	392.8
SD	15.4	16.5	19.9	25.8	33.2	36.9	35.3
N	15	15	15	15	15	15	10

[a] [RC:VALUE CONFIRMED]

Appendix 6
Individual Body Weights

5002400
Sex: Male Bodyweight (g)

0 ug/dose	Day(s) Relative to Start Date		
Group 1	35	42	43
1001	-	-	-
1002	-	-	-
1003	-	-	-
1004	-	-	-
1005	-	-	-
1006	-	-	-
1007	-	-	-
1008	-	-	-
1009	-	-	-
1010	-	-	-
1011	430	440	429
1012	444	468	464
1013	328	334	331
1014	423	448	431
1015	484	511	500
Mean	421.8	440.2	431.0
SD	57.5	65.4	63.0
N	5	5	5

Appendix 6
Individual Body Weights

5002400
Sex: Male Bodyweight (g)

10 ug/dose	Day(s) Relative to Start Date						
Group 2	-5	-1	7	14	21	28	30
2001	185	214	276	328	376	407	411
2002	194	218	275	324	364	400	409
2003	176	199	259	306	336	369	375
2004	195	212	257	298	326	353	352
2005	191	210	261	302	334	352	358
2006	172	195	256	318	362	401	404
2007	176	200	262	310	336	363	364
2008	205	237	311	380	427	483	480
2009	197	222	285	334	380	414	418
2010	190	204	268	321	358	386	383
Mean	188.1	211.1	271.0	322.1	359.9	392.8	395.4
SD	10.7	12.6	17.0	23.4	30.1	39.0	38.0
N	10	10	10	10	10	10	10
%Diff	1.5	1.2	2.5	1.3	-0.7	0.0	0.7

Appendix 6
Individual Body Weights

5002400
Sex: Male Bodyweight (g)

30 ug/dose	Day(s) Relative to Start Date						
Group 3	-5	-1	7	14	21	28	30
3001	171	186	234	290	319	344	338
3002	183	206	262	311	353	376	376
3003	190	210	276	322	368	397	391
3004	198	218	264	304	325	339	332
3005	194	217	270	323	358	380	378
3006	193	213	276	339	391	429	428
3007	173	200	265	329	377	417	412
3008	201	226	276	325	361	394	396
3009	187	208	265	315	363	394	386
3010	189	217	278	347	397	439	435
Mean	187.9	210.1	266.6	320.5	361.2	390.9	387.2
SD	9.9	11.2	12.9	16.6	25.0	32.9	33.9
N	10	10	10	10	10	10	10
%Diff	1.4	0.8	0.8	0.8	-0.4	-0.5	-1.4

Appendix 6
Individual Body Weights

5002400
Sex: Male Bodyweight (g)

96 ug/dose Group 4	Day(s) Relative to Start Date						
	-5	-1	7	14	21	28	30
4001	170	188	240	304	347	381	378
4002	193	217	265	317	357	390	381
4003	163	196	246	308	347	387	378
4004	197	224	292	362	411	457	452
4005	183	214	269	337	359	400	396
4006	201	233	272	329	362	400	396
4007	208	231	281	337	370	404	391
4008	192	220	265	306	327	356	338 [a]
4009	195	221	285	350	388	439	428
4010	168	197	245	310	337	383	367 [a]
4011	176	204	248	309	350	387	-
4012	189	217	248	305	342	373	-
4013	206	216	249	303	328	362	-
4014	165	188	242	309	359	398	-
4015	176	202	251	309	348	384	-
Mean	185.5	211.2	259.9	319.7	355.5	393.4	390.5
SD	15.0	14.5	16.9	18.7	21.9	26.2	31.6
N	15	15	15	15	15	15	10
%Diff	0.1	1.3	-1.7	0.6	-2.0	0.1	-0.6

[a] [RC:VALUE CONFIRMED]

Appendix 6
Individual Body Weights

5002400
Sex: Male Bodyweight (g)

96 ug/dose Group 4	Day(s) Relative to Start Date		
	35	42	43
4001	-	-	-
4002	-	-	-
4003	-	-	-
4004	-	-	-
4005	-	-	-
4006	-	-	-
4007	-	-	-
4008	-	-	-
4009	-	-	-
4010	-	-	-
4011	397	419	410
4012	385	410	404
4013	367	394	387
4014	429	468	448 [a]
4015	409	437	425
Mean	397.4	425.6	414.8
SD	23.5	28.3	23.0
N	5	5	5
%Diff	-5.8	-3.3	-3.8

[a] [RC:VALUE CONFIRMED]

Appendix 6
Individual Body Weights

5002400
Sex: Female Bodyweight (g)

0 ug/dose	Day(s) Relative to Start Date						
Group 1	-6	-5	-1	7	14	21	28
1501	184	-	200	227	241	252	267
1502	172	-	187	204	218	236	245
1503	169	-	186	210	225	231	246
1504	165	-	182	205	225	235	244
1505	177	-	198	224	243	252	268
1506	174	-	189	216	241	249	259
1507	149	-	167	191	208	225	232
1508	170	-	198	214	235	248	259
1509	164	-	188	208	229	244	254
1510	177	-	196	220	238	241	259
1511	-	179	197	231	250	265	276
1512	-	165	171	202	219	226	248
1513	-	162	173	187	208	224	240
1514	-	160	177	207	220	241	250
1515	-	153	164	190	211	219	237
Mean	170.1	163.8	184.9	209.1	227.4	239.2	252.3
SD	9.5	9.6	12.1	13.3	13.5	12.8	12.4
N	10	5	15	15	15	15	15

Appendix 6
Individual Body Weights

5002400
Sex: Female Bodyweight (g)

0 ug/dose	Day(s) Relative to Start Date			
Group 1	30	35	42	43
1501	257	-	-	-
1502	239	-	-	-
1503	237	-	-	-
1504	239	-	-	-
1505	260	-	-	-
1506	258	-	-	-
1507	232	-	-	-
1508	250	-	-	-
1509	249	-	-	-
1510	252	-	-	-
1511	-	282	285	274
1512	-	258	264	263
1513	-	241	256	245 [a]
1514	-	252	258	246 [a]
1515	-	242	248	248
Mean	247.3	255.0	262.2	255.2
SD	9.9	16.7	14.0	12.8
N	10	5	5	5

[a] [RC:VALUE CONFIRMED]

Appendix 6
Individual Body Weights

5002400
Sex: Female Bodyweight (g)

10 ug/dose	Day(s) Relative to Start Date						
Group 2	-6	-2	-1	7	14	21	28
2501	170	-	193	208	233	252	268
2502	164	-	182	202	219	229	249
2503	175	-	185	200	212	221	227
2604	185	203	203	225	248	262	268
2505	169	-	178	206	229	235	257
2506	163	-	178	199	221	230	235
2507	172	-	192	213	232	242	257
2508	161	-	176	195	209	216	224
2509	156	-	177	198	217	228	243
2510	174	-	191	214	223	235	247
Mean	168.9	203.0	185.5	206.0	224.3	235.0	247.5
SD	8.3	-	9.0	9.2	11.5	13.9	15.5
N	10	1	10	10	10	10	10
%Diff	-0.7	-	0.3	-1.5	-1.4	-1.8	-1.9

Appendix 6
Individual Body Weights

5002400
Sex: Female Bodyweight (g)

10 ug/dose Group 2	Day(s) Relative to Start Date 30
2501	258
2502	241
2503	223
2604	268
2505	254
2506	235
2507	245 [a]
2508	224
2509	228
2510	230
Mean	240.6
SD	15.4
N	10
%Diff	-2.7

[a] [RC:VALUE CONFIRMED]

Appendix 6
Individual Body Weights

5002400
Sex: Female Bodyweight (g)

30 ug/dose	Day(s) Relative to Start Date						
Group 3	-6	-1	7	14	21	28	30
3501	169	186	196	231	249	262	248
3502	165	173	201	217	227	231	225
3503	163	179	199	198	217	235	213
3504	175	187	212	224	231	250	236
3505	170	186	211	234	241	244	248
3506	160	175	197	218	230	236	230
3507	171	183	205	221	224	242	231
3508	165	184	209	230	239	245	241
3509	161	181	201	220	232	247	231
3510	174	199	215	231	240	258	233 [a]
Mean	167.3	183.3	204.6	222.4	233.0	245.0	233.6
SD	5.3	7.3	6.8	10.5	9.4	9.9	10.5
N	10	10	10	10	10	10	10
%Diff	-1.6	-0.8	-2.1	-2.2	-2.6	-2.9	-5.5

[a] [RC:VALUE CONFIRMED]

Appendix 6
Individual Body Weights

5002400
Sex: Female Bodyweight (g)

96 ug/dose Group 4	Day(s) Relative to Start Date						
	-6	-5	-1	7	14	21	28
4501	179	-	203	234	262	283	302
4502	169	-	180	194	206	205	223
4503	168	-	182	206	217	230	247
4504	170	-	191	212	232	240	257
4505	153	-	171	188	207	218	233
4506	158	-	173	184	202	212	219
4507	183	-	205	229	257	263	280
4508	181	-	190	213	234	243	248
4509	164	-	189	204	226	236	245
4510	154	-	165	186	204	209	215
4511	-	173	178	190	203	223	240
4512	-	161	173	188	208	222	245
4513	-	163	176	193	212	228	235
4514	-	176	187	209	220	233	247
4515	-	171	183	205	226	240	250
Mean	167.9	168.8	183.1	202.3	221.1	232.3	245.7
SD	10.8	6.5	11.3	15.4	18.9	20.5	22.3
N	10	5	15	15	15	15	15
%Diff	-1.3	3.1	-1.0	-3.2	-2.8	-2.9	-2.6

Appendix 6
Individual Body Weights

5002400
Sex: Female Bodyweight (g)

96 ug/dose Group 4	Day(s) Relative to Start Date			
	30	35	42	43
4501	293	-	-	-
4502	218	-	-	-
4503	234	-	-	-
4504	246	-	-	-
4505	220	-	-	-
4506	208	-	-	-
4507	273	-	-	-
4508	243	-	-	-
4509	230	-	-	-
4510	211	-	-	-
4511	-	247	252	247
4512	-	250	256	251
4513	-	244	255	247
4514	-	253	259	246 [a]
4515	-	256	263	251 [a]
Mean	237.6	250.0	257.0	248.4
SD	27.4	4.7	4.2	2.4
N	10	5	5	5
%Diff	-3.9	-2.0	-2.0	-2.7

[a] [RC:VALUE CONFIRMED]

Appendix 7

Individual Body Weight Gains Explanation Page

Abbreviation	Description	Abbreviation	Description
./-	Not scheduled to be performed/dead	RC	Result comment
< or >	Out of range	TERR	Technical error
		UPTD	Unable to perform due to technical difficulty

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 7
Individual Body Weight Gains

5002400
Sex: Male Bodyweight Gain (Interval)

0 ug/dose	Day(s) Relative to Start Date						
Group 1	-5 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 30	28 → 35
1001	18	55	50	43	29	-5	-
1002	24	57	53	44	32	-1	-
1003	26	43	44	40	25	-6	-
1004	24	47	42	30	25	-4	-
1005	20	47	49	41	36	0	-
1006	24	52	55	41	26	2	-
1007	23	60	56	49	31	8	-
1008	22	62	61	50	41	6	-
1009	24	63	58	46	28	-4	-
1010	29	65	65	57	35	2	-
1011	21	61	51	39	38	-	31
1012	26	64	55	54	33	-	37
1013	15	35	35	27	14	-	10
1014	27	59	57	47	33	-	31
1015	25	68	71	63	29	-	36
Mean	23.2	55.9	53.5	44.7	30.3	-0.2	29.0
SD	3.6	9.3	9.0	9.4	6.5	4.7	11.0
N	15	15	15	15	15	10	5

Appendix 7
Individual Body Weight Gains

5002400
Sex: Male Bodyweight Gain (Interval)

0 ug/dose	Day(s) Relative to Start Date	
Group 1	35 → 42	42 → 43
1001	-	-
1002	-	-
1003	-	-
1004	-	-
1005	-	-
1006	-	-
1007	-	-
1008	-	-
1009	-	-
1010	-	-
1011	10	-11
1012	24	-4
1013	6	-3
1014	25	-17
1015	27	-11
Mean	18.4	-9.2
SD	9.7	5.8
N	5	5

Appendix 7
Individual Body Weight Gains

5002400
Sex: Male Bodyweight Gain (Interval)

10 ug/dose	Day(s) Relative to Start Date					
Group 2	-5 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 30
2001	29	62	52	48	31	4
2002	24	57	49	40	36	9
2003	23	60	47	30	33	6
2004	17	45	41	28	27	-1
2005	19	51	41	32	18	6
2006	23	61	62	44	39	3
2007	24	62	48	26	27	1
2008	32	74	69	47	56	-3
2009	25	63	49	46	34	4
2010	14	64	53	37	28	-3
Mean	23.0	59.9	51.1	37.8	32.9	2.6
SD	5.3	7.8	8.7	8.4	10.0	4.0
N	10	10	10	10	10	10

Appendix 7
Individual Body Weight Gains

5002400
Sex: Male Bodyweight Gain (Interval)

30 ug/dose Group 3	Day(s) Relative to Start Date					
	-5 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 30
3001	15	48	56	29	25	-6
3002	23	56	49	42	23	0
3003	20	66	46	46	29	-6
3004	20	46	40	21	14	-7
3005	23	53	53	35	22	-2
3006	20	63	63	52	38	-1
3007	27	65	64	48	40	-5
3008	25	50	49	36	33	2
3009	21	57	50	48	31	-8
3010	28	61	69	50	42	-4
Mean	22.2	56.5	53.9	40.7	29.7	-3.7
SD	3.9	7.2	9.0	10.2	8.9	3.3
N	10	10	10	10	10	10

Appendix 7
Individual Body Weight Gains

5002400
Sex: Male Bodyweight Gain (Interval)

96 ug/dose Group 4	Day(s) Relative to Start Date						
	-5 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 30	28 → 35
4001	18	52	64	43	34	-3	-
4002	24	48	52	40	33	-9	-
4003	33	50	62	39	40	-9	-
4004	27	68	70	49	46	-5	-
4005	31	55	68	22	41	-4	-
4006	32	39	57	33	38	-4	-
4007	23	50	56	33	34	-13	-
4008	28	45	41	21	29	-18	-
4009	26	64	65	38	51	-11	-
4010	29	48	65	27	46	-16	-
4011	28	44	61	41	37	-	10
4012	28	31	57	37	31	-	12
4013	10	33	54	25	34	-	5
4014	23	54	67	50	39	-	31
4015	26	49	58	39	36	-	25
Mean	25.7	48.7	59.8	35.8	37.9	-9.2	16.6
SD	5.8	9.9	7.5	8.9	6.1	5.3	10.9
N	15	15	15	15	15	10	5

Appendix 7
Individual Body Weight Gains

5002400
Sex: Male Bodyweight Gain (Interval)

96 ug/dose Group 4	Day(s) Relative to Start Date	
	35 → 42	42 → 43
4001	-	-
4002	-	-
4003	-	-
4004	-	-
4005	-	-
4006	-	-
4007	-	-
4008	-	-
4009	-	-
4010	-	-
4011	22	-9
4012	25	-6
4013	27	-7
4014	39	-20
4015	28	-12
Mean	28.2	-10.8
SD	6.5	5.6
N	5	5

Appendix 7
Individual Body Weight Gains

5002400
Sex: Female Bodyweight Gain (Interval)

0 ug/dose	Day(s) Relative to Start Date						
Group 1	-5 → -1	-6 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 30
1501	-	16	27	14	11	15	-10
1502	-	15	17	14	18	9	-6
1503	-	17	24	15	6	15	-9
1504	-	17	23	20	10	9	-5
1505	-	21	26	19	9	16	-8
1506	-	15	27	25	8	10	-1
1507	-	18	24	17	17	7	0
1508	-	28	16	21	13	11	-9
1509	-	24	20	21	15	10	-5
1510	-	19	24	18	3	18	-7
1511	18	-	34	19	15	11	-
1512	6	-	31	17	7	22	-
1513	11	-	14	21	16	16	-
1514	17	-	30	13	21	9	-
1515	11	-	26	21	8	18	-
Mean	12.6	19.0	24.2	18.3	11.8	13.1	-6.0
SD	4.9	4.2	5.6	3.4	5.1	4.4	3.4
N	5	10	15	15	15	15	10

Appendix 7
Individual Body Weight Gains

5002400
Sex: Female Bodyweight Gain (Interval)

0 ug/dose	Day(s) Relative to Start Date		
Group 1	28 → 35	35 → 42	42 → 43
1501	-	-	-
1502	-	-	-
1503	-	-	-
1504	-	-	-
1505	-	-	-
1506	-	-	-
1507	-	-	-
1508	-	-	-
1509	-	-	-
1510	-	-	-
1511	6	3	-11
1512	10	6	-1
1513	1	15	-11
1514	2	6	-12
1515	5	6	0
Mean	4.8	7.2	-7.0
SD	3.6	4.5	6.0
N	5	5	5

Appendix 7
Individual Body Weight Gains

5002400
Sex: Female Bodyweight Gain (Interval)

10 ug/dose	Day(s) Relative to Start Date					
Group 2	-6 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 30
2501	23	15	25	19	16	-10
2502	18	20	17	10	20	-8
2503	10	15	12	9	6	-4
2604	18	22	23	14	6	0
2505	9	28	23	6	22	-3
2506	15	21	22	9	5	0
2507	20	21	19	10	15	-12
2508	15	19	14	7	8	0
2509	21	21	19	11	15	-15
2510	17	23	9	12	12	-17
Mean	16.6	20.5	18.3	10.7	12.5	-6.9
SD	4.5	3.8	5.3	3.7	6.1	6.4
N	10	10	10	10	10	10

Appendix 7
Individual Body Weight Gains

5002400
Sex: Female Bodyweight Gain (Interval)

30 ug/dose Group 3	Day(s) Relative to Start Date					
	-6 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 30
3501	17	10	35	18	13	-14
3502	8	28	16	10	4	-6
3503	16	20	-1	19	18	-22
3504	12	25	12	7	19	-14
3505	16	25	23	7	3	4
3506	15	22	21	12	6	-6
3507	12	22	16	3	18	-11
3508	19	25	21	9	6	-4
3509	20	20	19	12	15	-16
3510	25	16	16	9	18	-25
Mean	16.0	21.3	17.8	10.6	12.0	-11.4
SD	4.8	5.2	9.1	4.9	6.5	8.7
N	10	10	10	10	10	10

Appendix 7
Individual Body Weight Gains

5002400
Sex: Female Bodyweight Gain (Interval)

96 ug/dose Group 4	Day(s) Relative to Start Date						
	-5 → -1	-6 → -1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 30
4501	-	24	31	28	21	19	-9
4502	-	11	14	12	-1	18	-5
4503	-	14	24	11	13	17	-13
4504	-	21	21	20	8	17	-11
4505	-	18	17	19	11	15	-13
4506	-	15	11	18	10	7	-11
4507	-	22	24	28	6	17	-7
4508	-	9	23	21	9	5	-5
4509	-	25	15	22	10	9	-15
4510	-	11	21	18	5	6	-4
4511	5	-	12	13	20	17	-
4512	12	-	15	20	14	23	-
4513	13	-	17	19	16	7	-
4514	11	-	22	11	13	14	-
4515	12	-	22	21	14	10	-
Mean	10.6	17.0	19.3	18.7	11.3	13.4	-9.3
SD	3.2	5.8	5.4	5.3	5.7	5.6	3.9
N	5	10	15	15	15	15	10

Appendix 7
Individual Body Weight Gains

5002400
Sex: Female Bodyweight Gain (Interval)

96 ug/dose Group 4	Day(s) Relative to Start Date		
	28 → 35	35 → 42	42 → 43
4501	-	-	-
4502	-	-	-
4503	-	-	-
4504	-	-	-
4505	-	-	-
4506	-	-	-
4507	-	-	-
4508	-	-	-
4509	-	-	-
4510	-	-	-
4511	7	5	-5
4512	5	6	-5
4513	9	11	-8
4514	6	6	-13
4515	6	7	-12
Mean	6.6	7.0	-8.6
SD	1.5	2.3	3.8
N	5	5	5

Appendix 8

Individual Food Consumption Explanation Page

Abbreviation	Description	Abbreviation	Description
. / -	Not scheduled to be performed or dead / See Marker Information	REPL	Animal replaced during measurement interval

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Marker Information

Animal Number	Day	Comment/Marker
2604, 2505, 2506	-1 to 7	REPL

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 8
Individual Food Consumption

5002400
Sex: Male Food Mean Daily Consumption (g/animal/day)

0 ug/dose	Day(s) Relative to Start Date						
Group 1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29	28 → 35	35 → 42
1001	25	27	28	28	24	.	.
1002	25	27	28	28	24	.	.
1003	25	27	28	28	24	.	.
1004	25	26	28	27	28	.	.
1005	25	26	28	27	28	.	.
1006	25	26	28	27	28	.	.
1007	27	29	30	32	30	.	.
1008	27	29	30	32	30	.	.
1009	30	33	34	34	34	.	.
1010	30	33	34	34	34	.	.
1011	25	27	28	28	.	28	27
1012	25	27	28	28	.	28	27
1013	25	27	28	28	.	28	27
1014	29	32	32	32	.	32	33
1015	29	32	32	32	.	32	33
Mean	26.50	28.52	29.63	29.55	28.30	29.46	29.57
SD	1.98	2.57	2.26	2.47	3.71	1.86	2.87
N	15	15	15	15	10	5	5

Appendix 8
Individual Food Consumption

5002400
Sex: Male Food Mean Daily Consumption (g/animal/day)

10 ug/dose	Day(s) Relative to Start Date				
Group 2	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29
2001	26	28	29	30	30
2002	26	28	29	30	30
2003	26	28	29	30	30
2004	24	25	26	26	27
2005	24	25	26	26	27
2006	24	25	26	26	27
2007	28	31	32	32	31
2008	28	31	32	32	31
2009	26	29	30	29	28
2010	26	29	30	29	28
Mean	26.06	27.74	28.74	28.89	28.60
SD	1.69	2.27	2.26	2.32	1.52
N	10	10	10	10	10
%Diff	-1.65	-2.74	-2.99	-2.26	1.06

Appendix 8
Individual Food Consumption

5002400
Sex: Male Food Mean Daily Consumption (g/animal/day)

30 ug/dose	Day(s) Relative to Start Date				
Group 3	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29
3001	23	26	27	28	29
3002	23	26	27	28	29
3003	23	26	27	28	29
3004	26	29	29	29	29
3005	26	29	29	29	29
3006	26	29	29	29	29
3007	27	29	31	32	33
3008	27	29	31	32	33
3009	26	30	30	32	31
3010	26	30	30	32	31
Mean	25.27	28.26	28.93	29.87	30.10
SD	1.80	1.53	1.70	2.08	1.77
N	10	10	10	10	10
%Diff	-4.62	-0.93	-2.36	1.08	6.36

Appendix 8
Individual Food Consumption

5002400
Sex: Male Food Mean Daily Consumption (g/animal/day)

96 ug/dose Group 4	Day(s) Relative to Start Date						
	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29	28 → 35	35 → 42
4001	23	29	29	31	30	.	.
4002	23	29	29	31	30	.	.
4003	23	29	29	31	30	.	.
4004	25	29	29	30	32	.	.
4005	25	29	29	30	32	.	.
4006	25	29	29	30	32	.	.
4007	26	29	27	28	31	.	.
4008	26	29	27	28	31	.	.
4009	26	31	29	33	32	.	.
4010	26	31	29	33	32	.	.
4011	22	29	29	30	.	26	29
4012	22	29	29	30	.	26	29
4013	22	29	29	30	.	26	29
4014	25	30	31	33	.	32	35
4015	25	30	31	33	.	32	35
Mean	24.17	29.38	29.00	30.70	31.10	28.43	31.49
SD	1.34	0.60	1.03	1.67	0.58	3.13	3.27
N	15	15	15	15	10	5	5
%Diff	-8.77	3.01	-2.12	3.87	9.89	-3.49	6.47

Appendix 8
Individual Food Consumption

5002400
Sex: Female Food Mean Daily Consumption (g/animal/day)

0 ug/dose	Day(s) Relative to Start Date						
Group 1	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29	21 → 29	29 → 35
1501	20	21	21	21	18	.	.
1502	20	21	21	21	18	.	.
1503	20	21	21	21	18	.	.
1504	20	21	21	21	21	.	.
1505	20	21	21	21	21	.	.
1506	20	21	21	21	21	.	.
1507	21	21	21	21	23	.	.
1508	21	21	21	21	23	.	.
1509	20	20	21	21	20	.	.
1510	20	20	21	21	20	.	.
1511	19	19	20	.	.	20	21
1512	19	19	20	.	.	20	21
1513	19	19	20	.	.	20	21
1514	21	20	23	.	.	22	21
1515	21	20	23	.	.	22	21
Mean	20.10	20.24	20.93	20.70	20.00	20.58	20.67
SD	0.56	0.76	0.71	0.17	1.71	1.07	0.15
N	15	15	15	10	10	5	5

Appendix 8
Individual Food Consumption

5002400
Sex: Female Food Mean Daily Consumption (g/animal/day)

0 ug/dose Group 1	Day(s) Relative to Start Date 35 → 42
1501	.
1502	.
1503	.
1504	.
1505	.
1506	.
1507	.
1508	.
1509	.
1510	.
1511	20
1512	20
1513	20
1514	22
1515	22
Mean	20.97
SD	0.81
N	5

Appendix 8
Individual Food Consumption

5002400
Sex: Female Food Mean Daily Consumption (g/animal/day)

10 ug/dose	Day(s) Relative to Start Date				
Group 2	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29
2501	19	20	20	20	21
2502	19	20	20	20	21
2503	19	20	20	20	21
2604	.	8	17	12	13
2505	.	8	17	12	13
2506	.	8	17	12	13
2507	20	39	25	31	33
2508	20	39	25	31	33
2509	20	17	19	20	15
2510	20	17	19	20	15
Mean	19.49	19.66	19.84	19.93	19.60
SD	0.55	11.39	3.23	6.80	7.73
N	7	10	10	10	10
%Diff	-3.01	-2.87	-5.21	-3.73	-2.00

Appendix 8
Individual Food Consumption

5002400
Sex: Female Food Mean Daily Consumption (g/animal/day)

30 ug/dose Group 3	Day(s) Relative to Start Date				
	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29
3501	34	18	19	18	21
3502	34	18	19	18	21
3503	34	18	19	18	21
3504	20	20	20	21	21
3505	20	20	20	21	21
3506	20	20	20	21	21
3507	19	20	20	20	17
3508	19	20	20	20	17
3509	21	21	22	22	22
3510	21	21	22	22	22
Mean	24.16	19.50	20.11	19.93	20.30
SD	6.84	1.03	1.16	1.24	1.81
N	10	10	10	10	10
%Diff	20.21	-3.65	-3.91	-3.73	1.50

Appendix 8
Individual Food Consumption

5002400
Sex: Female Food Mean Daily Consumption (g/animal/day)

96 ug/dose Group 4	Day(s) Relative to Start Date						
	-1 → 7	7 → 14	14 → 21	21 → 28	28 → 29	21 → 29	29 → 35
4501	19	19	20	21	21	.	.
4502	19	19	20	21	21	.	.
4503	19	19	20	21	21	.	.
4504	17	19	17	19	22	.	.
4505	17	19	17	19	22	.	.
4506	17	19	17	19	22	.	.
4507	21	22	22	22	23	.	.
4508	21	22	22	22	23	.	.
4509	18	19	19	19	19	.	.
4510	18	19	19	19	19	.	.
4511	17	19	21	.	.	20	20
4512	17	19	21	.	.	20	20
4513	17	19	21	.	.	20	20
4514	18	18	19	.	.	19	19
4515	18	18	19	.	.	19	19
Mean	18.21	19.30	19.70	20.04	20.90	19.80	19.13
SD	1.38	1.22	1.41	1.46	1.44	0.79	0.50
N	15	15	15	10	10	5	5
%Diff	-9.38	-4.61	-5.87	-3.17	4.50	-3.77	-7.42

Appendix 8
Individual Food Consumption

5002400
Sex: Female Food Mean Daily Consumption (g/animal/day)

96 ug/dose Group 4	Day(s) Relative to Start Date 35 → 42
4501	.
4502	.
4503	.
4504	.
4505	.
4506	.
4507	.
4508	.
4509	.
4510	.
4511	22
4512	22
4513	22
4514	20
4515	20
Mean	21.17
SD	1.26
N	5
%Diff	0.95

Appendix 9

Individual Body Temperature Values Explanation Page

Abbreviation	Description	Abbreviation	Description
./-	Not scheduled to be performed/dead	NR	Not recorded
RC	Result comment	NT	Not taken
PR	Predose	6H	6 hours post dose
2H	2 hours post dose	24H	24 hours post dose

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 9
Individual Body Temperature Values

5002400
Sex: Male Body Temperature (oC)

0 ug/dose Group 1	Day(s) Relative to Start Date						
	1 (PR)	1 (2H)	1 (6H)	2 (24H)	29 (PR)	29 (2H)	29 (6H)
1001	38.2	37.7	37.7	39.1	38.2	36.5	37.7
1002	38.0	37.0	37.1	37.5	37.5	36.3	37.4
1003	38.1	37.8	37.5	37.8	37.6	36.7	37.1
1004	38.7	37.5	38.9	37.5	38.6	36.6	38.0
1005	38.5	37.1	38.2	37.3	37.2	36.4	37.0
1006	38.7	37.3	37.7	38.2	38.5	36.6	37.8
1007	38.1	38.4	39.1	37.8	36.6	36.8	36.7
1008	38.0	37.8	37.9	37.4	36.3	36.5	36.6
1009	38.9	37.8	38.5	37.1	37.7	36.3	38.2
1010	37.9	37.7	38.6	37.2	37.4	36.5	38.1
1011	38.3	37.3	36.6	37.5	38.3	38.1	38.3
1012	38.4	37.4	37.3	37.2	36.7	37.8	36.7
1013	38.6	36.9	36.9	37.0	37.4	38.1	36.6
1014	38.6	37.8	37.7	37.1	37.2	37.3	36.9
1015	37.9	36.9	36.9	37.0	36.0	36.2	36.4
Mean	38.33	37.49	37.77	37.51	37.41	36.85	37.30
SD	0.33	0.42	0.76	0.55	0.78	0.65	0.66
N	15	15	15	15	15	15	15

Appendix 9
Individual Body Temperature Values

5002400
Sex: Male Body Temperature (oC)

0 ug/dose Group 1	Day(s) Relative to Start Date						
	30 (24H)	33	34	35	37	38	39
1001	38.1	-	-	-	-	-	-
1002	36.4	-	-	-	-	-	-
1003	36.3	-	-	-	-	-	-
1004	38.4	-	-	-	-	-	-
1005	36.9	-	-	-	-	-	-
1006	37.1	-	-	-	-	-	-
1007	36.2	-	-	-	-	-	-
1008	36.0	-	-	-	-	-	-
1009	36.2	-	-	-	-	-	-
1010	36.6	-	-	-	-	-	-
1011	37.8	-	-	-	-	-	-
1012	36.5	36.5	37.8	-	-	-	-
1013	37.6	-	-	-	-	-	-
1014	36.5	36.4	36.5	37.2	-	-	-
1015	36.9	35.7 [a]	36.4	36.4	35.7	36.0	36.5
Mean	36.90	36.20	36.90	36.80	35.70	36.00	36.50
SD	0.75	0.44	0.78	0.57	-	-	-
N	15	3	3	2	1	1	1

[a] [RC:CONFIRMED VALUE]

Appendix 9
Individual Body Temperature Values

5002400
Sex: Male Body Temperature (oC)

0 ug/dose Group 1	Day(s) Relative to Start Date			
	40	41	42	43
1001	-	-	-	-
1002	-	-	-	-
1003	-	-	-	-
1004	-	-	-	-
1005	-	-	-	-
1006	-	-	-	-
1007	-	-	-	-
1008	-	-	-	-
1009	-	-	-	-
1010	-	-	-	-
1011	-	-	-	-
1012	-	-	-	-
1013	-	-	-	-
1014	-	-	-	-
1015	36.8	35.9	36.7	37.7
Mean	36.80	35.90	36.70	37.70
SD	-	-	-	-
N	1	1	1	1

Appendix 9
Individual Body Temperature Values

5002400
Sex: Male Body Temperature (oC)

10 ug/dose Group 2	Day(s) Relative to Start Date						
	1 (PR)	1 (2H)	1 (6H)	2 (24H)	3	29 (PR)	29 (2H)
2001	37.6	37.9	37.8	37.1	-	36.8	37.6
2002	38.4	38.6	38.0	37.1	-	37.6	38.1
2003	38.3	38.3	37.9	37.9	-	37.1	37.4
2004	38.7	37.4	38.8	36.6	38.4	36.9	37.3
2005	39.0	37.8	39.1	36.8	38.9	38.1	37.7
2006	38.7	37.4	38.9	37.4	-	37.5	37.0
2007	38.3	37.5	38.7	37.2	-	38.2	36.7
2008	38.4	36.9	38.9	37.1	-	37.4	36.9
2009	38.0	37.1	38.3	36.9	37.9	38.1	36.4
2010	38.2	37.3	38.3	36.8	37.6	37.9	36.5
Mean	38.36	37.62	38.47	37.09	38.20	37.56	37.16
SD	0.39	0.53	0.47	0.37	0.57	0.51	0.55
N	10	10	10	10	4	10	10
%Diff	0.09	0.34	1.84	-1.13	-	0.39	0.85

Appendix 9
Individual Body Temperature Values

5002400
Sex: Male Body Temperature (oC)

10 ug/dose Group 2	Day(s) Relative to Start Date	
	29 (6H)	30 (24H)
2001	37.0	36.6
2002	37.5	37.9
2003	36.8	36.7
2004	38.2	38.7
2005	37.9	37.2
2006	37.3	37.3
2007	37.4	36.8
2008	37.5	37.5
2009	37.4	36.0
2010	37.7	37.2
Mean	37.47	37.19
SD	0.41	0.75
N	10	10
%Diff	0.46	0.79

Appendix 9
Individual Body Temperature Values

5002400
Sex: Male Body Temperature (oC)

30 ug/dose Group 3	Day(s) Relative to Start Date						
	1 (PR)	1 (2H)	1 (6H)	2 (24H)	3	29 (PR)	29 (2H)
3001	38.4	38.3	38.0	37.9	-	36.8	38.1
3002	38.2	38.2	38.3	37.2	-	36.6	38.0
3003	38.3	38.2	39.0	37.6	-	36.7	38.1
3004	38.8	38.9	39.5	37.0	-	38.6	38.6
3005	38.4	38.5	38.9	37.0	-	38.6	37.8
3006	38.7	38.7	39.2	37.6	-	37.4	37.8
3007	38.3	37.3	38.6	37.9	-	36.6	37.1
3008	38.4	37.6	39.0	36.8	37.4	36.6	37.3
3009	38.6	37.1	38.4	37.5	-	37.5	37.3
3010	38.5	37.3	38.3	37.1	-	36.8	36.9
Mean	38.46	38.01	38.72	37.36	37.40	37.22	37.70
SD	0.19	0.64	0.47	0.39	-	0.80	0.53
N	10	10	10	10	1	10	10
%Diff	0.35	1.38	2.51	-0.41	-	-0.52	2.32

Appendix 9
Individual Body Temperature Values

5002400
Sex: Male Body Temperature (oC)

30 ug/dose Group 3	Day(s) Relative to Start Date	
	29 (6H)	30 (24H)
3001	37.4	36.8
3002	37.2	36.4
3003	37.3	36.4
3004	38.6	36.9
3005	37.7	37.2
3006	38.6	37.4
3007	37.2	36.7
3008	38.5	36.1
3009	38.2	37.2
3010	37.5	36.9
Mean	37.82	36.80
SD	0.59	0.41
N	10	10
%Diff	1.39	-0.27

Appendix 9
Individual Body Temperature Values

5002400
Sex: Male Body Temperature (oC)

96 ug/dose Group 4	Day(s) Relative to Start Date						
	1 (PR)	1 (2H)	1 (6H)	2 (24H)	29 (PR)	29 (2H)	29 (6H)
4001	38.0	37.6	38.4	38.2	38.2	36.8	37.9
4002	38.7	37.4	38.8	38.5	38.6	37.0	38.6
4003	37.8	37.1	38.8	37.7	38.2	37.3	37.8
4004	38.1	37.5	39.7	38.2	38.2	36.5	38.4
4005	38.6	37.1	39.3	38.0	38.5	36.4	39.0
4006	38.3	38.0	39.7	38.1	38.4	36.2	38.3
4007	39.3	37.3	40.1	39.2	39.2	37.1	38.9
4008	38.3	36.6	39.7	38.8	38.2	38.7	39.7
4009	38.4	38.0	39.7	38.2	38.4	36.7	39.9
4010	38.2	37.6	38.9	38.3	37.9	37.7	39.8
4011	38.1	38.6	38.6	38.4	37.7	37.9	37.9
4012	38.7	38.6	39.1	38.3	38.4	38.4	39.5
4013	38.9	38.4	38.3	38.3	38.1	38.5	39.0
4014	38.6	38.2	38.9	38.3	37.2	38.0	37.9
4015	38.5	38.2	38.9	38.2	38.2	38.2	38.8
Mean	38.43	37.75	39.13	38.31	38.23	37.43	38.76
SD	0.38	0.60	0.54	0.34	0.44	0.83	0.73
N	15	15	15	15	15	15	15
%Diff	0.28	0.68	3.58	2.13	2.17	1.57	3.91

Appendix 9
Individual Body Temperature Values

5002400
Sex: Male Body Temperature (oC)

96 ug/dose Group 4	Day(s) Relative to Start Date						
	30 (24H)	33	34	35	37	38	39
4001	37.4	-	-	-	-	-	-
4002	37.8	-	-	-	-	-	-
4003	37.5	-	-	-	-	-	-
4004	37.4	-	-	-	-	-	-
4005	36.8	-	-	-	-	-	-
4006	38.1	-	-	-	-	-	-
4007	38.5	-	-	-	-	-	-
4008	38.4	-	-	-	-	-	-
4009	38.0	-	-	-	-	-	-
4010	37.5	-	-	-	-	-	-
4011	36.7	36.0	36.7	36.8	36.5	36.1	38.4
4012	37.6	-	-	-	-	-	-
4013	38.1	-	-	-	-	-	-
4014	37.4	-	-	-	-	-	-
4015	37.6	-	-	-	-	-	-
Mean	37.65	36.00	36.70	36.80	36.50	36.10	38.40
SD	0.51	-	-	-	-	-	-
N	15	1	1	1	1	1	1
%Diff	2.04	-0.55	-0.54	0.00	2.24	0.28	5.21

Appendix 9
Individual Body Temperature Values

5002400
Sex: Female Body Temperature (oC)

0 ug/dose Group 1	Day(s) Relative to Start Date						
	1 (PR)	1 (2H)	1 (6H)	2 (24H)	3	29 (PR)	29 (2H)
1501	37.0	38.1	36.7	38.2	-	36.9	37.0
1502	37.1	38.9	37.6	39.0	-	37.7	36.9
1503	39.0	38.7	38.1	38.8	-	38.7	39.5
1504	37.8	38.0	38.1	39.2	-	39.5	37.3
1505	38.5	38.5	37.4	38.6	-	38.6	39.3
1506	37.9	38.6	37.7	38.8	-	38.9	37.4
1507	38.5	37.0	37.3	38.5	-	38.4	36.8
1508	38.6	37.3	37.6	38.9	-	38.2	36.9
1509	38.3	36.9	38.1	38.7	-	38.3	37.3
1510	38.4	37.4	37.6	38.2	-	39.0	38.7
1511	38.3	38.2	37.6	36.7	38.3	36.8	37.7
1512	38.5	38.3	37.0	37.8	-	38.4	36.5
1513	38.2	38.4	37.8	37.6	-	37.0	37.5
1514	37.9	38.9	37.1	37.8	-	38.7	38.0
1515	38.6	38.6	36.7	38.5	-	39.1	38.4
Mean	38.17	38.12	37.49	38.35	38.30	38.28	37.68
SD	0.55	0.67	0.46	0.66	-	0.83	0.92
N	15	15	15	15	1	15	15

Appendix 9
Individual Body Temperature Values

5002400
Sex: Female Body Temperature (oC)

0 ug/dose	Day(s) Relative to Start Date	
Group 1	29 (6H)	30 (24H)
1501	38.4	38.7
1502	37.2	39.1
1503	38.3	38.7
1504	39.4	39.0
1505	39.4	38.7
1506	38.6	39.0
1507	38.7	38.6
1508	39.6	39.6
1509	38.8	38.1
1510	38.6	38.8
1511	38.5	37.4
1512	37.8	37.1
1513	38.2	38.4
1514	39.0	38.4
1515	36.6	38.4
Mean	38.47	38.53
SD	0.81	0.63
N	15	15

Appendix 9
Individual Body Temperature Values

5002400
Sex: Female Body Temperature (oC)

10 ug/dose Group 2	Day(s) Relative to Start Date						
	-1 (PR)	1 (PR)	1 (2H)	1 (6H)	2 (24H)	3	29 (PR)
2501	-	37.5	38.4	37.4	37.1	-	36.9
2502	-	38.4	38.5	37.7	38.5	-	38.6
2503	-	37.6	38.8	37.3	38.6	-	38.5
2604	38.5	38.8	38.5	38.9	38.4	-	38.8
2505	-	37.8	37.5	37.1	37.8	-	38.1
2506	-	38.4	38.3	37.5	38.4	-	38.7
2507	-	39.3	37.2	37.0	37.7	-	39.6
2508	-	39.3	37.5	37.7	37.4	-	39.4
2509	-	38.9	36.1	38.1	37.9	-	38.6
2510	-	38.4	36.6	37.6	36.4	38.3	39.2
Mean	38.50	38.44	37.74	37.63	37.82	38.30	38.64
SD	-	0.65	0.91	0.55	0.71	-	0.76
N	1	10	10	10	10	1	10
%Diff	-	0.70	-1.00	0.36	-1.39	0.00	0.94

Appendix 9
Individual Body Temperature Values

5002400
Sex: Female Body Temperature (oC)

10 ug/dose Group 2	Day(s) Relative to Start Date		
	29 (2H)	29 (6H)	30 (24H)
2501	37.6	36.9	38.3
2502	38.8	37.0	38.8
2503	38.6	36.6	39.1
2604	37.7	38.5	38.8
2505	37.2	37.9	38.0
2506	38.1	38.4	39.3
2507	38.5	36.6	38.9
2508	38.4	39.0	38.8
2509	38.8	38.4	38.7
2510	38.3	39.0	38.9
Mean	38.20	37.83	38.76
SD	0.54	0.97	0.37
N	10	10	10
%Diff	1.38	-1.67	0.59

Appendix 9

Individual Body Temperature Values

5002400

Sex: Female Body Temperature (oC)

30 ug/dose Group 3	Day(s) Relative to Start Date						
	1 (PR)	1 (2H)	1 (6H)	2 (24H)	29 (PR)	29 (2H)	29 (6H)
3501	38.2	37.5	37.2	37.8	38.7	38.4	36.8
3502	38.7	37.1	38.2	38.7	39.0	39.0	37.8
3503	38.8	37.6	38.0	38.2	38.4	38.4	38.2
3504	38.5	38.2	37.4	38.6	38.8	38.9	37.2
3505	39.3	38.0	37.4	38.9	39.0	38.8	37.0
3506	38.3	37.4	37.1	38.8	38.9	38.3	36.9
3507	39.1	38.5	38.2	37.7	39.4	38.6	38.5
3508	38.6	38.9	38.3	38.4	39.1	38.5	38.2
3509	37.7	37.0	38.0	38.4	38.4	37.3	38.3
3510	39.1	39.0	39.5	38.5	38.8	38.2	38.7
Mean	38.63	37.92	37.93	38.40	38.85	38.44	37.76
SD	0.48	0.72	0.71	0.40	0.31	0.48	0.72
N	10	10	10	10	10	10	10
%Diff	1.20	-0.52	1.16	0.12	1.49	2.02	-1.85

Appendix 9
Individual Body Temperature Values

5002400
Sex: Female Body Temperature (oC)

30 ug/dose Group 3	Day(s) Relative to Start Date 30 (24H)
3501	38.9
3502	39.6
3503	39.5
3504	39.0
3505	39.7
3506	39.4
3507	39.3
3508	39.6
3509	38.6
3510	38.7
Mean	39.23
SD	0.40
N	10
%Diff	1.81

Appendix 9
Individual Body Temperature Values

5002400
Sex: Female Body Temperature (oC)

96 ug/dose Group 4	Day(s) Relative to Start Date						
	1 (PR)	1 (2H)	1 (6H)	2 (24H)	3	29 (PR)	29 (2H)
4501	37.8	37.3	38.7	39.5	-	38.0	37.4
4502	39.4	37.4	39.6	39.7	38.4	36.6	36.3
4503	38.5	37.7	37.9	39.8	37.8	37.1	36.7
4504	38.2	37.0	38.5	39.3	-	38.9	37.7
4505	38.8	37.2	38.9	39.5	-	39.5	37.8
4506	38.0	37.8	38.7	39.1	-	38.2	37.8
4507	37.8	37.4	38.3	39.3	-	38.8	37.6
4508	37.5	37.4	39.7	39.5	-	39.3	38.0
4509	37.7	37.5	37.8	39.0	-	38.7	37.2
4510	38.8	37.2	39.3	39.4	-	39.4	39.6
4511	39.0	39.1	39.5	38.1	-	38.7	39.3
4512	38.7	38.8	38.2	38.4	-	38.1	38.8
4513	38.9	38.9	38.1	38.9	-	38.7	39.0
4514	38.5	38.1	39.6	38.4	-	38.6	38.9
4515	38.2	38.0	38.7	38.4	-	38.8	38.8
Mean	38.39	37.79	38.77	39.09	38.10	38.49	38.06
SD	0.55	0.67	0.65	0.54	0.42	0.80	0.97
N	15	15	15	15	2	15	15
%Diff	0.56	-0.87	3.40	1.91	-0.52	0.56	1.01

Appendix 9
Individual Body Temperature Values

5002400
Sex: Female Body Temperature (oC)

96 ug/dose Group 4	Day(s) Relative to Start Date	
	29 (6H)	30 (24H)
4501	38.7	39.5
4502	38.8	39.2
4503	39.2	39.5
4504	39.1	39.9
4505	39.7	39.9
4506	38.0	38.8
4507	39.3	39.3
4508	39.6	40.1
4509	38.9	39.4
4510	39.8	39.9
4511	39.5	38.8
4512	38.6	38.3
4513	38.8	37.8
4514	37.9	37.4
4515	37.5	38.5
Mean	38.89	39.09
SD	0.68	0.81
N	15	15
%Diff	1.09	1.44

Appendix 10

Individual Hematology Values Explanation Page

ADVIA 120 Analyzer
Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Hematocrit	HCT	%	Calculated
Hemoglobin	HGB	g/dL	Colorimetric
Mean Corpuscular Hemoglobin	MCH	pg	Calculated
Mean Corpuscular Hemoglobin Concentration	MCHC	g/dL	Calculated
Mean Corpuscular Volume	MCV	fL	Calculated
Mean Platelet Volume	MPV	fL	Calculated
Platelet Count	PLT	$x10^3/\mu L$	Light scatter
Red Blood Cell Count	RBC	$x10^6/\mu L$	Light scatter
Red Blood Cell Distribution Width	RDW	%	Calculated
Reticulocytes	RETIC	$x10^9/L$	Calculated
Reticulocytes Percent	RETIC	%	Light scatter
White Blood Cell Count	WBC	$x10^3/\mu L$	Light scatter
White Blood Cell Differential Count			
Neutrophils Percent	NEUT	%	Light scatter
Lymphocytes Percent	LYMPH	%	Light scatter
Monocytes Percent	MONO	%	Light scatter
Eosinophils Percent	EOS	%	Light scatter
Basophils Percent	BASO	%	Light scatter
Large Unstained Cells Percent	LUC	%	Light scatter
Neutrophils	NEUT	$x10^3/\mu L$	Calculated
Lymphocytes	LYMPH	$x10^3/\mu L$	Calculated
Monocytes	MONO	$x10^3/\mu L$	Calculated
Eosinophils	EOS	$x10^3/\mu L$	Calculated
Basophils	BASO	$x10^3/\mu L$	Calculated
Large Unstained Cells	LUC	$x10^3/\mu L$	Calculated

Manual and Visual

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Count		% and/or $x10^3/\mu L$	Microscopic enumeration (100 white cells)
- Immature Neutrophils Count	IMM NEUT		
- Immature Neutrophils Percent	IMM NEUT		
- Immature Cells Percent	IMM CELL		
- Immature Cells Count	IMM CELL		
- Large Platelets	LPLT		
- Neutrophils Band Form	NEUT BAND		
- Neutrophils Band Form Percent	NEUT BAND		
- Packed Cell Volume	PCV		
- Neutrophils	NEUT		
- Lymphocytes	LYMPH		

Appendix 10

- Monocytes	MONO		
- Eosinophils	EOS		
- Basophils	BASO		
Bone Marrow Stain		None	Manual, Wright-Giemsa stain
Bone Marrow Slide Fixation		None	Manual, Fixative
Others			
- Nucleated Red Blood Cells/100 Leukocytes	RBCNUCLE	#/100 WBC	Microscopic enumeration (100 white cells) Reported as Number but not included in WBC Differential
CELL MORPHOLOGY			
- Cytoplasmic Basophilia	CYTO BASO	1+ (Minimal)	Microscopic Examination
Neutrophil	NEUT	2+ (Mild)	
- Polychromasia	POLY	3+ (Moderate)	
- Anisocytosis	ANISO	4+ (Marked)	
- Hypochromasia	HYPO		
- Reactive Lymphocytes	REACTIVE LYMPH		
- Megakaryocytes	MEGAK		
- Smudge Cells	SMUDGE CELL		
- Microcytes	MICROCYTES		
- Macrocytes	MACROCYTES		
- Poikilocytosis	POIK		
- Rouleaux Formation	ROULEAUX		
- Agglutination	AGGL		
- Red Blood Cell Clumping	RBC Clumping		
- Acanthocytes	ACAN		
- Codocytes	TARGET CELL		
- Dacryocytes	DACR		
- Platelet Clumps	PLATELET CLUMPS		
- Eccentrocytes	ECCENTCY		
- Schistocytes	SCHZ		
- Spherocytes	SPHR		
- Stomatocytes	STOM		
- Howell Jolly Bodies	HJB		
- Basophilic Stippling	BASO STIP		
- Echinocytes	ECHINO		
- Vacuolated Neutrophils	VAC NEUT		
- Vacuolated Lymphocyted	VAC LYM		
- Döhle Bodies	DOHLE BODY		
- Degenerated Cells	DEG CELL		
- Ovalocytes	OVAL		
- Large Platelets Alpha	LARGE PLATELETS		
- Immature Neutrophils	IMM NEUT		
Morphology	MORPH		
- Heinz Bodies	HEINZ BODY		

Appendix 10

- Plasmodium	PLASMOD			
- Kurloff Cell	KURL			
- Burr Cells	BURR			
- Neutrophils Band Form	NEUT BAND			
Morphology	MORPH			
- Nuclear Swelling	NUC SWELL NEUT			
- Red Blood Cell Morphology	RBC MORPH			
- White Blood Cell Morphology	WBC MORPH			
- Toxic Granulation	TOXG			
- Platelet Morphology	PLT MORPH			
Heinz Bodies Percent	HEINZ BODY	%	Microscopic examination. Methyl violet in physiological saline	
Reticulocyte Percent	RETIC	%	Microscopic enumeration, (b) (4)	

Aerospray Automated Slide Stainer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Stain		None	2 parts aqueous stain (Eosin-Thiazin)

Midas III Slide Stainer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
White Blood Cell Differential Stain		None	Wright-Giemsa stain
Bone Marrow Stain		None	Wright-Giemsa stain
Bone Marrow Slide Fixation		None	Fixative

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
./-	Not required for veterinary monitoring / Not scheduled to be performed / No findings / Not evaluated / Dead	NT	Not taken
ADQ	Adequate	OA	Omitted activity
CLOT	Sample clotted	QNS	Quantity not sufficient
COMM	Comment added	RC	Result comment
DEC	Decreased	SNR	Sample not received
INC	Increased	UPTD	Unable to perform due to technical difficulty
MDIFF	Manual differential	UTD	Unable to determine
NAF	No abnormal findings	UTDM	Unable to determine, not confirmed by microscopy
NSCH	Not scheduled to be performed	UTDR	Unable to determine, results not reproducible

Note: This is a comprehensive list of systems, parameters and/or abbreviations. Everything listed above may not be applicable to this report.

Appendix 10

Note: Additional morphology for flagged samples may be reported if applicable.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 10

Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
1001	9.01	1.03	7.70	0.13	0.06	0.01	0.08
1002	9.53	1.41	7.86	0.15	0.07	0.01	0.04
1003	8.15	0.99	6.92	0.09	0.06	0.00	0.07
1004	5.40	0.77	4.45	0.09	0.06	0.00	0.03
1005	13.21	1.05	11.66	0.19	0.10	0.01	0.19
1006	5.37	0.83	4.38	0.07	0.04	0.00	0.04
1007	5.58	0.85	4.55	0.09	0.05	0.01	0.03
1008	3.87	0.49	3.29	0.05	0.02	0.00	0.02
1009	6.03	0.81	5.06	0.05	0.06	0.00	0.04
1010	6.61	0.94	5.55	0.06	0.03	0.00	0.04
Mean	7.276	0.917	6.142	0.097	0.055	0.004	0.058
SD	2.742	0.237	2.463	0.046	0.022	0.005	0.050
N	10	10	10	10	10	10	10

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
1001	7.69	14.2	44.2	57.6	18.5	32.1	12.2
1002	7.75	14.7	45.3	58.4	19.0	32.5	12.3
1003	8.04	14.2	44.5	55.4	17.7	32.0	12.2
1004	8.57	14.6	44.4	51.9	17.0	32.8	11.6
1005	7.48	13.8	43.7	58.4	18.5	31.7	13.0
1006	7.33	13.8	42.8	58.4	18.8	32.3	12.2
1007	7.39	14.2	43.4	58.8	19.2	32.6	11.9
1008	7.28	13.9	43.2	59.3	19.0	32.1	12.6
1009	7.74	14.4	45.4	58.7	18.6	31.8	11.9
1010	7.46	14.0	43.2	57.9	18.7	32.4	12.7
Mean	7.673	14.18	44.01	57.48	18.50	32.23	12.26
SD	0.392	0.32	0.90	2.23	0.67	0.35	0.42
N	10	10	10	10	10	10	10

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
1001	1151	229.6
1002	1309	283.7
1003	1212	295.7
1004	1285	181.5
1005	1444	365.4
1006	1161	230.8
1007	1299	269.8
1008	1244	273.3
1009	1302	249.4
1010	1574	258.9
Mean	1298.1	263.81
SD	128.4	48.45
N	10	10

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
2001	10.73	2.90	7.20	0.19	0.19	0.01	0.24
2002	6.15	1.55	4.18	0.14	0.07	0.00	0.21
2003	11.71	3.02	8.18	0.19	0.14	0.02	0.17
2004	10.68	4.35	5.83	0.18	0.11	0.01	0.21
2005	7.73	1.26	6.16	0.10	0.10	0.01	0.11
2006	9.12	2.60	6.11	0.13	0.17	0.01	0.09
2007	6.89	2.25	4.31	0.19	0.07	0.01	0.06
2008	6.93	1.56	5.10	0.09	0.09	0.00	0.09
2009	6.02	1.78	3.98	0.08	0.07	0.00	0.10
2010	5.54	2.06	3.17	0.13	0.12	0.00	0.06
Mean	8.150	2.333	5.422	0.142	0.113	0.007	0.134
SD	2.243	0.924	1.563	0.043	0.042	0.007	0.067
N	10	10	10	10	10	10	10
tCtrl	1.12	2.54	0.88	1.46	2.05	1.75	2.31

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
2001	7.69	14.3	45.0	58.6	18.6	31.8	12.1
2002	7.47	13.6	41.5	55.5	18.2	32.8	12.3
2003	7.53	14.0	43.6	57.9	18.6	32.1	12.4
2004	8.05	14.1	44.3	55.1	17.6	31.9	13.1
2005	7.79	14.7	45.3	58.1	18.8	32.4	12.2
2006	7.42	13.9	43.9	59.2	18.7	31.6	12.7
2007	7.49	13.0	40.4	53.9	17.3	32.2	12.7
2008	7.22	13.9	43.3	60.0	19.3	32.1	11.7
2009	7.55	13.6	41.9	55.5	18.0	32.4	12.4
2010	7.45	13.8	42.8	57.5	18.5	32.2	13.4
Mean	7.566	13.89	43.20	57.13	18.36	32.15	12.50
SD	0.229	0.45	1.57	2.01	0.59	0.34	0.49
N	10	10	10	10	10	10	10
tCtrl	0.99	0.98	0.98	0.99	0.99	1.00	1.02

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
2001	1249	294.0
2002	1127	252.0
2003	1235	264.0
2004	1434	295.7
2005	1233	191.1
2006	1130	283.1
2007	1174	216.3
2008	1310	303.2
2009	1281	230.4
2010	1113	209.7
Mean	1228.6	253.95
SD	99.1	40.29
N	10	10
tCtrl	0.95	0.96

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
3001	14.15	8.60	5.03	0.24	0.15	0.00	0.13
3002	13.32	7.51	5.32	0.18	0.22	0.01	0.08
3003	15.63	9.37	5.92	0.13	0.12	0.00	0.10
3004	13.98	7.24	6.36	0.13	0.09	0.01	0.14
3005	13.54	5.58	7.45	0.12	0.28	0.01	0.09
3006	10.95	4.93	5.66	0.09	0.18	0.01	0.08
3007	11.29	6.13	4.84	0.16	0.11	0.00	0.05
3008	12.59	4.70	6.93	0.42	0.24	0.01	0.29
3009	9.98	4.29	5.19	0.23	0.20	0.00	0.07
3010	13.51	7.22	5.89	0.19	0.08	0.01	0.12
Mean	12.894	6.557	5.859	0.189	0.167	0.006	0.115
SD	1.705	1.709	0.846	0.094	0.068	0.005	0.068
N	10	10	10	10	10	10	10
tCtrl	1.77	7.15	0.95	1.95	3.04	1.50	1.98

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
3001	7.82	14.2	44.8	57.3	18.2	31.8	12.9
3002	7.65	13.4	41.6	54.4	17.4	32.1	13.6
3003	7.62	14.2	45.0	59.1	18.6	31.5	13.8
3004	7.93	13.7	43.4	54.7	17.3	31.6	13.1
3005	7.89	14.0	43.5	55.2	17.7	32.1	12.8
3006	7.30	12.9	41.3	56.5	17.7	31.3	13.7
3007	7.06	13.4	42.3	59.8	19.0	31.8	13.9
3008	7.67	13.7	42.0	54.7	17.9	32.7	13.1
3009	7.61	13.5	42.2	55.5	17.7	32.0	13.4
3010	7.07	13.2	42.8	60.5	18.7	30.9	13.7
Mean	7.562	13.62	42.89	56.77	18.02	31.78	13.40
SD	0.316	0.43	1.27	2.29	0.58	0.50	0.40
N	10	10	10	10	10	10	10
tCtrl	0.99	0.96	0.97	0.99	0.97	0.99	1.09

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
3001	1055	283.9
3002	1413	214.9
3003	1400	240.7
3004	1242	145.4
3005	1481	217.2
3006	1522	303.4
3007	1207	241.7
3008	1155	220.5
3009	1147	264.5
3010	1234	201.9
Mean	1285.6	233.41
SD	157.6	44.78
N	10	10
tCtrl	0.99	0.88

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
4001	12.84	8.32	4.15	0.18	0.14	0.01	0.04
4002	14.72	10.88	3.47	0.15	0.16	0.00	0.05
4003	15.99	11.31	4.29	0.17	0.14	0.01	0.07
4004	18.09	11.49	6.17	0.17	0.14	0.01	0.12
4005	19.20	11.35	7.11	0.25	0.28	0.03	0.19
4006	19.06	14.12	4.32	0.22	0.26	0.01	0.13
4007	16.48	10.69	5.29	0.29	0.11	0.01	0.09
4008	14.93	10.27	4.11	0.40	0.10	0.01	0.06
4009	14.62	8.69	5.30	0.26	0.25	0.01	0.12
4010	14.52	9.36	4.67	0.24	0.14	0.01	0.10
Mean	16.045	10.648	4.888	0.233	0.172	0.011	0.097
SD	2.136	1.660	1.095	0.075	0.066	0.007	0.045
N	10	10	10	10	10	10	10
tCtrl	2.21	11.61	0.80	2.40	3.13	2.75	1.67

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
4001	7.87	14.2	45.0	57.2	18.0	31.5	14.3
4002	7.82	13.9	43.0	55.0	17.8	32.3	13.9
4003	7.84	14.3	46.2	58.9	18.3	31.0	14.4
4004	7.46	14.2	44.1	59.1	19.0	32.2	14.4
4005	8.21	14.7	45.4	55.3	17.9	32.4	13.5
4006	7.84	14.4	44.6	56.8	18.4	32.3	14.4
4007	7.77	13.8	42.7	54.9	17.8	32.4	14.5
4008	7.51	13.7	41.9	55.7	18.2	32.6	13.9
4009	7.37	14.0	44.4	60.2	19.0	31.6	14.7
4010	7.71	13.1	42.7	55.4	17.0	30.7	14.4
Mean	7.740	14.03	44.00	56.85	18.14	31.90	14.24
SD	0.244	0.44	1.38	1.93	0.59	0.66	0.36
N	10	10	10	10	10	10	10
tCtrl	1.01	0.99	1.00	0.99	0.98	0.99	1.16

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
4001	1409	310.3
4002	1207	201.9
4003	1394	225.0
4004	1389	228.1
4005	1205	231.8
4006	1192	195.9
4007	1153	141.4
4008	1391	160.6
4009	906	191.6
4010	1329	150.1
Mean	1257.5	203.67
SD	158.4	49.47
N	10	10
tCtrl	0.97	0.77

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
1501	9.38	2.77	6.04	0.29	0.12	0.01	0.17
1502	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
1503	5.61	0.43	5.00	0.04	0.08	0.00	0.06
1504	6.33	0.94	5.17	0.12	0.06	0.01	0.03
1505	5.83	0.37	5.28	0.05	0.07	0.00	0.06
1506	6.49	0.76	5.49	0.12	0.07	0.01	0.05
1507	4.43	0.66	3.58	0.08	0.05	0.01	0.05
1508	5.63	0.63	4.82	0.06	0.07	0.01	0.04
1509	4.11	0.54	3.49	0.03	0.03	0.00	0.02
1510	9.83	0.71	8.85	0.09	0.07	0.01	0.10
Mean	6.404	0.868	5.302	0.098	0.069	0.007	0.064
SD	1.979	0.734	1.572	0.079	0.024	0.005	0.046
N	9	9	9	9	9	9	9

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
1501	7.33	13.9	41.0	55.9	19.0	34.0	11.0
1502	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT	CLOT
1503	7.90	14.7	44.4	56.2	18.6	33.0	10.5
1504	8.11	15.2	45.2	55.7	18.7	33.6	10.7
1505	7.42	13.6	41.0	55.2	18.3	33.2	10.8
1506	7.29	13.6	40.3	55.2	18.7	33.9	11.0
1507	6.71	13.1	39.5	58.8	19.5	33.1	10.6
1508	7.55	13.8	43.5	57.6	18.3	31.8	10.8
1509	7.20	13.3	40.6	56.4	18.4	32.7	11.2
1510	7.06	13.7	41.8	59.1	19.4	32.8	11.2
Mean	7.397	13.88	41.92	56.68	18.77	33.12	10.87
SD	0.422	0.67	1.98	1.48	0.45	0.68	0.25
N	9	9	9	9	9	9	9

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
1501	1316	235.8
1502	CLOT	CLOT
1503	1176	179.3
1504	1334	187.9
1505	1170	156.3
1506	1157	165.3
1507	908	214.1
1508	1288	253.1
1509	1347	217.5
1510	1280	233.8
Mean	1219.6	204.79
SD	138.0	33.97
N	9	9

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
2501	5.00	1.70	2.96	0.13	0.14	0.00	0.06
2502	8.74	2.35	5.83	0.16	0.22	0.01	0.17
2503	7.04	3.01	3.76	0.06	0.18	0.00	0.03
2604	9.69	3.58	5.73	0.11	0.17	0.01	0.08
2505	12.37	4.13	7.51	0.22	0.35	0.01	0.15
2506	7.73	3.14	4.16	0.14	0.21	0.00	0.08
2507	6.28	2.22	3.75	0.08	0.10	0.00	0.12
2508	9.95	3.82	5.69	0.14	0.18	0.00	0.12
2509	5.51	1.60	3.58	0.09	0.17	0.00	0.07
2510	9.21	3.46	5.28	0.16	0.16	0.00	0.15
Mean	8.152	2.901	4.825	0.129	0.188	0.003	0.103
SD	2.278	0.888	1.405	0.047	0.066	0.005	0.046
N	10	10	10	10	10	10	10
tCtrl	1.27	3.34	0.91	1.32	2.73	0.45	1.60

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
2501	7.32	13.3	40.6	55.4	18.2	32.9	11.2
2502	7.33	13.6	41.3	56.3	18.6	33.0	11.2
2503	7.21	13.4	40.7	56.5	18.6	32.9	11.3
2604	7.55	14.3	42.7	56.5	18.9	33.5	11.6
2505	7.33	13.6	40.8	55.7	18.5	33.3	11.2
2506	7.51	13.1	39.9	53.2	17.5	32.9	10.8
2507	7.28	13.7	41.3	56.6	18.8	33.1	10.8
2508	7.35	13.7	41.3	56.1	18.6	33.1	11.1
2509	7.39	13.2	40.6	54.8	17.8	32.5	10.9
2510	6.86	13.0	39.6	57.8	18.9	32.8	11.1
Mean	7.313	13.49	40.88	55.89	18.44	33.00	11.12
SD	0.189	0.38	0.86	1.24	0.47	0.27	0.24
N	10	10	10	10	10	10	10
tCtrl	0.99	0.97	0.98	0.99	0.98	1.00	1.02

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
2501	1095	242.6
2502	1130	170.4
2503	873	202.9
2604	1391	191.4
2505	1117	227.3
2506	1244	192.8
2507	1149	186.8
2508	1222	169.5
2509	1511	194.0
2510	1145	201.1
Mean	1187.7	197.88
SD	173.0	22.77
N	10	10
tCtrl	0.97	0.97

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
3501	7.99	5.24	2.32	0.20	0.14	0.00	0.09
3502	11.50	7.71	3.27	0.21	0.20	0.00	0.11
3503	9.98	5.53	3.95	0.17	0.26	0.00	0.06
3504	9.31	6.05	2.91	0.11	0.16	0.00	0.07
3505	11.42	5.97	5.13	0.08	0.18	0.01	0.05
3506	11.85	7.24	4.05	0.13	0.25	0.01	0.17
3507	10.52	6.31	3.86	0.10	0.18	0.01	0.07
3508	12.66	5.68	6.45	0.17	0.22	0.01	0.12
3509	15.51	9.32	5.50	0.26	0.34	0.01	0.07
3510	11.22	6.26	4.49	0.18	0.20	0.00	0.09
Mean	11.196	6.531	4.193	0.161	0.213	0.005	0.090
SD	2.030	1.235	1.246	0.056	0.058	0.005	0.036
N	10	10	10	10	10	10	10
tCtrl	1.75	7.53	0.79	1.65	3.09	0.75	1.40

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
3501	7.34	13.9	41.4	56.4	18.9	33.5	11.8
3502	7.63	13.4	40.9	53.6	17.6	32.8	12.2
3503	7.52	14.0	42.7	56.8	18.7	32.8	11.7
3504	7.59	13.9	41.6	54.8	18.4	33.5	11.5
3505	6.47	12.1	36.3	56.1	18.7	33.4	12.1
3506	7.51	14.0	42.0	55.9	18.7	33.4	11.9
3507	7.58	13.9	42.1	55.6	18.3	32.9	12.5
3508	7.20	13.2	39.7	55.2	18.3	33.2	11.6
3509	7.11	13.3	40.1	56.5	18.7	33.1	11.5
3510	7.52	13.3	40.0	53.2	17.7	33.2	12.0
Mean	7.347	13.50	40.68	55.41	18.40	33.18	11.88
SD	0.354	0.59	1.83	1.22	0.44	0.27	0.33
N	10	10	10	10	10	10	10
tCtrl	0.99	0.97	0.97	0.98	0.98	1.00	1.09

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
3501	1122	249.2
3502	1163	196.5
3503	1233	245.4
3504	1391	205.3
3505	961	188.2
3506	1137	216.7
3507	1018	179.6
3508	1280	125.3
3509	1216	205.2
3510	1030	229.8
Mean	1155.1	204.12
SD	131.1	36.03
N	10	10
tCtrl	0.95	1.00

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
4501	8.86	5.33	2.99	0.14	0.21	0.01	0.18
4502	8.54	5.95	2.14	0.11	0.27	0.00	0.07
4503	11.49	6.94	4.19	0.10	0.17	0.01	0.08
4504	6.25	4.54	1.39	0.09	0.18	0.00	0.05
4505	8.25	4.52	3.45	0.06	0.15	0.01	0.07
4506	7.59	5.73	1.62	0.12	0.08	0.00	0.04
4507	12.27	7.68	4.11	0.10	0.22	0.00	0.16
4508	6.82	4.59	1.97	0.07	0.14	0.00	0.05
4509	7.37	5.05	2.02	0.11	0.14	0.00	0.04
4510	8.38	4.67	3.37	0.08	0.18	0.00	0.08
Mean	8.582	5.500	2.725	0.098	0.174	0.003	0.082
SD	1.923	1.091	1.027	0.024	0.052	0.005	0.049
N	10	10	10	10	10	10	10
tCtrl	1.34	6.34	0.51	1.00	2.53	0.45	1.27

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
4501	7.64	14.3	43.3	56.6	18.6	33.0	12.0
4502	8.08	14.1	42.8	53.0	17.4	32.9	12.9
4503	7.57	13.5	41.0	54.1	17.8	32.9	12.6
4504	7.54	13.7	41.8	55.4	18.2	32.9	13.0
4505	7.86	14.0	41.9	53.2	17.8	33.5	12.0
4506	7.81	14.5	43.5	55.7	18.6	33.4	12.1
4507	7.00	13.3	40.2	57.4	19.0	33.0	12.4
4508	7.23	13.8	40.6	56.2	19.1	34.1	13.6
4509	7.12	13.6	40.6	57.0	19.1	33.5	12.7
4510	7.38	13.4	41.0	55.6	18.2	32.7	12.7
Mean	7.523	13.82	41.67	55.42	18.38	33.19	12.60
SD	0.344	0.40	1.19	1.53	0.60	0.43	0.50
N	10	10	10	10	10	10	10
tCtrl	1.02	1.00	0.99	0.98	0.98	1.00	1.16

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology				
	PLT (10^3/uL)	RETIC (10^9/L)	ANISO	PLT MORPH	WBC MORPH
4501	1101	161.3	-	-	-
4502	1247	194.3	-	-	-
4503	1199	188.5	-	-	-
4504	1205	226.5	-	-	-
4505	1092	161.6	-	-	-
4506	970	227.2	-	-	-
4507	1152	171.7	-	-	-
4508	398	153.9	1+	NAF	NAF
4509	1338	260.8	-	-	-
4510	1029	180.4	-	-	-
Mean	1073.1	192.62	-	-	-
SD	260.2	35.03	-	-	-
N	10	10	1	1	1
tCtrl	0.88	0.94	-	-	-

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
1011	6.13	0.83	5.04	0.12	0.06	0.00	0.08
1012	9.64	1.30	7.96	0.18	0.11	0.00	0.10
1013	5.16	1.08	3.87	0.10	0.04	0.00	0.08
1014	8.29	1.21	6.84	0.09	0.10	0.00	0.04
1015	6.70	0.92	5.55	0.12	0.02	0.01	0.08
Mean	7.184	1.068	5.852	0.122	0.066	0.002	0.076
SD	1.782	0.195	1.589	0.035	0.038	0.004	0.022
N	5	5	5	5	5	5	5

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
1011	8.00	14.5	46.2	57.7	18.1	31.4	11.9
1012	7.27	13.1	41.0	56.4	18.1	32.0	12.7
1013	7.99	14.1	43.4	54.3	17.6	32.4	12.4
1014	7.56	14.1	43.2	57.2	18.6	32.6	12.1
1015	7.15	12.9	41.0	57.3	18.1	31.6	14.6
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

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
1011	1150	211.1
1012	1061	223.3
1013	1450	214.5
1014	1196	192.9
1015	1273	277.5
Mean	1226.0	223.86
SD	146.9	31.96
N	5	5

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
4011	6.86	1.49	5.13	0.11	0.08	0.00	0.05
4012	8.00	1.96	5.66	0.22	0.09	0.01	0.06
4013	11.50	3.00	7.92	0.31	0.13	0.01	0.14
4014	13.48	1.41	11.53	0.24	0.04	0.02	0.25
4015	9.40	1.60	7.29	0.22	0.16	0.01	0.12
Mean	9.848	1.892	7.506	0.220	0.100	0.010	0.124
SD	2.668	0.654	2.523	0.072	0.046	0.007	0.080
N	5	5	5	5	5	5	5
tCtrl	1.37	1.77	1.28	1.80	1.52	5.00	1.63

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
4011	7.70	14.0	42.5	55.2	18.1	32.8	14.0
4012	7.74	13.4	42.3	54.6	17.3	31.7	14.2
4013	7.65	13.3	42.6	55.7	17.3	31.1	15.1
4014	7.85	14.5	46.0	58.6	18.5	31.5	14.3
4015	7.71	13.9	43.3	56.2	18.0	32.0	14.1
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

Appendix 10
Individual Hematology Values

5002400

Sex: Male Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
4011	1130	257.6
4012	1393	230.0
4013	1198	279.6
4014	1604	246.0
4015	1334	201.7
Mean	1331.8	242.98
SD	184.7	29.31
N	5	5
tCtrl	1.09	1.09

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
1511	6.05	0.59	5.23	0.10	0.03	0.00	0.10
1512	4.92	0.70	4.05	0.08	0.04	0.00	0.04
1513	4.31	0.67	3.45	0.11	0.04	0.00	0.04
1514	5.07	0.71	4.20	0.08	0.02	0.00	0.05
1515	5.27	1.23	3.80	0.12	0.04	0.01	0.08
Mean	5.124	0.780	4.146	0.098	0.034	0.002	0.062
SD	0.630	0.256	0.669	0.018	0.009	0.004	0.027
N	5	5	5	5	5	5	5

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
1511	7.27	13.3	41.5	57.1	18.3	32.1	10.8
1512	7.19	13.2	40.7	56.6	18.4	32.5	12.0
1513	7.19	13.0	40.6	56.5	18.1	32.1	11.4
1514	7.47	14.1	42.8	57.4	18.8	32.8	11.1
1515	6.95	13.0	40.2	57.8	18.8	32.5	11.6
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

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
1511	1107	207.6
1512	1114	185.5
1513	1262	253.7
1514	1276	182.9
1515	1205	189.8
Mean	1192.8	203.90
SD	79.7	29.46
N	5	5

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology						
	WBC (10^3/uL)	NEUT (10^3/uL)	LYMPH (10^3/uL)	MONO (10^3/uL)	EOS (10^3/uL)	BASO (10^3/uL)	LUC (10^3/uL)
4511	9.33	2.16	6.59	0.25	0.08	0.01	0.24
4512	5.80	0.95	4.48	0.18	0.13	0.00	0.05
4513	8.98	1.72	6.90	0.20	0.05	0.01	0.09
4514	9.33	1.27	7.77	0.09	0.11	0.01	0.09
4515	6.53	2.12	4.11	0.14	0.11	0.00	0.05
Mean	7.994	1.644	5.970	0.172	0.096	0.006	0.104
SD	1.696	0.529	1.594	0.061	0.031	0.005	0.079
N	5	5	5	5	5	5	5
tCtrl	1.56	2.11	1.44	1.76	2.82	3.00	1.68

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology						
	RBC (10^6/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
4511	7.35	13.4	40.6	55.2	18.3	33.1	13.4
4512	7.47	13.5	41.3	55.2	18.0	32.6	13.7
4513	7.54	13.5	41.3	54.7	17.9	32.7	13.2
4514	7.45	13.0	39.7	53.4	17.4	32.7	13.0
4515	7.02	12.6	38.7	55.2	18.0	32.5	13.6
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
tCtrl	1.02	0.99	0.98	0.96	0.97	1.01	1.18

Appendix 10
Individual Hematology Values

5002400

Sex: Female Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Hematology	
	PLT (10^3/uL)	RETIC (10^9/L)
4511	1339	190.8
4512	1512	203.3
4513	1521	205.0
4514	1586	205.4
4515	1344	249.9
Mean	1460.4	210.88
SD	112.2	22.63
N	5	5
tCtrl	1.22	1.03

Appendix 11

Individual Coagulation Values Explanation Page

START 4 Compact Stago Analyzer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Activated Partial Thromboplastin Time	APTT	sec	Viscosity
Fibrinogen	FIB	mg/dL	Viscosity
Prothrombin Time	PT	sec	Viscosity

STA Compact Stago Analyzer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Prothrombin Time	PT	sec	Viscosity
Activated Partial Thromboplastin Time	APTT	sec	Viscosity
Fibrinogen	FIB	mg/dL	Viscosity

Plasma Appearance (Reported as SAMQ Coagulation)

Analyzed Parameter Descriptions

Parameter	Abbreviation	Degree is graded as	Methodology
Normal sample	N	Normal	Manual and visual
Hemolyzed sample	H	+ = slight (pale/light red) ++ = moderate (red) +++ = severe (dark red)	Manual and visual
Lipemic sample	L	+ = slight (cloudy) ++ = moderate (turbid) +++ = severe (lactescent)	Manual and visual
Icterus sample	I	+ = slight (dark yellow) ++ = moderate (very dark yellow) +++ = severe (dark yellow-green)	Manual and visual

Appendix 11

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
./-	Not required for veterinary monitoring / Not scheduled to be performed / No findings / Not evaluated / Dead	OA	Omitted activity
CLOT	Sample clotted	QNS	Quantity not sufficient
COMM	Comment added	RC	Result comment
NCD	No clot detected	SNR	Sample not received
NSCH	Not scheduled to be performed	UPTD	Unable to perform due to technical difficulty
NT	Not taken	UTD	Unable to determine
		UTDR	Unable to determine, results not reproducible

Note: This is a comprehensive list of systems, parameters and/or abbreviations. Everything listed above may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 11
Individual Coagulation Values

5002400

Sex: Male Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
1001	15.7	15.0	330	N
1002	16.0	16.0	319	N
1003	16.9	16.0	358	N
1004	16.7	16.9	289	N
1005	17.5	15.5	327	N
1006	17.1	16.5	269	N
1007	17.4	15.9	286	N
1008	16.7	16.0	274	N
1009	16.8	15.6	328	N
1010	16.4	14.5	327	N
Mean	16.72	15.79	310.7	-
SD	0.57	0.69	29.2	-
N	10	10	10	10

Appendix 11
Individual Coagulation Values

5002400

Sex: Male Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
2001	17.1	15.4	460	N
2002	15.7	16.3	510	N
2003	16.6	17.0	548	N
2004	16.1	16.8	690	N
2005	16.0	16.3	587	N
2006	15.1	15.4	505	N
2007	15.6	16.1	545	N
2008	16.7	15.4	451	N
2009	17.1	15.4	590	N
2010	15.7	17.0	553	N
Mean	16.17	16.11	543.8	-
SD	0.68	0.68	69.7	-
N	10	10	10	10
tCtrl	0.97	1.02	1.75	-

Appendix 11
Individual Coagulation Values

5002400

Sex: Male Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
3001	15.6	17.5	797	N
3002	16.3	18.4	720	N
3003	15.9	18.1	770	N
3004	15.9	17.7	981	N
3005	15.7	17.2	744	N
3006	16.5	17.1	661	N
3007	15.7	16.7	720	N
3008	15.4	16.6	690	N
3009	16.0	16.6	625	N
3010	16.6	17.6	632	N
Mean	15.96	17.35	734.1	-
SD	0.39	0.62	103.4	-
N	10	10	10	10
tCtrl	0.95	1.10	2.36	-

Appendix 11
Individual Coagulation Values

5002400

Sex: Male Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
4001	16.3	19.3	965	N
4002	16.8	21.1	765	N
4003	16.3	22.5	1023	N
4004	15.8	23.1	859	N
4005	15.7	19.4	792	N
4006	16.5	18.5	815	N
4007	16.4	19.8	1061	N
4008	16.9	19.1	809	N
4009	16.3	17.9	803	N
4010	15.0	21.2	841	N
Mean	16.20	20.19	873.2	-
SD	0.56	1.72	104.5	-
N	10	10	10	10
tCtrl	0.97	1.28	2.81	-

Appendix 11
Individual Coagulation Values

5002400

Sex: Female Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
1501	16.5	16.4	245	N
1502	CLOT	CLOT	CLOT	CLOT
1503	16.8	15.4	251	N
1504	17.1	15.1	268	N
1505	17.2	14.7	193	N
1506	17.0	14.6	188	N
1507	16.3	16.0	219	N
1508	16.2	15.6	206	N
1509	17.9	15.0	198	N
1510	16.8	15.1	209	L+
Mean	16.87	15.32	219.7	-
SD	0.52	0.59	28.4	-
N	9	9	9	9

Appendix 11
Individual Coagulation Values

5002400

Sex: Female Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
2501	16.7	16.3	359	N
2502	17.3	15.0	322	N
2503	17.1	16.1	451	N
2604	16.2	15.5	221	N
2505	15.6	18.8	281	N
2506	16.4	17.6	306	N
2507	16.7	15.8	460	N
2508	17.0	17.0	449	N
2509	15.6	16.6	328	N
2510	17.1	17.1	448	N
Mean	16.57	16.58	362.4	-
SD	0.61	1.11	84.9	-
N	10	10	10	10
tCtrl	0.98	1.08	1.65	-

Appendix 11
Individual Coagulation Values

5002400

Sex: Female Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
3501	16.5	17.1	564	N
3502	17.7	18.8	629	N
3503	16.1	17.1	618	N
3504	16.8	17.3	677	N
3505	17.0	18.3	482	N
3506	16.7	20.9	612	N
3507	17.0	19.2	632	N
3508	14.5	16.7	584	N
3509	16.7	19.0	650	N
3510	17.9	18.8	720	N
Mean	16.69	18.32	616.8	-
SD	0.94	1.29	64.9	-
N	10	10	10	10
tCtrl	0.99	1.20	2.81	-

Appendix 11
Individual Coagulation Values

5002400

Sex: Female Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
4501	17.1	19.9	702	N
4502	16.0	19.4	698	N
4503	16.6	19.5	643	N
4504	18.1	19.7	694	N
4505	17.5	19.2	716	N
4506	16.4	19.8	730	N
4507	16.5	20.4	744	N
4508	17.3	20.6	781	N
4509	15.2	18.2	749	N
4510	16.3	20.1	669	N
Mean	16.70	19.68	712.6	-
SD	0.83	0.68	40.4	-
N	10	10	10	10
tCtrl	0.99	1.28	3.24	-

Appendix 11
Individual Coagulation Values

5002400

Sex: Male Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
1011	15.8	15.4	336	N
1012	15.8	14.6	289	N
1013	16.0	15.4	249	N
1014	15.4	15.1	307	N
1015	16.0	14.8	287	N
Mean	15.80	15.06	293.8	-
SD	0.24	0.36	31.7	-
N	5	5	5	5

Appendix 11
Individual Coagulation Values

5002400

Sex: Male Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
4011	16.3	14.0	299	N
4012	16.6	16.6	264	N
4013	16.0	15.4	218	N
4014	15.2	14.6	338	N
4015	16.3	16.4	300	N
Mean	16.08	15.40	283.6	-
SD	0.54	1.12	45.3	-
N	5	5	5	5
tCtrl	1.02	1.02	0.97	-

Appendix 11
Individual Coagulation Values

5002400

Sex: Female Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
1511	15.8	14.9	194	N
1512	16.9	16.1	189	N
1513	16.0	16.9	199	N
1514	13.6	UTD [a]	229	N
1515	16.0	15.7	204	N
Mean	15.66	15.90	203.0	-
SD	1.23	0.83	15.6	-
N	5	4	5	5

[a] [RC:technical difficulty]

Appendix 11
Individual Coagulation Values

5002400

Sex: Female Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Coagulation			
	PT (sec)	APTT (sec)	FIB (mg/dL)	SAMQ Coagulation
4511	15.4	16.0	210	N
4512	CLOT	CLOT	CLOT	CLOT
4513	15.9	16.6	197	N
4514	15.9	17.3	201	N
4515	16.2	16.1	195	N
Mean	15.85	16.50	200.7	-
SD	0.33	0.59	6.8	-
N	4	4	4	4
tCtrl	1.01	1.04	0.99	-

Appendix 12

Individual Clinical Chemistry Values Explanation Page

Modular Analytics / Cobas 6000 Analyzer

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Alanine Aminotransferase	ALT	U/L	ALT IFCC UV
Albumin	ALB	g/dL	Bromcresol green colorimetric
Alkaline Phosphatase	ALP	U/L	ALP IFCC liquid colorimetric
Amylase	AMYL	U/L	Enzymatic colorimetric
Aspartate Aminotransferase	AST	U/L	AST IFCC UV
Calcium	CA	mg/dL	O-cresolphthalein complexone colorimetric
Cholesterol	CHOL	mg/dL	CHOD-PAP enzymatic colorimetric
Creatinine	CREAT	mg/dL	Jaffe kinetic colorimetric. Rate-blanked and compensated
Creatine Kinase	CK	U/L	NAC activated UV
Direct Bilirubin	DBIL	mg/dL	Jendrassik colorimetric
GAMMA-Glutamyl Transferase	GGT	U/L	Nitro-Anilide, Glycylglycine; enzymatic colorimetric
Glucose	GLUC	mg/dL	Hexokinase UV
Iron	FE	µg/dL	Colorimetric
Lactate	LACT	mg/dL	Enzymatic colorimetric
Magnesium	MG	mg/dL	Colorimetric
Phosphorus	PHOS	mg/dL	Molybdate UV
Sodium, Potassium, Chloride (SI)	NA,K,CL	mmol/L	Indirect measurement (Ion selective electrode)
Total Bilirubin	TBIL	mg/dL	DPD colorimetric
Total Protein	TPROT	g/dL	Biuret colorimetric
Triglycerides	TRIG	mg/dL	GPO-PAP enzymatic colorimetric
Urea Nitrogen	UREAN	mg/dL	Urease kinetic UV

Calculations

Analyzed Parameter Descriptions

Parameter	Abbreviation	Units	Calculation
Albumin/Globulin ratio	A/G	Ratio	Albumin / Globulin
Globulin	GLOB	g/dL	Total Protein - Albumin
Indirect Bilirubin	IBIL	mg/dL	Total Bilirubin - Direct Bilirubin
Urea Nitrogen / Creatinine ratio	UREAN/CREAT	mmol/L	Urea Nitrogen / Creatinine
Sodium / Potassium ratio	NA/K	mmol/L	Sodium / Potassium

Appendix 12

Serum Appearance (Reported as SAMQ)

Analyzed Parameter Descriptions

Parameter	Abbreviation	Key to Results (Code)	Methodology
Normal sample	N	Normal	Manual and visual
Hemolyzed sample	H	+ = slight (pale/light red) ++ = moderate (red) +++ = severe (dark red)	Manual and visual
Lipemic sample	L	+ = slight (cloudy) ++ = moderate (turbid) +++ = severe (lactescent)	Manual and visual
Icterus sample	I	+ = slight (dark yellow) ++ = moderate (very dark yellow) +++ = severe (dark yellow-green)	Manual and visual

Other Abbreviations

Abbreviation	Description	Abbreviation	Description
./-	Not required for veterinary monitoring / Not scheduled to be performed / No findings / Not evaluated / Dead	RC	Result comment
CLOT	Sample clotted	SNR	Sample not received
COMM	Comment added	TNR	Test not reported
FC	Flag comment	TTSM	Sample was analyzed 3 times (original, 1st and 2nd repeats), values not comparable (not reported)
LLOQ	Less than lower limit of quantitation	UPTD	Unable to perform due to technical difficulty
NC	Not calculable	UTD	Unable to determine
NSCH	Not scheduled to be performed	UTDH	Unable to determine due to marked hemolysis
NT	Not taken	UTDL	Unable to determine due to marked lipemia
OA	Omitted activity	UTDR	Unable to determine, results not reproducible
QNS	Quantity not sufficient		

Note: This is a comprehensive list of systems, parameters and/or abbreviations. Everything listed above may not be applicable to this report.

Appendix 12

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
1001	60	46	135	2 [a]	235	0.04	14
1002	95	38	122	2 [a]	829	0.07	13
1003	55	34	138	2 [a]	138	0.07	16
1004	88	42	154	2 [a]	702	0.03	13
1005	75	50	224	2 [a]	327	0.08	18
1006	124	44	192	2 [a]	1119	0.03	17
1007	52	32	202	2 [a]	115	0.00 [a]	15
1008	60	36	107	2 [a]	352	0.04	16
1009	64	36	199	2 [a]	236	0.04	20
1010	67	43	147	2 [a]	162	0.00 [a]	15
Mean	74.0	40.1	162.0	1.5	421.5	0.040	15.7
SD	22.4	5.8	39.3	0.0	342.5	0.027	2.2
N	10	10	10	10	10	10	10

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
1001	0.2	176	80	67	5.4	3.6	1.8
1002	0.4	141	60	34	5.7	3.9	1.8
1003	0.3	203	52	19	5.2	3.7	1.5
1004	0.2	207	65	74	5.3	3.7	1.6
1005	0.3	207	67	27	5.4	3.9	1.5
1006	0.3	173	44	87	5.3	3.6	1.7
1007	0.3	215	61	51	4.9	3.4	1.5
1008	0.3	291	69	66	5.3	3.7	1.6
1009	0.4	228	80	79	6.0	4.2	1.8
1010	0.3	178	81	91	5.7	4.0	1.7
Mean	0.30	201.9	65.9	59.5	5.42	3.77	1.65
SD	0.07	40.3	12.3	25.5	0.31	0.23	0.13
N	10	10	10	10	10	10	10

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
1001	2.0	9.7	7.2	136	4.2	96	N
1002	2.2	9.9	7.8	139	5.0	100	N
1003	2.5	9.5	7.6	138	5.6	100	N
1004	2.3	10.1	7.4	135	5.1	94	N
1005	2.6	10.1	9.1	139	5.6	101	N
1006	2.1	9.8	8.0	136	5.2	98	N
1007	2.3	9.4	7.2	134	4.9	96	N
1008	2.3	10.0	8.8	139	5.0	98	N
1009	2.3	10.2	7.3	142	4.8	102	N
1010	2.4	10.4	6.7	141	4.8	102	N
Mean	2.30	9.91	7.71	137.9	5.02	98.7	-
SD	0.18	0.31	0.75	2.6	0.41	2.8	-
N	10	10	10	10	10	10	10

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
2001	76	34	167	2 [a]	438	0.00 [a]	17
2002	76	41	161	2 [a]	361	0.03	14
2003	63	49	137	2 [a]	136	0.05	13
2004	48	36	133	2 [a]	131	0.04	13
2005	58	36	140	2 [a]	220	0.03	17
2006	70	39	102	2 [a]	296	0.05	15
2007	119	37	146	2 [a]	1149	0.00 [a]	19
2008	85	51	217	2 [a]	477	0.06	17
2009	60	48	185	2 [a]	268	0.00 [a]	18
2010	88	42	141	2 [a]	526	0.00 [a]	15
Mean	74.3	41.3	152.9	1.5	400.2	0.026	15.8
SD	20.0	6.1	31.6	0.0	296.0	0.024	2.1
N	10	10	10	10	10	10	10
tCtrl	1.00	1.03	0.94	1.00	0.95	0.65	1.01

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
2001	0.3	207	69	87	5.4	3.6	1.8
2002	0.3	187	51	71	4.8	3.1	1.7
2003	0.3	210	63	84	5.3	3.6	1.7
2004	0.3	149	57	20	5.2	3.4	1.8
2005	0.3	192	86	21	5.4	3.7	1.7
2006	0.4	170	64	45	5.6	3.7	1.9
2007	0.3	180	79	37	5.6	3.4	2.2
2008	0.3	190	101	52	5.9	4.1	1.8
2009	0.3	206	75	66	5.8	3.8	2.0
2010	0.3	191	61	41	5.8	3.6	2.2
Mean	0.31	188.2	70.6	52.4	5.48	3.60	1.88
SD	0.03	18.6	15.0	24.0	0.33	0.27	0.19
N	10	10	10	10	10	10	10
tCtrl	1.03	0.93	1.07	0.88	1.01	0.95	1.14

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
2001	2.0	9.9	8.4	135	5.7	96	N
2002	1.8	9.5	6.5	133	4.8	94	N
2003	2.1	10.3	7.9	134	5.0	96	N
2004	1.9	9.7	7.2	131	4.9	94	N
2005	2.2	9.8	7.5	137	5.0	98	N
2006	1.9	10.1	7.5	137	5.1	98	N
2007	1.5	9.4	7.7	135	5.2	96	N
2008	2.3	10.4	8.2	140	5.2	99	N
2009	1.9	10.7	7.8	139	5.3	100	N
2010	1.6	10.5	8.9	140	5.0	98	N
Mean	1.92	10.03	7.76	136.1	5.12	96.9	-
SD	0.25	0.44	0.66	3.0	0.25	2.0	-
N	10	10	10	10	10	10	10
tCtrl	0.83	1.01	1.01	0.99	1.02	0.98	-

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
3001	59	26	132	2 [a]	199	0.03	17
3002	51	34	132	2 [a]	152	0.04	16
3003	73	33	147	2 [a]	591	0.05	14
3004	87	45	151	2 [a]	632	0.04	14
3005	154	35	163	2 [a]	2038	0.00 [a]	17
3006	61	39	186	2 [a]	203	0.06	15
3007	87	45	154	2 [a]	599	0.07	19
3008	85	58	178	2 [a]	591	0.00 [a]	17
3009	78	33	155	2 [a]	389	0.04	19
3010	50	42	121	2 [a]	138	0.05	22
Mean	78.5	39.0	151.9	1.5	553.2	0.038	17.0
SD	30.1	9.0	20.4	0.0	560.2	0.023	2.5
N	10	10	10	10	10	10	10
tCtrl	1.06	0.97	0.94	1.00	1.31	0.95	1.08

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
3001	0.3	161	75	33	5.6	3.3	2.3
3002	0.3	191	65	60	5.4	3.4	2.0
3003	0.3	207	60	59	5.6	3.4	2.2
3004	0.3	178	69	66	5.2	3.4	1.8
3005	0.3	136	66	37	5.7	3.5	2.2
3006	0.3	183	95	41	5.5	3.4	2.1
3007	0.4	241	89	49	5.8	3.5	2.3
3008	0.3	228	91	100	6.1	3.4	2.7
3009	0.4	167	63	24	5.6	3.6	2.0
3010	0.4	289	64	56	5.8	3.4	2.4
Mean	0.33	198.1	73.7	52.5	5.63	3.43	2.20
SD	0.05	44.7	13.1	21.4	0.25	0.08	0.25
N	10	10	10	10	10	10	10
tCtrl	1.10	0.98	1.12	0.88	1.04	0.91	1.33

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
3001	1.4	10.3	10.3	138	5.2	98	N
3002	1.7	10.0	6.9	135	4.7	95	N
3003	1.5	10.4	8.5	138	5.9	99	N
3004	1.9	10.2	7.7	137	5.3	96	N
3005	1.6	10.1	8.0	139	5.8	99	N
3006	1.6	10.3	7.8	135	5.1	96	N
3007	1.5	10.2	8.0	139	6.1	99	N
3008	1.3	11.0	7.7	141	5.5	98	N
3009	1.8	10.4	8.4	141	5.4	100	N
3010	1.4	10.5	8.5	141	5.6	100	N
Mean	1.57	10.34	8.18	138.4	5.46	98.0	-
SD	0.19	0.28	0.89	2.3	0.41	1.8	-
N	10	10	10	10	10	10	10
tCtrl	0.68	1.04	1.06	1.00	1.09	0.99	-

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
4001	140	40	157	2 [a]	1645	0.09	16
4002	73	34	146	2 [a]	414	0.04	17
4003	174	41	164	2 [a]	1855	0.07	14
4004	132	34	134	2 [a]	1502	0.03	13
4005	58	31	161	2 [a]	173	0.09	20
4006	86	36	189	2 [a]	425	0.08	13
4007	131	40	130	2 [a]	999	0.05	16
4008	73	32	123	2 [a]	132	0.04	17
4009	114	34	137	2 [a]	1019	0.04	15
4010	66	37	172	2 [a]	247	0.03	19
Mean	104.7	35.9	151.3	1.5	841.1	0.056	16.0
SD	38.9	3.5	20.9	0.0	651.9	0.024	2.4
N	10	10	10	10	10	10	10
tCtrl	1.41	0.90	0.93	1.00	2.00	1.40	1.02

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
4001	0.3	189	66	47	5.6	3.4	2.2
4002	0.3	152	73	37	5.6	3.2	2.4
4003	0.3	120	65	80	6.1	3.5	2.6
4004	0.3	132	76	57	6.2	3.6	2.6
4005	0.3	161	103	66	5.9	3.6	2.3
4006	0.3	117	58	77	5.4	3.2	2.2
4007	0.4	177	60	41	6.0	3.2	2.8
4008	0.3	179	47	27	5.7	3.3	2.4
4009	0.4	216	55	39	6.0	3.4	2.6
4010	0.4	216	71	66	6.4	3.6	2.8
Mean	0.33	165.9	67.4	53.7	5.89	3.40	2.49
SD	0.05	36.1	15.3	18.1	0.31	0.17	0.22
N	10	10	10	10	10	10	10
tCtrl	1.10	0.82	1.02	0.90	1.09	0.90	1.51

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
4001	1.5	10.0	9.0	139	5.7	99	N
4002	1.3	10.3	7.8	140	5.1	99	N
4003	1.3	10.9	10.1	140	6.2	100	N
4004	1.4	10.6	9.0	136	5.5	94	N
4005	1.6	10.5	9.5	139	5.4	97	N
4006	1.5	10.2	8.7	140	5.2	98	N
4007	1.1	10.6	7.8	137	6.4	96	N
4008	1.4	10.8	8.5	141	5.5	101	N
4009	1.3	10.6	8.3	141	5.8	100	N
4010	1.3	11.0	8.2	139	5.7	97	N
Mean	1.37	10.55	8.69	139.2	5.65	98.1	-
SD	0.14	0.31	0.73	1.6	0.41	2.1	-
N	10	10	10	10	10	10	10
tCtrl	0.60	1.06	1.13	1.01	1.13	0.99	-

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
1501	170	56	98	2 [a]	450 E[b]	0.04	19
1502	105	53	121	2 [a]	674	0.05	11
1503	78	43	108	2 [a]	341	0.00 [a]	14
1504	119	36	99	2 [a]	923	0.03	16
1505	64	49	93	2 [a]	135	0.08	18
1506	93	35	88	2 [a]	547	0.06	14
1507	65	42	118	2 [a]	200	0.03	19
1508	84	34	83	2 [a]	445	0.06	10
1509	65	31	80	2 [a]	112	0.05	20
1510	76	32	109	2 [a]	281	0.06	19
Mean	91.9	41.1	99.7	1.5	406.4	0.046	16.0
SD	32.9	9.0	14.1	0.0	269.9	0.022	3.6
N	10	10	10	10	9	10	10

E = Exclude
[a] [RC:Assigned value below the reportable range]
[b] [FC:Sample analysed outside of established stability, results for information only]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
1501	0.5	154	73	25	7.1	5.2	1.9
1502	0.4	188	73	41	6.1	4.4	1.7
1503	0.3	223	94	41	5.6	4.1	1.5
1504	0.3	173	95	37	6.1	4.4	1.7
1505	0.4	223	64	32	6.3	4.7	1.6
1506	0.4	149	55	26	6.3	4.9	1.4
1507	0.4	229	75	52	6.1	4.9	1.2
1508	0.4	188	54	36	6.5	4.9	1.6
1509	0.4	203	62	48	5.9	4.7	1.2
1510	0.5	192	78	77	6.0	4.5	1.5
Mean	0.40	192.2	72.3	41.5	6.20	4.67	1.53
SD	0.07	28.1	14.3	15.2	0.40	0.32	0.22
N	10	10	10	10	10	10	10

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
1501	2.7	10.6	6.7	140	4.4	100	N
1502	2.6	9.8	4.9	139	4.9	101	H+
1503	2.7	10.2	6.6	140	4.3	102	N
1504	2.6	10.3	7.0	141	4.7	100	N
1505	2.9	10.6	7.7	143	4.9	103	N
1506	3.5	10.4	8.3	143	4.8	103	N
1507	4.1	10.4	6.9	143	5.1	102	N
1508	3.1	10.3	6.9	144	4.7	103	N
1509	3.9	10.2	7.2	144	5.0	105	N
1510	3.0	10.5	7.1	145	4.8	103	N
Mean	3.11	10.33	6.93	142.2	4.76	102.2	-
SD	0.54	0.24	0.87	2.0	0.25	1.5	-
N	10	10	10	10	10	10	10

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
2501	62	41	120	2 [a]	125	0.07	14
2502	67	42	85	2 [a]	188	0.06	10
2503	65	32	79	2 [a]	128	0.07	16
2604	99	53	97	2 [a]	469	0.06	15
2505	61	44	125	2 [a]	163	0.03	17
2506	73	42	150	2 [a]	153	0.04	15
2507	75	41	71	2 [a]	274	0.05	18
2508	68	46	92	2 [a]	109	0.04	15
2509	68	33	98	2 [a]	168	0.07	15
2510	85	35	100	2 [a]	380	0.05	16
Mean	72.3	40.9	101.7	1.5	215.7	0.054	15.1
SD	11.7	6.3	23.8	0.0	120.9	0.014	2.1
N	10	10	10	10	10	10	10
tCtrl	0.79	1.00	1.02	1.00	0.53	1.17	0.94

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
2501	0.3	200	95	42	6.3	4.6	1.7
2502	0.3	205	76	36	5.9	4.5	1.4
2503	0.4	202	69	34	5.6	4.0	1.6
2604	0.3	162	83	41	5.9	4.3	1.6
2505	0.4	172	82	31	6.7	4.9	1.8
2506	0.3	224	72	47	5.7	4.0	1.7
2507	0.4	178	89	62	6.2	4.3	1.9
2508	0.4	192	74	32	5.5	3.8	1.7
2509	0.4	184	97	32	6.7	5.1	1.6
2510	0.4	212	82	38	6.6	4.6	2.0
Mean	0.36	193.1	81.9	39.5	6.11	4.41	1.70
SD	0.05	19.2	9.5	9.4	0.46	0.41	0.17
N	10	10	10	10	10	10	10
tCtrl	0.90	1.00	1.13	0.95	0.99	0.94	1.11

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

10 ug/dose Group 2	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
2501	2.7	10.9	7.7	142	4.4	103	N
2502	3.2	10.6	6.5	137	4.6	99	N
2503	2.5	10.2	7.7	143	4.5	104	N
2604	2.7	10.4	7.8	137	4.5	97	N
2505	2.7	10.9	7.6	141	5.1	97	N
2506	2.4	10.4	7.1	140	4.7	100	N
2507	2.3	10.7	6.9	143	5.2	103	N
2508	2.2	10.5	6.7	139	5.1	100	N
2509	3.2	11.3	8.6	142	5.2	101	N
2510	2.3	11.0	8.6	143	5.0	100	N
Mean	2.62	10.69	7.52	140.7	4.83	100.4	-
SD	0.36	0.33	0.73	2.4	0.32	2.4	-
N	10	10	10	10	10	10	10
tCtrl	0.84	1.03	1.09	0.99	1.01	0.98	-

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
3501	69	32	111	2 [a]	277	0.03	14
3502	71	34	74	2 [a]	263	0.06	14
3503	114	22	92	2 [a]	753	0.07	14
3504	66	30	68	2 [a]	173	0.05	16
3505	65	36	97	2 [a]	88	0.05	22
3506	89	38	76	2 [a]	368	0.06	19
3507	116	48	70	2 [a]	732	0.07	16
3508	66	32	66	2 [a]	217	0.05	18
3509	186	166	82	2 [a]	675	0.00 [a]	19
3510	86	39	92	2 [a]	98	0.07	21
Mean	92.8	47.7	82.8	1.5	364.4	0.051	17.3
SD	38.0	42.1	14.7	0.0	259.5	0.022	2.9
N	10	10	10	10	10	10	10
tCtrl	1.01	1.16	0.83	1.00	0.90	1.11	1.08

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
3501	0.4	140	90	52	6.4	4.3	2.1
3502	0.4	153	65	35	5.9	4.0	1.9
3503	0.4	168	65	33	5.9	4.1	1.8
3504	0.4	116	66	36	6.2	3.8	2.4
3505	0.5	226	81	26	5.8	3.8	2.0
3506	0.5	172	74	24	6.4	4.3	2.1
3507	0.4	166	85	30	6.7	4.5	2.2
3508	0.4	157	81	59	6.8	4.7	2.1
3509	0.5	159	99	65	6.5	4.5	2.0
3510	0.4	188	77	28	6.4	4.2	2.2
Mean	0.43	164.5	78.3	38.8	6.30	4.22	2.08
SD	0.05	29.0	11.3	14.5	0.34	0.30	0.17
N	10	10	10	10	10	10	10
tCtrl	1.08	0.86	1.08	0.93	1.02	0.90	1.36

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

30 ug/dose Group 3	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
3501	2.0	10.7	7.0	142	4.2	102	N
3502	2.1	10.3	7.1	141	4.4	100	N
3503	2.3	10.7	7.5	140	4.9	101	N
3504	1.6	10.9	8.1	140	4.6	100	N
3505	1.9	10.5	7.5	141	5.3	102	N
3506	2.0	11.0	6.3	142	4.9	100	N
3507	2.0	10.8	8.8	143	5.3	102	N
3508	2.2	11.0	7.6	143	4.6	100	N
3509	2.3	10.6	6.3	142	5.0	100	N
3510	1.9	10.9	6.3	142	5.1	100	N
Mean	2.03	10.74	7.25	141.6	4.83	100.7	-
SD	0.21	0.23	0.83	1.1	0.37	0.9	-
N	10	10	10	10	10	10	10
tCtrl	0.65	1.04	1.05	1.00	1.01	0.99	-

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
4501	175	38	96	2 [a]	1616	0.06	14
4502	164	62	112	2 [a]	1045	0.05	15
4503	122	40	83	2 [a]	634	0.06	16
4504	98	39	94	2 [a]	634	0.07	12
4505	87	31	81	2 [a]	357	0.12	12
4506	66	29	87	2 [a]	107	0.10	11
4507	50	28	85	2 [a]	96	0.10	15
4508	126	39	117	2 [a]	658	0.06	11
4509	125	72	82	2 [a]	503	0.08	10
4510	76	42	69	2 [a]	146	0.06	13
Mean	108.9	42.0	90.6	1.5	579.6	0.076	12.9
SD	41.0	14.2	14.6	0.0	471.8	0.023	2.0
N	10	10	10	10	10	10	10
tCtrl	1.18	1.02	0.91	1.00	1.43	1.65	0.81

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
4501	0.5	154	78	47	6.2	4.1	2.1
4502	0.4	153	91	35	5.8	3.8	2.0
4503	0.4	151	58	27	6.3	4.4	1.9
4504	0.4	131	87	48	6.5	4.4	2.1
4505	0.4	112	73	47	6.3	3.9	2.4
4506	0.4	162	75	38	6.3	4.0	2.3
4507	0.4	175	80	35	6.7	4.4	2.3
4508	0.4	166	66	49	6.2	3.8	2.4
4509	0.3	113	100	64	7.1	4.8	2.3
4510	0.4	142	53	34	6.2	4.0	2.2
Mean	0.40	145.9	76.1	42.4	6.36	4.16	2.20
SD	0.05	21.4	14.5	10.6	0.35	0.33	0.17
N	10	10	10	10	10	10	10
tCtrl	1.00	0.76	1.05	1.02	1.03	0.89	1.44

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 30 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
4501	2.0	10.6	9.0	140	4.6	97	N
4502	1.9	10.1	8.1	140	4.8	99	N
4503	2.3	10.3	7.7	140	5.1	101	N
4504	2.1	11.3	7.7	143	5.1	102	N
4505	1.6	10.9	8.7	143	4.9	101	N
4506	1.7	10.7	8.0	145	4.7	102	N
4507	1.9	11.5	7.8	143	5.4	101	N
4508	1.6	10.5	7.0	141	4.5	100	N
4509	2.1	11.2	7.8	145	4.9	103	N
4510	1.8	10.7	7.1	143	4.6	102	N
Mean	1.90	10.78	7.89	142.3	4.86	100.8	-
SD	0.23	0.45	0.62	1.9	0.28	1.8	-
N	10	10	10	10	10	10	10
tCtrl	0.61	1.04	1.14	1.00	1.02	0.99	-

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
1011	122	56	169	2 [a]	819	0.06	16
1012	104	40	137	2 [a]	720	0.05	17
1013	114	55	146	2 [a]	643	0.08	16
1014	119	48	156	2 [a]	1043	0.08	17
1015	64	39	135	2 [a]	184	0.12	16
Mean	104.6	47.6	148.6	1.5	681.8	0.078	16.4
SD	23.7	8.0	14.1	0.0	316.3	0.027	0.5
N	5	5	5	5	5	5	5

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
1011	0.3	185	64	67	5.9	4.1	1.8
1012	0.3	217	79	43	5.5	3.6	1.9
1013	0.3	199	64	43	5.5	4.1	1.4
1014	0.3	213	74	54	5.8	4.0	1.8
1015	0.4	266	70	86	5.2	3.8	1.4
Mean	0.32	216.0	70.2	58.6	5.58	3.92	1.66
SD	0.04	30.7	6.5	18.2	0.28	0.22	0.24
N	5	5	5	5	5	5	5

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
1011	2.3	9.9	6.7	140	4.9	103	N
1012	1.9	10.0	8.3	139	5.4	101	N
1013	2.9	9.7	8.2	139	5.3	102	N
1014	2.2	9.7	7.0	141	5.3	103	N
1015	2.7	10.0	7.5	140	5.2	101	N
Mean	2.40	9.86	7.54	139.8	5.22	102.0	-
SD	0.40	0.15	0.71	0.8	0.19	1.0	-
N	5	5	5	5	5	5	5

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
4011	106	48	133	2 [a]	648	0.09	15
4012	76	44	160	2 [a]	163	0.07	16
4013	98	51	131	2 [a]	215	0.05	17
4014	92	45	153	2 [a]	411	0.08	15
4015	78	41	150	2 [a]	463	0.09	15
Mean	90.0	45.8	145.4	1.5	380.0	0.076	15.6
SD	12.9	3.8	12.8	0.0	196.2	0.017	0.9
N	5	5	5	5	5	5	5
tCtrl	0.86	0.96	0.98	1.00	0.56	0.97	0.95

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
4011	0.3	178	73	56	5.5	3.9	1.6
4012	0.3	211	50	33	5.8	4.0	1.8
4013	0.3	223	75	51	5.6	3.8	1.8
4014	0.4	133	78	40	5.9	4.2	1.7
4015	0.3	239	57	38	6.1	4.1	2.0
Mean	0.32	196.8	66.6	43.6	5.78	4.00	1.78
SD	0.04	42.1	12.3	9.6	0.24	0.16	0.15
N	5	5	5	5	5	5	5
tCtrl	1.00	0.91	0.95	0.74	1.04	1.02	1.07

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Male Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
4011	2.4	9.8	7.2	141	4.7	103	N
4012	2.2	10.3	9.0	140	5.1	103	N
4013	2.1	10.2	9.3	142	4.9	104	N
4014	2.5	10.0	8.2	141	4.9	102	N
4015	2.0	10.2	7.2	140	5.2	101	N
Mean	2.24	10.10	8.18	140.8	4.96	102.6	-
SD	0.21	0.20	0.98	0.8	0.19	1.1	-
N	5	5	5	5	5	5	5
tCtrl	0.93	1.02	1.08	1.01	0.95	1.01	-

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
1511	58	29	76	2 [a]	103	0.04	15
1512	69	47	50	2 [a]	177	0.09	17
1513	91	34	93	2 [a]	483	0.04	22
1514	89	35	77	2 [a]	273	0.07	22
1515	90	65	76	2 [a]	130	0.05	16
Mean	79.4	42.0	74.4	1.5	233.2	0.058	18.4
SD	15.0	14.5	15.4	0.0	153.9	0.022	3.4
N	5	5	5	5	5	5	5

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
1511	0.3	142	53	29	6.7	5.2	1.5
1512	0.4	165	71	59	6.7	5.0	1.7
1513	0.4	186	68	40	6.5	4.6	1.9
1514	0.4	191	82	35	5.9	4.5	1.4
1515	0.4	237	74	38	6.5	4.9	1.6
Mean	0.38	184.2	69.6	40.2	6.46	4.84	1.62
SD	0.04	35.3	10.6	11.3	0.33	0.29	0.19
N	5	5	5	5	5	5	5

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 43 Relative to Start Date

0 ug/dose Group 1	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
1511	3.5	10.3	9.9	144	4.3	105	N
1512	2.9	10.5	7.5	139	4.4	104	N
1513	2.4	10.1	7.9	138	4.7	103	N
1514	3.2	10.4	8.8	138	4.6	100	N
1515	3.1	10.7	9.1	138	4.8	101	N
Mean	3.02	10.40	8.64	139.4	4.56	102.6	-
SD	0.41	0.22	0.96	2.6	0.21	2.1	-
N	5	5	5	5	5	5	5

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	CK (U/L)	TBIL (mg/dL)	UREAN (mg/dL)
4511	83	42	91	2 [a]	329	0.03	21
4512	101	49	90	2 [a]	580	0.09	17
4513	150	48	87	2 [a]	1550	0.05	14
4514	79	31	63	2 [a]	239	0.06	17
4515	99	31	75	2 [a]	223	0.05	19
Mean	102.4	40.2	81.2	1.5	584.2	0.056	17.6
SD	28.3	8.8	12.0	0.0	558.5	0.022	2.6
N	5	5	5	5	5	5	5
tCtrl	1.29	0.96	1.09	1.00	2.51	0.97	0.96

[a] [RC:Assigned value below the reportable range]

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	CREAT (mg/dL)	GLUC (mg/dL)	CHOL (mg/dL)	TRIG (mg/dL)	TPROT (g/dL)	ALB (g/dL)	GLOB (g/dL)
4511	0.4	143	77	36	7.0	5.0	2.0
4512	0.4	165	82	46	6.9	5.1	1.8
4513	0.3	137	79	54	6.6	4.8	1.8
4514	0.4	151	61	25	7.1	5.0	2.1
4515	0.4	142	68	41	5.7	4.2	1.5
Mean	0.38	147.6	73.4	40.4	6.66	4.82	1.84
SD	0.04	10.9	8.7	10.9	0.57	0.36	0.23
N	5	5	5	5	5	5	5
tCtrl	1.00	0.80	1.05	1.00	1.03	1.00	1.14

Appendix 12
Individual Clinical Chemistry Values

5002400

Sex: Female Day: 43 Relative to Start Date

96 ug/dose Group 4	Reporting Biochemistry						
	A/G (ratio)	CA (mg/dL)	PHOS (mg/dL)	NA (mmol/L)	K (mmol/L)	CL (mmol/L)	SAMQ
4511	2.5	10.3	6.5	140	4.6	104	N
4512	2.8	10.4	6.4	136	4.9	100	N
4513	2.7	10.0	6.8	140	4.5	103	N
4514	2.4	10.5	8.4	139	4.9	103	N
4515	2.8	10.2	7.6	140	4.5	104	N
Mean	2.64	10.28	7.14	139.0	4.68	102.8	-
SD	0.18	0.19	0.85	1.7	0.20	1.6	-
N	5	5	5	5	5	5	5
tCtrl	0.87	0.99	0.83	1.00	1.03	1.00	-

Appendix 13

Individual Blood Marker (α1-acid Glycoprotein and α2-macroglobulin) Values Explanation Page

Abbreviation	Description	Abbreviation	Description
./--	No findings / Dead	QNS	Quantity not sufficient
CLOT	Sample clotted	SNR	Sample not received
NC	Not calculable	TNR	Test not reported
NR	Not reported	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 13

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

Scheduled Euthanasia - Day 30
Males

Group 1 - Reference Item

Group	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
1	1001	26396.52	17288.07
	1002	23174.16	17260.22
	1003	36777.99	18753.96
	1004	36237.95	14399.91
	1005	20415.21	12198.38
	1006	53456.50	23796.72
	1007	24420.57	13295.90
	1008	31086.47	15821.51
	1009	39958.21	8734.83
	1010	41157.37	9686.13

Appendix 13

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

Scheduled Euthanasia - Day 30
Males

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
2	2001	60755.62	10199.29
	2002	121775.15	13395.56
	2003	108554.99	35129.93
	2004	150513.87	41784.61
	2005	175275.23	143503.21
	2006	508147.75	387911.80
	2007	150428.55	36612.64
	2008	106967.49	8989.39
	2009	146163.81	64134.70
	2010	120128.69	73864.04

Appendix 13

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

Scheduled Euthanasia - Day 30
Males

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
3	3001	282903.49	350881.78
	3002	247110.79	197979.90
	3003	398221.73	156650.21
	3004	599343.33	117678.64
	3005	238377.50	539936.00
	3006	314791.97	200412.55
	3007	458390.34	310755.91
	3008	611951.33	496536.39
	3009	379635.95	222373.15
	3010	316105.11	211328.71

Appendix 13

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

Scheduled Euthanasia - Day 30
Males

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
4	4001	495995.98	176206.63
	4002	435464.79	566929.17
	4003	559835.60	928325.18
	4004	601453.77	543125.62
	4005	543478.84	931978.52
	4006	600747.33	1162478.63
	4007	819977.15	2704407.69
	4008	870283.53	2206412.80
	4009	934641.29	1377130.77
	4010	1041647.55	1627070.62

Appendix 13

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

Scheduled Euthanasia - Day 30
Females

Group 1 - Reference Item

Group	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
1	1501	19766.76	9134.90
	1502	40488.16	10008.82
	1503	30842.32	7025.20
	1504	30110.41	12355.40
	1505	20679.64	8995.39
	1506	20632.91	9047.92
	1507	27460.06	6754.16
	1508	24380.62	9017.17
	1509	22228.30	8623.75
	1510	21665.72	7070.00

Appendix 13

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

Scheduled Euthanasia - Day 30
Females

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
2	2501	72839.70	6656.66
	2502	58050.84	2735.62
	2503	79638.96	14621.02
	2505	35858.21	16489.47
	2506	48669.39	12184.00
	2507	113707.51	5342.89
	2508	114068.44	8910.72
	2509	50870.80	19351.24
	2510	65571.03	8372.44
	2604	32286.68	10455.03

Appendix 13

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

Scheduled Euthanasia - Day 30
Females

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
3	3501	262417.54	25938.66
	3502	341510.20	106581.54
	3503	267052.66	19170.67
	3504	265338.68	34602.18
	3505	117196.58	13682.43
	3506	283407.28	118003.28
	3507	381693.55	30108.75
	3508	171339.85	30019.94
	3509	485357.39	14690.52
	3510	452220.11	308177.98

Appendix 13

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

Scheduled Euthanasia - Day 30
Females

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
4	4501	481832.35	445942.05
	4502	478876.51	50287.35
	4503	598602.57	122908.01
	4504	615584.22	423127.33
	4505	788455.85	361202.96
	4506	719395.05	1054847.18
	4507	555033.92	961354.37
	4508	1062697.72	1089688.75
	4509	595366.16	109847.88
	4510	603984.55	347461.25

Appendix 13

Individual 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	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
1	1011	55881.40	9943.34
	1012	34474.28	10731.55
	1013	32329.51	7406.61
	1014	27590.25	7439.91
	1015	24607.11	6007.16
4	4011	41512.72	16056.57
	4012	33404.68	18850.71
	4013	35666.78	41359.42
	4014	29036.89	17307.38
	4015	20332.81	22092.68

Appendix 13

Individual 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	Animal Number	α1-acid Glycoprotein ng/mL	α2-macroglobulin ng/mL
1	1511	14444.36	7058.09
	1512	20435.75	13358.05
	1513	24553.02	5757.68
	1514	35771.21	5120.24
	1515	15259.80	5819.72
4	4511	22420.80	14550.84
	4512	21136.20	21607.62
	4513	20451.79	11741.92
	4514	9944.11	11055.74
	4515	30191.98	3333.09

Appendix 14

charles river

FINAL REPORT

Study Phase: Ophthalmology Evaluation

Test Facility Study No. 5002400

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

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Appendix 14

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Appendix 14

LIST OF APPENDICES

Appendix 14

1. INTRODUCTION

This report presents the ophthalmology evaluations for the study entitled *A 1-Month (3 doses) Intramuscular Injection Toxicity Study of mRNA-1893 in Sprague-Dawley Rats followed by a 2-Week Recovery Period* (Study No. 5002400).

For the work detailed in this report, the ophthalmology phase start date was 13 Nov 2018, and the ophthalmology phase completion date was 28 Dec 2018.

2. MATERIALS AND METHODS

Experimental procedures applicable to ophthalmology evaluations are summarized in Text Table 1.

Text Table 1
Experimental Design

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

2.1. Ophthalmic Examinations

Frequency: Examinations were performed once prior to start of dosing, toward the end of Week 4 of the dosing period and during Week 2 of the recovery period (Week 6).

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

2.2. Computerized Systems

The following critical computerized system was used by the Test Facility in the generation of this report (Text Table 2).

Text Table 2
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	10	Ophthalmic evaluations

Appendix 14

3. RESULTS AND DISCUSSION

(Appendix 1)

3.1. Prestudy Evaluation

Background findings were recorded and recommendations for rejection from study groups were made when appropriate.

3.2. Weeks 4 and 6 Evaluation

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

4. CONCLUSIONS

Administration of mRNA-1893 by intramuscular injection for 1 month (3 doses administered every other week) to rats at dose levels of 10, 30, and 96 µg/dose did not result in any test item-related ophthalmic changes.

Appendix 14

5. REPORT APPROVAL

DocuSigned by:
(b) (6)
Signer Name: (b) (6)
Signing Reason: I approve this document
Signing Time: 12-Sep-2019 | 11:39:12 EDT
53F87B1F069C40578B598019F92A3E37

(b) (6)

Appendix 14

Appendix 1
Individual Ophthalmic Findings

Appendix 14

Individual Ophthalmology Observations Explanation Page

Abbreviation	Description	Abbreviation	Description
Abs	Absence	Incomp Dil	Incomplete Dilation
Alt Ref	Altered Reflection	Inc	Increased
Ant	Anterior	Irreg	Irregular Reflectivity
Cap	Capsule	Mac	Macula
Ch	Chamber	Multi	Multifocal
Chor	Choroid	Myd	Mydriatic
C-L	Cell-like	Op	Opacity
C/NJ	Cortical/Nuclear Junction	Pers	Persistent
Conj	Conjunctiva	Pers Pup	Persistent Pupillary
Cont	Control	Pig	Pigmented/Pigmentation
Cort	Cortex	Post	Posterior
Depig	Depigmentation	Refl	Reflectivity
Detach	Detachment	Rej	Rejected
Diff	Diffuse	Ret	Retina
Disch	Discharge	Rupt	Rupture
Dru	Drusen	Subcap	Subcapsular
Endo	Endothelium	Subconj	Subconjunctiva
Foll	Follicular	Sut	Suture
Fov	Fovea	TA	Test Article
Hemo	Hemmorhage	Vac	Vacuole
Hyper	HyperPigmentation	Var Rx	Variation from dosing
Hyperpl	Hyperplasia	Vasc	Vascularization
Hypo	HypoPigmentation	V	Visualize
OD	Right Eye	Visu/Visuali	Visualized
OU	Both Eyes	OS	Left Eye

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note: Only animals with findings are presented in this appendix.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 14

Individual Ophthalmology Observations

5002400

0 ug/dose Group 1 Sex: Male	Observation Type: All Types	Week(s) Relative to Start Date						
		-1	4	6				
1001	Lens Opacity - Nucleus, Right, 1 Very slight	.	X	.				
1002	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	.				
1003	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Focal	X	X	.				
	Cornea, Loss of Luster, Right	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
1004	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	.				
1005	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Focal	X	X	.				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X	.				
1006	Cornea, Loss of Luster, Left	.	X	.				
	Cornea, Loss of Luster, Right	.	X	.				
1007	Lens Opacity - Nucleus, Left, 1 Very slight	.	X	.				
1009	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
1010	Retina/Choroid, Atrophy,Linear, Right, 1 Very slight, Focal	.	X	.				
	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Focal	X	X	.				
1011	Cornea, Loss of Luster, Left	.	X	.				
	Cornea, Loss of Luster, Right	.	X	.				

X=Present

Appendix 14

Individual Ophthalmology Observations

5002400

10 ug/dose Group 2 Sex: Male	Observation Type: All Types	Week(s) Relative to Start Date						
		-1	4	6				
2002	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
2005	Retina/Choroid, Atrophy,Linear, Left, 1 Very slight, Focal	.	X	.				
2007	Cornea, Loss of Luster, Left	.	X	.				
2008	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				

X=Present

Appendix 14

Individual Ophthalmology Observations

5002400

30 ug/dose Group 3 Sex: Male	Observation Type: All Types	Week(s) Relative to Start Date						
		-1	4	6				
3001	Vitreous, Hemorrhage, Right, 2 Slight	.	X	.				
3002	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Focal	.	X	.				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X	.				
3005 !	Lens Opacity - Nucleus, Left, 1 Very slight	X	X	.				
	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Focal	.	X	.				
	Other (see comment)	X	X	.				
3006	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	.				
3008	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
3009	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Multifocal	X	X	.				
3010	Iris, Persist Pupil Membrane, Left	X	X	.				

!=Result comment recorded against 1 or more clinical observations. X=Present

Appendix 14

Individual Ophthalmology Observations

5002400

96 ug/dose Group 4 Sex: Male	Observation Type: All Types	Week(s) Relative to Start Date						
		-1	4	6				
4001	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X	.				
4002	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
4003	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X	.				
4004	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Focal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
4005	Lens Nucleus Prominent, Left	X	X	.				
	Lens Nucleus Prominent, Right	X	X	.				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	.				
4009	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X	.				
4010	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
4011	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	X				
4012	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Focal	.	X	X				

X=Present

Appendix 14

Individual Ophthalmology Observations

5002400

96 ug/dose Group 4 Sex: Male	Observation Type: All Types	Week(s) Relative to Start Date						
		-1	4	6				
4014	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Multifocal	.	X	X				
	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Multifocal	.	X	X				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	.	X				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
4015	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	X				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	X				

X=Present

Appendix 14

Individual Ophthalmology Observations

5002400

0 ug/dose Group 1 Sex: Female	Observation Type: All Types	Week(s) Relative to Start Date						
		-1	4	6				
1501	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X	.				
1504	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
1505	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
1506	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
1507	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	.				
1508	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	.				
1509	Cornea, Loss of Luster, Right	.	X	.				
1510	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	.				
1512	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	X				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	X				
1513	Retina/Choroid, Atrophy,Linear, Right, 2 Slight, Focal	.	X	X				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	X				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	X				
1515	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	X				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	X				

X=Present

Appendix 14

Individual Ophthalmology Observations

5002400

10 ug/dose Group 2 Sex: Female	Observation Type: All Types	Week(s) Relative to Start Date						
		-1	4	6				
2501	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X	.				
2503	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
2505	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Focal	.	X	.				
	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Focal	.	X	.				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	.				
2506	Lens Opacity - Nucleus, Right, 1 Very slight	.	X	.				
	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Focal	.	X	.				
2509	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	.	X	.				

X=Present

Appendix 14

Individual Ophthalmology Observations

5002400

30 ug/dose Group 3 Sex: Female	Observation Type: All Types	Week(s) Relative to Start Date						
		-1	4	6				
3501	Lens Opacity - Nucleus, Right, 1 Very slight	.	X	.				
3504	Vitreous, Hemorrhage, Right, 1 Very slight	X	X	.				
	Lens Opacity, Cortex, Anterior, Right Nasal, 1 Very slight, Focal	X	X	.				
3508	Lens Nucleus Prominent, Left	X	X	.				
	Lens Nucleus Prominent, Right	X	X	.				
3509	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Focal	.	X	.				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				

X=Present

Appendix 14

Individual Ophthalmology Observations

5002400

96 ug/dose Group 4 Sex: Female	Observation Type: All Types	Week(s) Relative to Start Date						
		-1	4	6				
4501	Lens Opacity, Cortex, Anterior, Right, 1 Very slight, Multifocal	.	X	.				
4503	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
4504	Lens Opacity, Cortex, Anterior, Left, 1 Very slight, Focal	.	X	.				
4508	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	.				
4509	Lens Opacity, Cortex, Anterior, Left Superior, 1 Very slight, Focal	X	X	.				
	Lens Opacity, Cortex, Anterior, Right Superior, 1 Very slight, Focal	.	X	.				
4510	Lens Nucleus Prominent, Left	X	X	.				
	Lens Nucleus Prominent, Right	X	X	.				
4511	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	X				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	X	X				
4513	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	.	X	X				
4515	Lens Opacity, Cortex, Anterior, Left Superior, 1 Very slight, Focal	.	X	X				
	Cornea, Opacity, Pinpoint, Left, 1 Very slight, Multifocal	X	.	.				
	Cornea, Opacity, Pinpoint, Left, 2 Slight, Multifocal	.	X	X				
	Cornea, Opacity, Pinpoint, Right, 1 Very slight, Multifocal	X	X	.				
	Cornea, Opacity, Pinpoint, Right, 2 Slight, Multifocal	.	.	X				

X=Present

Appendix 14

Individual Ophthalmology Observations

5002400

Comment Information

Group	Sex	Animal	Week	Observation Type	Comment
3	Male	3005	-1	All Types	OS VITREOUS OPACITY FROM RESOLVING HEMORRHAGE
3	Male	3005	4	All Types	OS VITREOUS OPACITY FROM RESOLVING HEMORRHAGE

Appendix 15

FINAL REPORT

Study Phase: Bioanalytical Report: α1-Acid Glycoprotein and α2-Macroglobulin Analysis

Test Facility Study No. 5002400

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

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Appendix 15

TABLE OF CONTENTS

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LIST OF APPENDICES

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1. LIST OF ABBREVIATIONS

APP	Acute Phase Protein
AGP	α1-Acid Glycoprotein
A2M	α2-Macroglobulin
QC	Quality Control
tQC	Trending Quality Control (Endogenous QC)
LLOQ	Lower Limit of Quantitation
ULOQ	Upper Limit of Quantitation
HQC	High Quality Control
MQC	Mid Quality Control
LQC	Low Quality Control
APP-	Acute Phase Protein Assay Run
APs	Analytical Procedure
SOPs	Standard Operating Procedures

Appendix 15

2. INTRODUCTION

This report describes the biomarker evaluation of α1-acid Glycoprotein and α2-Macroglobulin in rat serum samples from Study No. 5002400 titled *"A 1-Month (3 doses) Intramuscular Injection Toxicity Study of mRNA-1893 in Sprague-Dawley Rats followed by a 2-Week Recovery Period".*

For the work detailed in this report, the AGP and A2M phase experimental start and end dates were 01 Mar 2019 and 07 Mar 2019, respectively.

3. EXPERIMENTAL PROCEDURES

3.1. Materials and Methods

The methodology and materials used for the biomarker analyses was detailed in its respective analytical procedure (only the latest version is appended) and listed in the table below:

Biomarker	Analytical Procedure(s) No.	Validation Study No.(s)
APP	AP.5002400.rtsAPP.01	3600390

3.2. Computerized Systems

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

Text Table 1
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Statistical Reporting System (SRS)	1.4	Statistical analysis
Deviations Information Library	2.1.29	Recording of deviation reports
Mesoscale Discovery Workbench Software (MSD)	4.0.12.1	Data collection for A2M and AGP
Watson LIMS	7.4.2 SP1	Data regression and analysis
Microsoft Excel	2013	Descriptive statistics
Microsoft Word	2013	Reporting of data in the report
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

Appendix 15

4. RESULTS AND DISCUSSIONS

4.1. Standards and Quality Control Samples for APP

Standard, QC preparation and acceptance criteria are described in the latest version of the analytical procedure (Appendix 2). Standard curve and quality control specifications are presented in Text Table 2.

Text Table 2
APP Standard Curve and Quality Controls Specifications

APP ID	Range of the Curve (ng/mL)	LLOQ (ng/mL)	ULOQ (ng/mL)	LQC (ng/mL)	MQC (ng/mL)	HQC (ng/mL)	tQC (ng/mL)
AGP	0.79 to 202.40*	0.79	101.20	2.37	10.12	55.66	8.21
A2M	0.50 to 128.00	0.50	128.00	1.50	12.80	70.40	5.55

* Accessory standard above the ULOQ use to better define the upper portion of the curve.

A total of 5 APP assays were performed (APP-01 to APP-05) and all met the method acceptance criteria. All results were reported from the assays that met the acceptance criteria.

4.2. Study Sample

All study samples collected for APP analyses on Day 30 (for main animals) and on Day 43 (for recovery animals) were analyzed within validated limitations.

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

Appendix 15

5. CONCLUSION

All samples collected for the APP analyses were analyzed using a validated immunoassay method. Based on the acceptable performance of the standards and QCs during sample analysis, it is concluded that the concentration values reported for the study samples are valid. All samples collected during the course of this study were analyzed within validated limitations.

The sample results are presented and interpreted in the Toxicology Report.

Appendix 15

6. REPORT APPROVAL

DocuSigned by:
(b) (6)
Signer Name: (b) (6)
Signing Reason: I approve this document
Signing Time: 12-Sep-2019 | 14:46:39 EDT
83D247F44E394651A4FFAD47F8D9F561

(b) (6)

Appendix 15

Appendix 1
Deviations

Appendix 15

DEVIATIONS

All deviations that occurred during this study phase have been acknowledged by the Study Director, assessed for impact, and documented in the study records. AP deviations occurred. None of the deviations were considered to have impacted the overall integrity of this study phase or the interpretation of the study phase results and conclusions.

Appendix 15

Appendix 2
AP.5002400.rtsAPP.01

Appendix 15

charles river | every step of the way.

ANALYTICAL PROCEDURE

Title: **QUANTITATION OF A2-MACROGLOBULIN AND A1-ACID GLYCOPROTEIN IN RAT SERUM BY MSD® MULTI-SPOT ASSAY SYSTEM**	AP Number: AP.5002400.rtsAPP.01	Effective Date: Signature of AP
	Page 1 of 7 pages	Supersedes: N/A
Prepared by (b) (6) (b) (6)		Date: 28 Feb 2019
Verified by: (b) (6) (b) (6)		Date: 28 Feb 2019
Approved by: (b) (6) (b) (6)		Date: 28 Feb 2019
Approved and Authorization by: (b) (6) (b) (6)		Date: 28 Feb 2019

1. **PURPOSE**

   To describe a multiplex method for the quantitation of α2-macroglobulin (A2M) and α1- acid glycoprotein (AGP) in rat serum by a multi-spot assay system using the MSD® (Meso Scale Discovery) platform.

2. **SCOPE**

   This analytical procedure applies to all personnel performing activities related to this method.

3. **RESPONSIBILITY**

   All staff performing this assay are responsible for compliance with this analytical procedure.

4. **REQUIRED FORM**

   Notes:

   i. *Appendices should be verified by the Scientist or delegate prior to use.*

   ii. *Appendix 1 should be completed and verified by the Scientist or delegate prior to the start of the first assay. Once the appendix is verified, it is valid for use until the end of the study or until it is updated.*

   iii. *Appendix #6 will only be used in the case of repeat analyses.*

   Appendix #1: Assay Information Sheet (*Example of a document*)
   Appendix #2: APP Standards and QCs Preparation Sheet (*Example of a spreadsheet*)
   Appendix #3: Solutions Preparation Sheet (*Example of a spreadsheet*)
   Appendix #4: Study Samples Dilution Sheet (*Example of a spreadsheet*)
   Appendix #5: Acute Phase Protein Panel I Assay Sheet
   Appendix #6: Sample Analysis Instruction Sheet (*Example of a spreadsheet*)

5. **MATERIALS/EQUIPMENT/REAGENT**

   (b) (4)

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No: AP.5002400.rtsAPP.01	Effective Date: Signature of AP	Supersedes: N/A	Page 2 of 7 pages

5.1. Materials/Equipment

(b) (4)

5.2. Acute Phase Protein Panel 1 (rat) kit

(b) (4)

5.2.1. Kit components

(b) (4)

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No: AP.5002400.rtsAPP.01	Effective Date: Signature of AP	Supersedes: N/A	Page 3 of 7 pages

5.3. (b) (4)

5.4. Other reagents

Reagent	Supplier/manufacturer	Catalog #
(b) (4)		

6. **PREPARATION OF ASSAY SOLUTIONS, STANDARDS, QUALITY CONTROLS (QCS) AND STUDY SAMPLES**

(b) (4)

Appendix 15

No: AP.5002400.rtsAPP.01	Effective Date: Signature of AP	Supersedes: N/A	Page 4 of 7 pages

(b) (4)

7. VALIDATED PARAMETERS

Based on the validation study # 3600390						
Parameters	**Results**					
Validated range	Analytes	QCs (ng/mL)				
		LLOQ	ULOQ	LQC	MQC	HQC
	A2M	(b) (4)				
	AGP					
Stability	Analytes	Treatment	Duration			
	A2M and AGP	(b) (4)				
Dilution in Diluent 100	Analytes	Dilution range based on parallelism				
	A2M	(b) (4)				
	AGP					

8. ASSAY PROCEDURE

(b) (4)

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No: AP.5002400.rtsAPP.01	Effective Date: Signature of AP	Supersedes: N/A	Page 5 of 7 pages

(b) (4)

9. **DATA ACQUISITION**

(b) (4)

10. **EXPORTING DATA TO WATSON LIMS**

(b) (4)

Watson Master Assay settings	
Details	
Regression type	(b) (4)
Analyte Info	
Concentration units	(b) (4)
Weighting Factor	
Decimal Places	
Regression Type	

Concentrations of analyte in the Study samples are determined by computer interpolation from the plot of the calibration curve.

Appendix 15

No: AP.5002400.rtsAPP.01	Effective Date: Signature of AP	Supersedes: N/A	Page 6 of 7 pages

11. ACCEPTANCE CRITERIA

11.1. Standard curve

(b) (4)

11.2. Quality Controls (QCs)

(b) (4)

11.3. Run acceptance criteria

(b) (4)

11.4. Samples acceptance criteria

(b) (4)

Appendix 15

No: AP.5002400.rtsAPP.01	Effective Date: Signature of AP	Supersedes: N/A	Page 7 of 7 pages

(b) (4)

11.5. Samples reporting

(b) (4)

12. REVISION HISTORY

Version	Effective date of this version	Updates
01	Signature of AP	N/A

Appendix 15

Assay Information Sheet

Study/Reference number: 5002400 Assay ID:_____

Verified by/date:_____

1-Kit information

Kit	Lot # to be used
Acute Phase Protein Panel 1 (rat) kit	

2-Standards and QC information

2.1 Standard vial

Calibrator ID	Lot # to be used	A2M concentration (ng/mL)	AGP concentration (ng/mL)
Acute Phase Protein Panel 1 (rat) Calibrator Blend			

2.2 Curve range

Curve limit	Standard ID	A2M concentration (ng/mL)	AGP concentration (ng/mL)
ULOQ-2			
ULOQ-1			
LLOQ			

2.3 Standards and quality controls

Standard ID	A2M concentration (ng/mL)	AGP concentration (ng/mL)
STD 9		
STD 8		
STD 7		
STD 6		
STD 5		
STD 4		
STD 3		
STD 2		
STD 1		
STD 0		
HQC-2		
HQC-1		
MQC-2		
MQC-1		
LQC		
ULOQ threshold		
LLOQ threshold		

2.4 Trending QCs

Lot #	A2M Established concentration (ng/mL)	AGP Established concentration (ng/mL)	Study/Assay ID	Assay Date

3. List of analytes to be analyzed

A2M	☐	AGP	☐

4. Additional information or N/A (___)

_____

Reviewed by/date:_____

Appendix #1 (AP.5002400.rtsAPP.01) 1 of 1

Appendix 15

APP Standards and QCs Preparation Sheet

Study/reference number: 5002400 Assay ID: _____

Verified by/date: _____

Reagent ID	Lot #	Inventory ID
(b) (4)		

Frozen **APP Calibrator** thawed **on wet ice** and vortex briefly ( )

Dilution Start time: _____

Standard/ QC ID	Target concentration* (ng/mL)	ID	Stock concentration* (ng/mL)	Stock Volume (µL)	Diluent 100 Volume (µL)	Preparation Performed (√)	Total volume (µL)	Final calculated concentration* (ng/mL)
STD 9	(b) (4)	APP Calibrator	(b) (4)		(b) (4)	( )	(b) (4)	
STD 8		STD 9				( )		
STD 7		STD 8				( )		
STD 6		STD 7				( )		
STD 5		STD 6				( )		
STD 4		STD 5				( )		
STD 3		STD 4				( )		
STD 2		STD 3				( )		
STD 1		STD 2				( )		
STD 0		N/A	N/A	N/A		( )		
HQC-2		STD 9	(b) (4)			( )		
HQC-1		STD 8				( )		
MQC-2		HQC-2				( )		
MQC-1		HQC-1				( )		
LQC		MQC-2				( )		

*For practical reason, only AZM concentrations are represented. Refer to Appendix #1 for the AGP concentrations.

Performed by/date: _____

Comment(s): _____

Reviewed by/date: _____

Appendix #2 (AP.5002400.rtsAPP.01) 1 of 1

Appendix 15

Solutions Preparation Sheet

Study/reference number: 5002400 Assay ID:_____

Verified by/date:_____

Preparation of: **Detection Antibody Solution**				
Reagent ID	Lot #	Inventory ID	Volume (µL)	Performed by/date
(b) (4)			(b) (4)	
Diluent 100				
		Required volume (mL)		

Preparation of: **2X Read Buffer T preparation (RB 2X)**				
Reagent ID	Lot #	Inventory ID	Volume (mL)	Performed by/date
(b) (4)			(b) (4)	
	N/A			
		Required volume (mL)		

Comment(s):_____

_____

Reviewed by/date:_____

Appendix #3 (AP.5002400.rtsAPP.01) 1 of 1

Appendix 15

Study Samples Dilution Sheet

Study/reference number: 5002400 Assay ID:_____

Verified by/date:_____

Reagent	Lot #	Inventory ID
(b) (4)		

Sample ID	Dilution Fold	Stock ID	Sample Volume (µL)	Diluent 100 Volume (µL)	Dilution Performed (√)	Total Volume (µL)
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	
					( )	

Performed by/date:_____

Comment(s):_____

_____

Reviewed by/date:_____
Appendix #4 (AP.5002400.rtsAPP.01) 1 of 1

Appendix 15

Acute Phase Protein Panel I Assay Sheet

Study/reference number: 5002400 Assay ID:_____

Reagents/solutions/instruments/material used		
Name	**Lot #/ batch #/ Inventory ID/ ID**	**Entered by/date**
(b) (4)	Lot #:_____ Inventory ID:_____	
	Refer to Appendix #3.	

PLATE SEQUENCE (printed from Watson)

Comments:_____

Reviewed by/date:_____
Appendix #5 (AP.5002400.rtsAPP.01) 1 of 4

Appendix 15

Acute Phase Protein Panel I Assay Sheet

Study/reference number: 5002400

Steps	Time /Performed (√)				Performed by/date
	Assay ID:	Assay ID:	Assay ID:	Assay ID:	
(b) (4)	( )	( )	( )	( )	
	Start: Finish:	Start: Finish:	Start: Finish:	Start: Finish:	
	( )	( )	( )	( )	
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*Refers to Standards, QCs and Study samples

Comment(s):_____

Reviewed by/date:_____

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Appendix 15

Acute Phase Protein Panel I Assay Sheet

Study/reference number: 5002400

DATA REVIEW				
Assay acceptance criteria	Assay ID:		Assay ID:	
	A2M	AGP	A2M	AGP
Number of working STDs*	/	/	/	/
Number of LQCs**	/	/	/	/
Number of MQCs**	/	/	/	/
Number of HQCs**	/	/	/	/
Number of APP tQCs**	/	/	/	/
Total number of QCs meeting acceptance criteria.	/	/	/	/
Entered by/date				

*with a % theoretical within 80 - 120%.

** with a % theoretical within 70 - 130% and %CV between replicate values ≤ 20%.

SCIENTIFIC REVIEW				
Assay acceptance criteria	Assay ID:		Assay ID:	
	A2M	AGP	A2M	AGP
Assay is acceptable	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A
Entered by/date				

Comment(s): _____

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Reviewed by/date:_____

Appendix #5 (AP.5002400.rtsAPP.01) 3 of 4

Appendix 15

Acute Phase Protein Panel I Assay Sheet

Study/reference number: 5002400

DATA REVIEW				
Assay acceptance criteria	Assay ID:		Assay ID:	
	A2M	AGP	A2M	AGP
Number of working STDs*	/	/	/	/
Number of LQCs**	/	/	/	/
Number of MQCs**	/	/	/	/
Number of HQCs**	/	/	/	/
Number of APP tQCs**	/	/	/	/
Total number of QCs meeting acceptance criteria.	/	/	/	/
Entered by/date				

*with a % theoretical within 80 - 120%.

** with a % theoretical within 70 - 130% and %CV between replicate values ≤ 20%.

SCIENTIFIC REVIEW				
Assay acceptance criteria	Assay ID:		Assay ID:	
	A2M	AGP	A2M	AGP
Assay is acceptable	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A
Entered by/date				

Comment(s): _____

Reviewed by/date:_____

Appendix #5 (AP.5002400.rtsAPP.01)

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Appendix 15

Sample Analysis Instruction Sheet

Study/reference number: 5002400 Assay ID:_____

Verified by / Date: _____

Time: _____

	Analyte(s) to be analyzed for each sample ID	
Sample ID	A2M	AGP

✓ = To be analyzed

Comment(s): _____

_____

Reviewed by/date:_____

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Appendix 16

NON-GLP FINAL REPORT

Study Phase: Biomarkers

Test Facility Study No. 5002400

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

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LIST OF TABLES

LIST OF APPENDICES

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1. LIST OF ABBREVIATIONS

QC	Quality Control
LQC	Low concentration Quality Control
MQC	Mid concentration Quality Control
HQC	High concentration Quality Control
LLOQ	Lower Limit of Quantitation
ULOQ	Upper Limit of Quantitation
Cyt-	Cytokines
IL-1β	Interleukin 1-beta
IL-6	Interleukin 6
TNF-α	Tumor Necrosis Factor-alpha
IP-10	Interferon gamma-induced protein 10
MCP-1	Monocyte Chemoattractant Protein-1
MIP-1α	Macrophage Inflammatory Proteins-1α
APs	Analytical Procedures
SOPs	Standard Operating Procedures
PIS	Post Infusion Start

Appendix 16

2. INTRODUCTION

This report describes the biomarkers evaluation of cytokines (IL-1ß, IL-6, IP-10, MCP-1, MIP-1α, and TNF-α) in rat plasma (K_2EDTA) samples from Study No. 5002400 titled "*A 1-Month (3 doses) Intramuscular Injection Toxicity Study of mRNA-1893 in Sprague-Dawley Rats followed by a 2-Week Recovery Period".*

For the work detailed in this report, the Biomarkers phase experimental start and end dates were 09 Jan 2019 and 05 Feb 2019, respectively.

3. EXPERIMENTAL PROCEDURES

3.1. Materials and Methods

The methodology and materials used for the biomarkers analyses was detailed in its respective analytical procedure and listed in the table below (only the latest version is appended):

Biomarker	Analytical Procedures Nos.
Cytokines (IL-1β, IL-6, IP-10, MCP-1, MIP-1α and TNF-α)	AP.5002400.Cyt.01

3.2. Computerized Systems

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

Text Table 1
Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Deviations Informations Library	2.1.29	Deviations
Bio Plex Manager (Bio-Rad)	6.1	Data acquisition for IL-1β, IL-6, IP-10, MCP-1, MIP-1α and TNF-α cytokines
Watson LIMS	7.4.2 SP1	Data regression and analysis
Microsoft Excel	2013	Descriptive statistics
Microsoft Word	2013	Reporting of data in the report
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

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4. RESULTS AND DISCUSSIONS

4.1. Standards and Quality Control Samples for Cytokines

Standard, Quality control (QC) preparation and acceptance criteria are described in the latest version of the analytical procedure (Appendix 2). Standard curve and quality control specifications are presented in Text Table 2.

Text Table 2
Cytokines Standard Curve and Quality Controls Specifications

Cytokine ID	Range of the Curve (pg/mL)	LLOQ (pg/mL)	ULOQ (pg/mL)	LQC (pg/mL)	tQC (pg/mL)	MQC (pg/mL)	HQC (pg/mL)
IL-1β	2.93* to 3000.00*	46.88	1500.00	75.00	357.77	600.00	900.00
IL-6	87.89* to 90000.00*	351.56	45000.00	900.00	1575.73	18000.00	27000.00
IP-10	2.93* to 3000.00*	11.72	1500.00	30.00	88.19	600.00	900.00
MCP-1	35.16* to 36000.00*	140.63	9000.00	360.00	714.15	2700.00	7200.00
MIP-1α	2.93* to 3000.00*	11.72	1500.00	30.00	174.84	600.00	900.00
TNF-α	2.93 to 3000.00*	2.93	375.00	8.44	89.63	75.00	225.00

* Accessory Standards below the LLOQ or above the ULOQ used to better define the lower or upper ends of the curve.

A total of 11 study sample assays runs (2Cyt-01 to 2Cyt-11) were performed for cytokines IP-10 and MCP-1, and all assays met the method acceptance criteria. All acceptable results were reported.

A total of 17 study sample assays runs (4Cyt-01 to 4Cyt-17) were performed for cytokines IL-1β, IL-6, MIP-1α, and TNF-α, and 12 out of 17 assay runs met the method acceptance criteria. All results were reported from the assays that met the acceptance criteria.

In assay run 4Cyt-01, QC samples for all cytokines (IL-1β, IL-6, MIP-1α, and TNF-α) did not meet acceptance criteria (% theoretical < 75%). A technical oversight was suspected during the preparation of the QCs for all cytokines. The samples in this assay run were repeated in assay run 4Cyt-13 and the assay met acceptance criteria indicating a technical oversight was the issue of the failed assay and not a method related issue.

In assay runs 4Cyt-03 and 4Cyt-05, both tQCs for IL-1β did not meet acceptance criteria (% theoretical > 125%). A technical oversight was suspected during the preparation and/or loading of the tQCs. The samples in these assay runs were repeated in runs 4Cyt-14 and 4Cyt-15 and both met acceptance criteria.

In assay runs 4Cyt-12 and 4Cyt-14, the QCs for TNF-α did not meet acceptance criteria (% theoretical < 75%). A technical oversight was suspected during the preparation and/or loading of the QCs for TNF-α. The samples in this assay run were repeated in assay runs 4Cyt-16 and 4Cyt-17 and both met acceptance criteria.

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4.2. Study Sample

All blood samples collected for cytokines analyses at 2 and 6 hours PIS on Days 1, 15, and 29, and on Day 43 were processed to plasma, and analyzed in duplicate using a multiplex bead assay method. Based on the acceptable performance of the standards and QCs during sample analysis, it is concluded that the concentration values reported for the study samples are valid.

Sample 3006 Day 29 6 hours PIS, during IP-10 analysis, had a % CV between replicate wells greater than 20% on the first and repeat analysis. The mean of the original and the repeat values was reported for information purposes and excluded from the calculations.

4.3. Cytokines Interpretation

The upper limit of the baseline range of concentrations was defined as the overall baseline mean (Reference group values for all animals, all timepoints) plus 2 standard deviations. Calculations were done separately for females and males. Fold changes are determined by the ratio of the measured Cytokine concentrations over the upper limit of the baseline range of concentrations. Any fold change that was greater than the reference group fold changes was considered to be mRNA-1893-related. Results are presented in Table 1 and Appendix 3.

4.3.1. Cytokines

The upper limit of the baseline ranges are presented in Text Table 3. Fold increases of cytokines (IL-1β, IL-6, IP-10, MCP-1, MIP-1α, and TNF-α) are presented in Text Table 4.

Text Table 3
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

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Text Table 4
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	-
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	-

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

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Text Table 4
Fold Increase of Cytokines (Cont'd)

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
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).

4.3.1.1. IL-1ß

mRNA-1893-related increase in IL-1β concentration was observed at ≥ 30 ug/dose at 6 hours PIS on Days 15 and 29 and at 96 ug/dose at 2 hours PIS on Day 1 for males and at 6 hours PIS on Day 1 for females. Peak increases were observed at 6 hours PIS 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 ug/dose, respectively. All animals returned to baseline levels at Day 43.

4.3.1.2. IL-6

mRNA-1893-related increases in IL-6 concentration were observed at 30 ug/dose on Day 15 2 hours PIS (females) and on Day 29 6 hours PIS (males). Increases were also observed at 96 ug/dose at 6 hours PIS on Day 15 for males only. IL-6 concentration fold increases, gender

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combined, over the upper limit of baseline levels ranged from 1.5-3.0 and 1.7 at 30, and 96 ug/dose, respectively. All animals returned to baseline levels at Day 43.

4.3.1.3. IP-10

mRNA-1893-related increases in IP-10 concentration were observed at ≥ 30 ug/dose at 2 and 6 hours PIS on Days 1, 15, and 29 for males. In females, mRNA-1893-related increases in IP-10 concentration were observed at 10 ug/dose at 2 and 6 hours PIS on Days 1, 15, and 29 and at ≥ 30 ug/dose at 6 hours PIS 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 ug/dose, respectively and from 1.1-2.3 for female only at 10 ug/dose. All animals returned to baseline levels at Day 43.

4.3.1.4. MCP-1

mRNA-1893-related increases in MCP-1 concentration were observed in females only at 10 ug/dose on Day 15 at 2 hours PIS and at 96 ug/dose on Days 1 and 15 at 6 hours PIS. MCP-1 concentration fold increases, in female 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 ug/dose, respectively. All animals returned to baseline levels at Day 43.

4.3.1.5. MIP-1α

mRNA-1893-related increases in MIP-1α concentration were observed at 96 ug/dose at 2 hours PIS 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 ug/dose for the male. All animals returned to baseline levels at Day 43.

4.3.1.6. TNF-a

There were no mRNA-1893-related increases in TNF-α concentration were observed.

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5. CONCLUSION

mRNA-1893-related increases in IL-1β, IL-6, IP-10, MCP-1and MIP-1α (male) concentrations were observed. mRNA-1893-related increases were observed as follows:

- For IL-1β, at ≥ 30 ug/dose at 6 hours PIS on Days 15 and 29 and at 96 ug/dose at 2 hours PIS on Day 1 for males and at 6 hours PIS on Day 1 for females. Peak increases were observed at 6 hours PIS on Day 29 in males and Day 15 in females.
- For IL-6, at 30 ug/dose on Day 15 2 hours PIS (females) and on Day 29 6 hours PIS (males). Increases were also observed at 96 ug/dose at 6 hours PIS on Day 15 for males only.
- For IP-10, at ≥ 30 ug/dose at 2 and 6 hours PIS on Days 1, 15, and 29 for males. In females, mRNA-1893-related increases in IP-10 concentration were observed at 10 ug/dose at 2 and 6 hours PIS on Days 1, 15, and 29 and at ≥ 30 ug/dose at 6 hours PIS on Days 1, 15, and 29.
- For MCP-1, in females only, at 10 ug/dose on Day 15 at 2 hours PIS and at 96 ug/dose on Days 1 and 15 at 6 hours PIS.
- For MIP-1α, at 96 ug/dose at 2 hours PIS on Days 1 and 15 in males only.
- For IL-1β, IL-6, IP-10, MCP-1 and MIP-1α, all animals returned to baseline levels at Day 43.

Appendix 16

6. REPORT APPROVAL

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Signing Reason: I approve this document
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Appendix 16

Table 1
Summary of Cytokines Values

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Summary of Cytokines Values

IL-1β (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	46.880	46.880	46.880	46.880	46.880	59.630	46.880
	SD	0.000	0.000	0.000	0.000	0.000	28.510	0.000
	N	5	5	5	5	5	5	5
2	Mean	46.880	46.880	46.880	46.880	46.880	46.880	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	0	0	0	-21	
3	Mean	46.880	46.880	46.880	133.586	46.880	67.080	
	SD	0.000	0.000	0.000	193.881	0.000	45.169	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	0	185	0	12	
4	Mean	96.958	46.880	46.880	90.420	46.880	181.542	46.880
	SD	111.978	0.000	0.000	65.288	0.000	301.113	0.000
	N	5	5	5	5	5	5	5
	% Diff (G1)	107	0	0	93	0	204	0

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

Appendix 16

Summary of Cytokines Values

IL-6 (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	351.560	351.560	443.044	351.560	351.560	351.560	351.560
	SD	0.000	0.000	204.564	0.000	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
2	Mean	351.560	351.560	351.560	351.560	351.560	351.560	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	-21	0	0	0	
3	Mean	351.560	351.560	351.560	351.560	351.560	485.434	
	SD	0.000	0.000	0.000	0.000	0.000	299.351	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	-21	0	0	38	
4	Mean	351.560	351.560	351.560	462.366	351.560	351.560	351.560
	SD	0.000	0.000	0.000	247.770	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
	% Diff (G1)	0	0	-21	32	0	0	0

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

Appendix 16

Summary of Cytokines Values

IP-10 (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	219.712	207.056	216.828	254.364	251.398	250.200	163.814
	SD	37.325	59.405	36.535	94.375	81.059	89.944	41.313
	N	5	5	5	5	5	5	5
2	Mean	235.770	286.484	257.558	266.708	238.380	235.244	
	SD	61.463	68.860	70.028	73.902	49.956	75.928	
	N	5	5	5	5	5	5	
	% Diff (G1)	7	38	19	5	-5	-6	
3	Mean	261.868	382.598 A	233.208	403.934	251.738	368.698	
	SD	117.338	91.430	89.733	231.624	125.248	198.917	
	N	5	5	5	5	5	4	
	% Diff (G1)	19	85	8	59	0	47	
4	Mean	227.458	481.888 B	283.052	657.816 D	258.590	656.202 A	223.398
	SD	94.988	130.702	112.620	254.115	77.595	375.311	64.512
	N	5	5	5	5	5	5	5
	% Diff (G1)	4	133	31	159	3	162	36

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

Appendix 16

Summary of Cytokines Values

MCP-1 (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	703.150	703.150	1014.942	703.150	864.292	703.150	703.150
	SD	0.000	0.000	697.188	0.000	360.324	0.000	0.000
	N	5	5	5	5	5	5	5
2	Mean	703.150	859.250	880.202	703.150	703.150	703.150	
	SD	0.000	349.050	395.900	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	22	-13	0	-19	0	
3	Mean	703.150	703.150	884.732	703.150	879.228	1086.050	
	SD	0.000	0.000	406.030	0.000	393.722	543.770	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	-13	0	2	54	
4	Mean	703.150	1059.836	703.150	703.150	703.150	877.354	703.150
	SD	0.000	490.736	0.000	0.000	0.000	389.532	0.000
	N	5	5	5	5	5	5	5
	% Diff (G1)	0	51	-31	0	-19	25	0

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

Appendix 16

Summary of Cytokines Values

MIP-1α (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	11.720	11.720	14.736	11.720	11.720	11.720	11.720
	SD	0.000	0.000	6.744	0.000	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
2	Mean	11.720	11.720	11.720	11.720	11.720	11.720	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	-20	0	0	0	
3	Mean	11.720	11.720	11.720	11.720	11.720	11.720	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	-20	0	0	0	
4	Mean	39.888	11.720	17.794	11.720	11.720	11.720	11.720
	SD	62.986	0.000	13.582	0.000	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
	% Diff (G1)	240	0	21	0	0	0	0

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

Appendix 16

Summary of Cytokines Values

TNF-α (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	2.930	2.930	2.930	2.930	2.930	2.930	2.930
	SD	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
2	Mean	2.930	2.930	2.930	2.930	2.930	2.930	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	0	0	0	0	
3	Mean	2.930	2.930	2.930	2.930	2.930	2.930	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	0	0	0	0	
4	Mean	2.930	2.930	2.930	2.930	2.930	2.930	2.930
	SD	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
	% Diff (G1)	0	0	0	0	0	0	0

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

Appendix 16

Summary of Cytokines Values

IL-1β (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	61.000	46.880	63.956	62.352	76.056	46.880	46.880
	SD	31.573	0.000	38.183	34.596	65.240	0.000	0.000
	N	5	5	5	5	5	5	5
2	Mean	77.254	46.880	46.880	46.880	46.880	46.880	
	SD	67.918	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	27	0	-27	-25	-38	0	
3	Mean	46.880	46.880	46.880	104.794	46.880	168.982	
	SD	0.000	0.000	0.000	92.247	0.000	219.412	
	N	5	5	5	5	5	5	
	% Diff (G1)	-23	0	-27	68	-38	260	
4	Mean	46.880	145.560	46.880	317.806	46.880	158.660	46.880
	SD	0.000	220.655	0.000	605.809	0.000	249.948	0.000
	N	5	5	5	5	5	5	5
	% Diff (G1)	-23	210	-27	410	-38	238	0

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

Appendix 16

Summary of Cytokines Values

IL-6 (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	351.560	754.376	351.560	1224.226	421.914	351.560	1069.838
	SD	0.000	900.724	0.000	1714.137	157.316	0.000	1606.118
	N	5	5	5	5	5	5	5
2	Mean	981.652	351.560	551.026	351.560	351.560	351.560	
	SD	1408.929	0.000	446.020	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	179	-53	57	-71	-17	0	
3	Mean	461.344	351.560	1792.092	351.560	1033.880	351.560	
	SD	245.484	0.000	3221.127	0.000	1525.714	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	31	-53	410	-71	145	0	
4	Mean	351.560	351.560	351.560	432.118	351.560	351.560	351.560
	SD	0.000	0.000	0.000	180.133	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
	% Diff (G1)	0	-53	0	-65	-17	0	-67

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

Appendix 16

Summary of Cytokines Values

IP-10 (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	174.448	146.446	200.000	203.444	209.086	129.876	144.636
	SD	43.797	28.581	46.909	45.380	61.847	4.938	16.071
	N	5	5	5	5	5	5	5
2	Mean	203.092	252.414	320.048	260.030	242.568	182.616	
	SD	76.156	83.586	179.642	80.795	101.379	58.924	
	N	5	5	5	5	5	5	
	% Diff (G1)	16	72	60	28	16	41	
3	Mean	142.770	384.030 D	170.598	547.292 D	197.180	573.070 D	
	SD	49.466	158.980	34.483	331.773	61.346	414.891	
	N	5	5	5	5	5	5	
	% Diff (G1)	-18	162	-15	169	-6	341	
4	Mean	141.182	678.100 E	177.016	752.920 E	166.010	1133.914 E	122.586
	SD	14.891	538.053	29.906	611.455	46.354	848.055	37.925
	N	5	5	5	5	5	5	5
	% Diff (G1)	-19	363	-11	270	-21	773	-15

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

Appendix 16

Summary of Cytokines Values

MCP-1 (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	703.150	703.150	703.150	703.150	703.150	703.150	703.150
	SD	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
2	Mean	703.150	703.150	861.458	703.150	703.150	703.150	
	SD	0.000	0.000	353.987	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	23	0	0	0	
3	Mean	703.150	703.150	703.150	703.150	703.150	703.150	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	0	0	0	0	
4	Mean	703.150	851.774	703.150	1222.286	703.150	703.150	703.150
	SD	0.000	332.333	0.000	778.538	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
	% Diff (G1)	0	21	0	74	0	0	0

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

Appendix 16

Summary of Cytokines Values

MIP-1α (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	11.720	11.720	11.720	11.720	11.720	11.720	11.720
	SD	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
2	Mean	11.720	11.720	11.720	11.720	11.720	11.720	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	0	0	0	0	
3	Mean	11.720	11.720	11.720	11.720	11.720	11.720	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	0	0	0	0	0	0	
4	Mean	11.720	11.720	11.720	11.720	11.720	11.720	11.720
	SD	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
	% Diff (G1)	0	0	0	0	0	0	0

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

Appendix 16

Summary of Cytokines Values

TNF-α (pg/mL)
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	Occasion						
		Day 1 - 2 h PD	Day 1 - 6 h PD	Day 15 - 2 h PD	Day 15 - 6 h PD	Day 29 - 2 h PD	Day 29 - 6 h PD	Day 43
1	Mean	6.174	2.930	2.930	2.930	2.930	2.930	2.930
	SD	7.254	0.000	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5	5	5
2	Mean	2.930	2.930	2.930	2.930	2.930	2.930	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	-53	0	0	0	0	0	
3	Mean	2.930	2.930	2.930	2.930	2.930	2.930	
	SD	0.000	0.000	0.000	0.000	0.000	0.000	
	N	5	5	5	5	5	5	
	% Diff (G1)	-53	0	0	0	0	0	
4	Mean	2.930	2.930	2.930	2.930	5.322	4.128	7.376
	SD	0.000	0.000	0.000	0.000	5.349	2.679	9.942
	N	5	5	5	5	5	5	5
	% Diff (G1)	-53	0	0	0	82	41	152

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

Appendix 16

Appendix 1
Deviations

Appendix 16

DEVIATIONS

All deviations that occurred during this study phase have been acknowledged by the Study Director, assessed for impact, and documented in the study records. No Study Plan deviation occurred during this study phase. However, some APs and SOPs deviations occurred. None of the deviations were considered to have impacted the overall integrity of this study phase or the interpretation of the study phase results and conclusions.

Appendix 16

Appendix 2
AP.5002400.Cyt.01

Appendix 16

ANALYTICAL PROCEDURE

charles river | every step of the way.

Title: **MULTIPLEX METHOD FOR THE QUANTITATIVE DETECTION OF IL-1β, IL-6, IP-10, MCP-1, MIP-1α AND TNF-α IN RAT PLASMA**	AP Number: AP.5002400.Cyt.01 Page 1 of 9 pages	Effective Date: Signature of AP Supersedes: N/A
Prepared by: (b) (6) (b) (6)		Date: 08 Jan 2019
Verified by: (b) (6) (b) (6)		Date: 08 Jan 2019
Approved by: (b) (6) (b) (6)		Date: 08 Jan 2019
Authorized by: (b) (6) (b) (6)		Date: 08 Jan 2019

1. **PURPOSE**

   To describe a multiplex method for the quantitation of IL-1β, IL-6, IP-10, MCP-1, MIP-1α and TNF-α in Rat plasma.

2. **SCOPE**

   This analytical procedure applies to all personnel performing activities related to this method.

3. **RESPONSIBILITY**

   All staff performing this assay are responsible for compliance with this analytical procedure.

4. **REQUIRED FORM**

   Notes:
   i. *Appendices should be verified by the Scientist or delegate prior to use.*
   ii. *Appendix #1 should be filled out and verified by the Scientist or delegate prior to the start of the first assay. Once the Appendix #1 is verified, it is valid for use until the end of the study or until it is updated.*

   Appendix #1: Assay Information Sheet (*Example of a document*)
   Appendix #2a: Cytokine Standards and QCs Preparation Sheet (*Example of a spreadsheet*)
   Appendix #2b: tQCs Preparation Sheet (*Example of a spreadsheet*)
   Appendix #3: Study Samples Dilution Sheet (*Example of a spreadsheet*)
   Appendix #4: Beads Working Solution Preparation Sheet (*Example of a spreadsheet*)
   Appendix #5: Cytokine Assay Sheet

5. **MATERIALS/EQUIPMENT/REAGENT**

(b) (4)

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(b) (4)

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6. **PREPARATION OF SOLUTIONS, STANDARDS, QUALITY CONTROLS (QCs) AND STUDY SAMPLES**

(b) (4)

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(b) (4)

7. ASSAY PROCEDURE

(b) (4)

8. LINEARITY OF DILUTION

(b) (4)

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9. **THE BIO-PLEX SUSPENSION ARRAY PROTOCOL**

(b) (4)

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10. EXPORTING DATA TO WATSON LIMS

(b) (4)

11. THE BIO-PLEX MANAGER PRINTOUT

(b) (4)

12. CALCULATION

(b) (4)

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13. **ACCEPTANCE CRITERIA**

(b) (4)

13.2. QC samples

(b) (4)

13.3. Run Acceptance Criteria

(b) (4)

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(b) (4)

13.4. Sample acceptance criteria

(b) (4)

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13.5. Sample reporting

(b) (4)

14. **VERSION HISTORY**

Version	Effective date of this AP	Updates
01	Signature of AP	N/A

Appendix 16

Assay Information Sheet

Study/reference number: 5002400

Verified by/date: _____

1-Kit information

Kit	Lot # to be used
Rat Cytokine/Chemokine Magnetic Bead Panel Kit	

2-Standards and QCs information

2.1 Standard lot to be used

Rat Cytokine/Chemokine Standard lot #: _____

2.2 Working range

Working range	Cytokines (pg/mL)					
	IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
ULOQ						
LLOQ						

2.3 Standard concentration

Standards ID	Cytokines (pg/mL)					
	IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Standard stock						
STD 11						
STD 10						
STD 9						
STD 8						
STD 7						
STD 6						
STD 5						
STD 4						
STD 3						
STD 2						
STD 1						
STD 0						

2.4 Quality control concentration

QC ID	Cytokines (pg/mL)					
	IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
QC 6						
QC 5						
QC 4						
QC 3						
QC 2						
QC 1						

2.5 Trending Quality control to be used

QC ID	Batch #	tQC Concentration (pg/mL)*						Assay ID/date
		IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α	
tQC								

*Dilution is 2 (IL-1β, IL-6, TNF-α and MIP-1α) or 10 (IP-10 and MCP-1).

3-Threshold values

The threshold value for a replicate to reach a limit of 20% CV from LLOQ or ULOQ*							
Cytokines		IL-1β	IL-6	IP-10	MCP-1	MIP-1α	TNF-α
Threshold values (pg/mL)	LLOQ						
	ULOQ						

*Fold dilutions not taken into account.

4-Additional information or N/A (____)

_____

_____

Appendix #1 (AP.5002400.Cyt.01) 1 of 1

Appendix 16

Cytokine Standards and QCs Preparation Sheet

Study/reference number: 5002400 Assay ID:_____

Verified by/date: _____

Reagent ID	Lot #	Inventory ID
Rat Cytokine/Chemokine Standard		
Assay Buffer		

Standard ID	Stock ID	# of vial(s) to be used	Volume of UPW to be added to each vial (µL)	Reconstitution Performed (√)	Invert the vial several times, vortex than left at RT for at least 5 minutes.		Pool vials Performed (√)
STD stock	Standard*	(b) (4)		( )	Start:	End:	Pool vials ( ) or N/A ( )

Standard/ QC ID	Stock ID	Stock Concentration (pg/mL) IL-1β, IP-10, MIP-1α, TNF-α	Stock Concentration (pg/mL) IL-6	Stock Concentration (pg/mL) MCP-1	Stock volume (µL)	Assay Buffer volume (µL)	Preparation performed (√)	Total volume (µL)	Final calculated concentration (pg/mL)** IL-1β, IP-10, MIP-1α, TNF-α	Final calculated concentration (pg/mL)** IL-6	Final calculated concentration (pg/mL)** MCP-1
STD 11	STD stock	(b) (4)					( )	(b) (4)			
STD 10	STD 11						( )				
STD 9	STD 10						( )				
STD 8	STD 9						( )				
STD 7	STD 8						( )				
STD 6	STD 7						( )				
STD 5	STD 6						( )				
STD 4	STD 5						( )				
STD 3	STD 4						( )				
STD 2	STD 3						( )				
STD 1	STD 2						( )				
STD 0	N/A						( )				
QC 6	STD 10						( )				
QC 5	STD 10						( )				
QC 4	STD 10						( )				
QC 3	STD 10						( )				
QC 2	STD 10						( )				
QC 1	STD 5						( )				

*Rat Cytokine/Chemokine Standard. ** Refer to Appendix #1 for target concentrations.

Performed by/date: _____

Comments: _____

Reviewed by/date:_____

Appendix #2a (AP.5002400.Cyt.01) 1 of 1

Appendix 16

tQCs Preparation Sheet

Study/reference number: 5002400 Assay ID:_____

Verified by/date: _____

Reagent ID	Lot #	Inventory ID
Rat Cytokine/Chemokine Standard		
Rat plasma		

Sample ID	Stock ID	# of vial(s) to be used	Volume of Rat plasma to be added to each vial (µL)	Reconstitution Performed (√)	Invert the vial several times, vortex than left at RT for at least 5 minutes.		Pool vials Performed (√)
Spike stock	Standard*	(b) (4)		( )	Start:	End:	Pool vials ( ) or N/A ( )

*Rat Cytokine/Chemokine Standard.

Sample ID	Target concentration(pg/mL)		
	IL-1β, IP-10, MIP-1α, TNF-α	IL-6	MCP-1
tQC	(b) (4)		

Sample ID	Batch #	ID	Stock concentration (pg/mL)			volume (µL)	Rat plasma volume (µL)	Preparation performed (√)	Total volume (µL)	Final calculated concentration (pg/mL)		
			IL-1β, IP-10, MIP-1α, TNF-α	IL-6	MCP-1					IL-1β, IP-10, MIP-1α, TNF-α	IL-6	MCP-1
tQC		STD Stock	(b) (4)					( )	(b) (4)			

Performed by/date: _____

Pipette(s): _____

tQC stored DF or N/A ( ) Freezer ID: _____ Time: _____

Place label here:

Pipette(s): _____

X No aliquots: _____ (if applicable)

Prepared by/date: _____

Comments: _____

Reviewed by/date:_____

Appendix #2b (AP.5002400.Cyt.01) 1 of 1

Appendix 16

Study Samples Dilution Sheet

Study/reference number: 5002400 Assay ID:________________

Verified by/date: ______________________

Reagent	Lot # or Batch #	Inventory ID
Assay Buffer		
tQC		N/A

Sample ID	Dilution fold	Stock volume (µL)	Assay Buffer volume (µL)	Dilution performed (√)	Total volume (µL)
				( )	
				( )	
				( )	
				( )	
				( )	
				( )	
				( )	
				( )	
				( )	
				( )	
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				( )	
				( )	
				( )	

Performed by/date: ______________________

Comment(s): ____

____

Reviewed by/date:________________

Appendix #3 (AP.5002400.Cyt.01) 1 of 1

Appendix 16

Beads Working Solution Preparation Sheet

Study/reference number: 5002400 Assay ID:_____

Verified by/date: _____

Sonicate Rat Antibody Magnetic Beads bottles and then vortex thoroughly before the solution preparation (√)			Performed (√)	( )
Preparation of: **Antibody-Immobilized Beads Working Solution (ABWS)**				
Reagent	Lot #	Inventory ID	Volume (µL)	Performed (√)
(b) (4)			(b) (4)	( )
				( )
				( )
				( )
				( )
				( )
				( )
		Total volume (µL)		Performed (√)
		The Antibody-Immobilized Beads Working Solution was protected from light until use		( )

Sonic bath ID: _____

Performed by/date: _____

Comment(s): _____

Reviewed by/date:_____
Appendix #4 (AP.5002400.Cyt.01) 1 of 1

Appendix 16

Cytokine Assay Sheet

Study/reference number: 5002400 Assay ID:_____

Verified by/date:_____

Reagents/solutions/instruments/material used on Day 1		
Name	**Lot # / Batch # / ID**	**Entered by/date**
(b) (4)	Lot #:_____ Inventory ID:_____	
	Refer to Appendix #4.	

Reagents/solutions/instruments/material used on Day 2		
Name	**Lot # / Batch # / ID**	**Entered by/date**
(b) (4)	Lot #:_____ Inventory ID:_____	

PLATE SEQUENCE (printed from Watson)

Comment(s):

Reviewed by/date:_____

Appendix #5 (AP.5002400.Cyt.01) 1 of 4

Appendix 16

Study/reference number: 5002400 Cytokine Assay Sheet

Steps	Time / Performed (√) Assay ID:	Assay ID:	Assay ID:	Assay ID:	Performed by/date
(b) (4)	( )	( )	( )	( )	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	Start:	Start:	Start:	Start:	
	Finish:	Finish:	Finish:	Finish:	
	( )	( )	( )	( )	
	Wash 1st ( ) 2nd ( )	Wash 1st ( ) 2nd ( )	Wash 1st ( ) 2nd ( )	Wash 1st ( ) 2nd ( )	
	Start:	Start:	Start:	Start:	
	Finish:	Finish:	Finish:	Finish:	
	Start:	Start:	Start:	Start:	
	Finish:	Finish:	Finish:	Finish:	
	( )	( )	( )	( )	
	Wash 1st ( ) 2nd ( )	Wash 1st ( ) 2nd ( )	Wash 1st ( ) 2nd ( )	Wash 1st ( ) 2nd ( )	
	Start:	Start:	Start:	Start:	
	Finish:	Finish:	Finish:	Finish:	
	Prime ( ) Unclog ( ) or N/A ( )	Prime ( ) Unclog ( ) or N/A ( )	Prime ( ) Unclog ( ) or N/A ( )	Prime ( ) Unclog ( ) or N/A ( )	
	( ) or N/A ( )	( ) or N/A ( )	( ) or N/A ( )	( ) or N/A ( )	
	( )	( )	( )	( )	
	( )	( )	( )	( )	
	( )	( )	( )	( )	

* Refers to Standards, QCs and diluted Study samples.

Comment(s):_____

Reviewed by/date:_____

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Appendix 16

Study/reference number: 5002400 Cytokine Assay Sheet

DATA REVIEW						
Acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**IP-10 N/A ( )**	**MCP-1 N/A ( )**	**MIP-1α N/A ( )**	**TNF-α N/A ( )**
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of working STDs*	/	/	/	/	/	/
Number of LQCs**	/	/	/	/	/	/
Number of MQCs**	/	/	/	/	/	/
Number of HQCs**	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/
Assay acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**IP-10 N/A ( )**	**MCP-1 N/A ( )**	**MIP-1α N/A ( )**	**TNF-α N/A ( )**
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of working STDs*	/	/	/	/	/	/
Number of LQCs**	/	/	/	/	/	/
Number of MQCs**	/	/	/	/	/	/
Number of HQCs**	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/

* with a % theoretical within 75 - 125% except for LLOQ and ULOQ which should be within 70 - 130%.
** with a % theoretical within 75 - 125 % and ≤ 20% CV between duplicate values. In addition, at least one replicate has ≥ 30 beads acquired.

Performed by/date: _____

SCIENTIFIC REVIEW						
Acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**TNF-α N/A ( )**	**IP-10 N/A ( )**	**MIP-1α N/A ( )**	**MCP-1 N/A ( )**
Cytokine assay is acceptance	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of beads acquired ≥ 30	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A
Acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**TNF-α N/A ( )**	**IP-10 N/A ( )**	**MIP-1α N/A ( )**	**MCP-1 N/A ( )**
Cytokine assay is acceptance	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of beads acquired ≥ 30	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A

Performed by/date: _____

Reviewed by/date:_____
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Appendix 16

Study/reference number: 5002400 Cytokine Assay Sheet

DATA REVIEW						
Acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**IP-10 N/A ( )**	**MCP-1 N/A ( )**	**MIP-1α N/A ( )**	**TNF-α N/A ( )**
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of working STDs*	/	/	/	/	/	/
Number of LQCs**	/	/	/	/	/	/
Number of MQCs**	/	/	/	/	/	/
Number of HQCs**	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/
Assay acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**IP-10 N/A ( )**	**MCP-1 N/A ( )**	**MIP-1α N/A ( )**	**TNF-α N/A ( )**
(FI) Blank < (FI) LLOQ	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of working STDs*	/	/	/	/	/	/
Number of LQCs**	/	/	/	/	/	/
Number of MQCs**	/	/	/	/	/	/
Number of HQCs**	/	/	/	/	/	/
Total number of QCs meeting the above mentioned acceptance criteria.	/	/	/	/	/	/

* with a % theoretical within 75 - 125% except for LLOQ and ULOQ which should be within 70 - 130%.
** with a % theoretical within 75 - 125 % and ≤ 20% CV between duplicate values. In addition, at least one replicate has ≥ 30 beads acquired.

Performed by/date: _____

SCIENTIFIC REVIEW						
Acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**TNF-α N/A ( )**	**IP-10 N/A ( )**	**MIP-1α N/A ( )**	**MCP-1 N/A ( )**
Cytokine assay is acceptance	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of beads acquired ≥ 30	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A
Acceptance criteria Assay ID:	**IL-1β N/A ( )**	**IL-6 N/A ( )**	**TNF-α N/A ( )**	**IP-10 N/A ( )**	**MIP-1α N/A ( )**	**MCP-1 N/A ( )**
Cytokine assay is acceptance	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Number of beads acquired ≥ 30	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
Study samples to repeat	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A	Yes or No or N/A

Performed by/date: _____

Reviewed by/date:_____
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Appendix 16

Appendix 3
Individual Cytokines Values

Appendix 16

Individual Cytokine Values Explanation Page

Abbreviation	Description	Abbreviation	Description
./--	No findings / Dead	QNS	Quantity not sufficient
CLOT	Sample clotted	SNR	Sample not received
NC	Not calculable	TNR	Test not reported
NR	Not reported	X	Excluded from mean
a	%CV between singlicate values is > 20%. Mean of original and repeat values reported for information purposes only. Not included in the calculations.	PD	Post Dose

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Note:

For IL-1β

Lower Limit of Quantitation (LLOQ) = 46.88 pg/mL (93.76 pg/mL with the dilution factor taken into account), <93.76 was assigned as 93.76/2 (46.88 pg/mL) for statistical analysis purposes.

For IL-6

Lower Limit of Quantitation (LLOQ) = 351.56 pg/mL (703.12 pg/mL with the dilution factor taken into account), <703.12 was assigned as 703.12/2 (351.56 pg/mL) for statistical analysis purposes.

For IP-10

Lower Limit of Quantitation (LLOQ) = 11.72 pg/mL (117.20 pg/mL with the dilution factor taken into account), <111.72 was assigned as 111.72/2 (58.60 pg/mL) for statistical analysis purposes.

For MCP-1

Lower Limit of Quantitation (LLOQ) = 140.63 pg/mL (1406.30 pg/mL with the dilution factor taken into account), <1406.30 was assigned as 1406.30/2 (703.15 pg/mL) for statistical analysis purposes.

For MIP-1α

Lower Limit of Quantitation (LLOQ) = 11.72 pg/mL (23.44 pg/mL with the dilution factor taken into account), <23.44 was assigned as 23.44/2 (11.72 pg/mL) for statistical analysis purposes.

Appendix 16

For TNF-α

Lower Limit of Quantitation (LLOQ) = 2.93 pg/mL (5.86 pg/mL with the dilution factor taken into account), <5.86 was assigned as 5.86/2 (2.93 pg/mL) for statistical analysis purposes.

The upper limit of the normal range of concentrations was defined as:
The overall baseline mean (predose/pretreatment values for all animal* in all groups)** + 2 standard deviations

Incidence of cytokines elevations was reported as:
The number of individual animals* per group with cytokines concentrations > upper limit of baseline range of concentrations.

Fold change was reported as:
The ratio of the measured Cytokine concentration/upper limit of the normal range of concentrations.
The fold change was calculated for each sample and for each group mean, when applicable.

*Calculations was done separately for females and males.
**If predose values were not available, values from all animals of the non-treated group(s) will be used to generate the overall baseline mean.

Dosing Information
Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 16

Individual Cytokines Values

Males

Group 1 - Reference Item

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1006	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	223.23	0	0.6
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	323.10	0	0.9
		Day 29 - 6 h PD	110.63	1	1.6	< 703.12	0	0.7	392.19	1	1.1
	1007	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	216.54	0	0.6
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	145.41	0	0.4
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	168.91	0	0.5
	1008	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	156.82	0	0.4
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	205.68	0	0.6
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	207.05	0	0.6
	1009	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	145.39	0	0.4
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	219.10	0	0.6
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	199.15	0	0.6
	1010	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	293.30	0	0.8
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	378.53	1	1.1
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	283.70	0	0.8

Appendix 16

Individual Cytokines Values

Males

Group 1 - Reference Item

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1011	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	185.81	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	175.16	0	0.5
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	186.32	0	0.5
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	120.05	0	0.3
	1012	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	252.99	0	0.7
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	228.06	0	0.6
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	364.03	0	1.0
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	163.55	0	0.5
	1013	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	208.94	0	0.6
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	256.03	0	0.7
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	200.29	0	0.6
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	207.42	0	0.6
	1014	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	265.00	0	0.7
		Day 15 - 2 h PD	< 93.76	0	0.7	808.98	1	1.6	243.28	0	0.7
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	311.24	0	0.9
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	202.82	0	0.6

Appendix 16

Individual Cytokines Values

Males

Group 1 - Reference Item

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1015	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	185.82	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	181.61	0	0.5
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	195.11	0	0.5
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	125.23	0	0.3

Appendix 16

Individual Cytokines Values

Males

Group 1 - Reference Item

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1006	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	1007	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	1008	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	1009	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	1010	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Males

Group 1 - Reference Item

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1011	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	1012	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	1508.86	1	1.1	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	1013	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	1014	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	2262.11	1	1.7	26.80	1	1.6	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Males

Group 1 - Reference Item

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1015	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Males

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
2	2001	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	269.32	0	0.7
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	309.30	0	0.9
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	238.96	0	0.7
	2002	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	280.69	0	0.8
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	315.48	0	0.9
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	282.55	0	0.8
	2003	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	162.49	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	177.66	0	0.5
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	247.77	0	0.7
	2004	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	175.80	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	184.55	0	0.5
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	154.40	0	0.4
	2005	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	290.55	0	0.8
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	300.80	0	0.8
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	268.22	0	0.7

Appendix 16

Individual Cytokines Values

Males

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
2	2006	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	239.89	0	0.7
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	191.07	0	0.5
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	225.13	0	0.6
	2007	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	191.79	0	0.5
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	230.48	0	0.6
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	203.78	0	0.6
	2008	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	312.65	0	0.9
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	308.85	0	0.9
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	234.65	0	0.7
	2009	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	360.13	0	1.0
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	374.39	0	1.0
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	358.99	0	1.0
	2010	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	327.96	0	0.9
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	228.75	0	0.6
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	153.67	0	0.4

Appendix 16

Individual Cytokines Values

Males

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
2	2001	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	2002	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	2003	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	1588.41	1	1.2	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	2004	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	2005	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Males

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
2	2006	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	2007	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	2008	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	2009	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	2010	Day 1 - 6 h PD	1483.65	1	1.1	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Males

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
3	3001	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	185.20	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	208.13	0	0.6
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	140.50	0	0.4
	3002	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	349.96	0	1.0
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	333.35	0	0.9
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	400.36	1	1.1
	3003	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	424.16	1	1.2
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	320.94	0	0.9
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	371.04	0	1.0
	3004	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	176.87	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	134.45	0	0.4
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	203.21	0	0.6
	3005	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	173.15	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	169.17	0	0.5
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	143.58	0	0.4

Appendix 16

Individual Cytokines Values

Males

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
3	3006	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	323.33	0	0.9
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	244.20	0	0.7
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	170.64 a	NC	NC
	3007	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	350.23	0	1.0
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	263.38	0	0.7
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	210.67	0	0.6
	3008	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	421.85	1	1.2
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	459.49	1	1.3
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	613.93	1	1.7
	3009	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	522.73	1	1.5
		Day 15 - 6 h PD	480.41	1	6.8	< 703.12	0	0.7	787.35	1	2.2
		Day 29 - 6 h PD	147.88	1	2.1	1020.93	1	2.0	447.14	1	1.2
	3010	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	294.85	0	0.8
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	265.25	0	0.7
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	203.05	0	0.6

Appendix 16

Individual Cytokines Values

Males

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
3	3001	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	1611.06	1	1.2	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	3002	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	1583.54	1	1.2	< 23.44	0	0.7	< 5.86	0	1.0
	3003	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	3004	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	3005	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Males

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
3	3006	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	1456.50	1	1.1	< 23.44	0	0.7	< 5.86	0	1.0
	3007	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	3008	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	1864.30	1	1.4	< 23.44	0	0.7	< 5.86	0	1.0
	3009	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	3010	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Males

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4006	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	409.80	1	1.1
		Day 15 - 6 h PD	193.36	1	2.8	< 703.12	0	0.7	960.29	1	2.7
		Day 29 - 6 h PD	720.19	1	10.3	< 703.12	0	0.7	1279.17	1	3.6
	4007	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	378.37	1	1.1
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	349.62	0	1.0
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	272.46	0	0.8
	4008	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	676.45	1	1.9
		Day 15 - 6 h PD	118.10	1	1.7	< 703.12	0	0.7	690.37	1	1.9
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	646.08	1	1.8
	4009	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	387.60	1	1.1
		Day 15 - 6 h PD	< 93.76	0	0.7	905.59	1	1.7	832.02	1	2.3
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	571.14	1	1.6
	4010	Day 1 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	557.22	1	1.5
		Day 15 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	456.78	1	1.3
		Day 29 - 6 h PD	< 93.76	0	0.7	< 703.12	0	0.7	512.16	1	1.4

Appendix 16

Individual Cytokines Values

Males

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4011	Day 1 - 2 h PD	297.27	1	4.2	< 703.12	0	0.7	378.90	1	1.1
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	388.59	1	1.1
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	350.00	0	1.0
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	317.62	0	0.9
	4012	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	165.05	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	180.43	0	0.5
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	157.08	0	0.4
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	211.09	0	0.6
	4013	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	200.69	0	0.6
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	231.26	0	0.6
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	281.80	0	0.8
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	147.68	0	0.4
	4014	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	138.85	0	0.4
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	195.27	0	0.5
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	203.05	0	0.6
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	250.84	0	0.7

Appendix 16

Individual Cytokines Values

Males

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4015	Day 1 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	253.80	0	0.7
		Day 15 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	419.71	1	1.2
		Day 29 - 2 h PD	< 93.76	0	0.7	< 703.12	0	0.7	301.02	0	0.8
		Day 43	< 93.76	0	0.7	< 703.12	0	0.7	189.76	0	0.5

Appendix 16

Individual Cytokines Values

Males

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4006	Day 1 - 6 h PD	1662.32	1	1.2	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	4007	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	4008	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	4009	Day 1 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	4010	Day 1 - 6 h PD	1527.41	1	1.1	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 6 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 6 h PD	1574.17	1	1.2	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Males

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4011	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	4012	Day 1 - 2 h PD	< 1406.30	0	0.5	152.56	1	8.8	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	42.09	1	2.4	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	4013	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
	4014	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Males

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4015	Day 1 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 15 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 29 - 2 h PD	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0
		Day 43	< 1406.30	0	0.5	< 23.44	0	0.7	< 5.86	0	1.0

Appendix 16

Individual Cytokines Values

Females

Group 1 - Reference Item

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1506	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	192.30	0	0.7
		Day 15 - 6 h PD	< 93.76	0	0.4	795.20	0	0.3	168.39	0	0.6
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	122.70	0	0.5
	1507	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	117.96	0	0.4
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	207.14	0	0.8
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	130.10	0	0.5
	1508	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	147.15	0	0.6
		Day 15 - 6 h PD	124.24	0	1.0	< 703.12	0	0.1	253.85	0	1.0
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	130.19	0	0.5
	1509	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	127.67	0	0.5
		Day 15 - 6 h PD	< 93.76	0	0.4	4271.25	1	1.7	240.14	0	0.9
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	136.65	0	0.5
	1510	Day 1 - 6 h PD	< 93.76	0	0.4	2365.64	0	0.9	147.15	0	0.6
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	147.70	0	0.6
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	129.74	0	0.5

Appendix 16

Individual Cytokines Values

Females

Group 1 - Reference Item

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1511	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	246.69	0	0.9
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	178.05	0	0.7
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	199.58	0	0.7
		Day 43	< 93.76	0	0.4	< 703.12	0	0.1	136.06	0	0.5
	1512	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	170.19	0	0.6
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	174.72	0	0.7
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	213.33	0	0.8
		Day 43	< 93.76	0	0.4	< 703.12	0	0.1	121.18	0	0.5
	1513	Day 1 - 2 h PD	117.48	0	1.0	< 703.12	0	0.1	170.00	0	0.6
		Day 15 - 2 h PD	132.26	1	1.1	< 703.12	0	0.1	269.02	0	1.0
		Day 29 - 2 h PD	192.76	1	1.6	703.33	0	0.3	299.74	1	1.1
		Day 43	< 93.76	0	0.4	< 703.12	0	0.1	159.73	0	0.6
	1514	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	156.78	0	0.6
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	225.71	0	0.8
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	207.18	0	0.8
		Day 43	< 93.76	0	0.4	< 703.12	0	0.1	148.74	0	0.6

Appendix 16

Individual Cytokines Values

Females

Group 1 - Reference Item

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
1	1515	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	128.58	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	152.50	0	0.6
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	125.60	0	0.5
		Day 43	< 93.76	0	0.4	3942.95	1	1.6	157.47	0	0.6

Appendix 16

Individual Cytokines Values

Females

Group 1 - Reference Item

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1506	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	1507	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	1508	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	1509	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	1510	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3

Appendix 16

Individual Cytokines Values

Females

Group 1 - Reference Item

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1511	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	1512	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	1513	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	1514	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3

Appendix 16

Individual Cytokines Values

Females

Group 1 - Reference Item

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
1	1515	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	19.15	1	2.2
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3

Appendix 16

Individual Cytokines Values

Females

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
2	2501	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	224.03	0	0.8
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	211.91	0	0.8
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	348.97	1	1.3
	2502	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	189.94	0	0.7
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	294.81	1	1.1
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	193.91	0	0.7
	2503	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	135.29	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	626.25	1	2.3
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	155.09	0	0.6
	2505	Day 1 - 2 h PD	< 93.76	0	0.4	3502.02	1	1.4	143.13	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.4	1348.89	0	0.5	170.15	0	0.6
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	159.13	0	0.6
	2506	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	202.54	0	0.8
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	153.49	0	0.6
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	127.90	0	0.5

Appendix 16

Individual Cytokines Values

Females

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
2	2507	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	359.82	1	1.3
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	371.38	1	1.4
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	224.55	0	0.8
	2508	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	320.69	1	1.2
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	266.29	0	1.0
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	160.23	0	0.6
	2509	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	163.55	0	0.6
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	220.87	0	0.8
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	263.51	0	1.0
	2510	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	215.47	0	0.8
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	288.12	1	1.1
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	136.89	0	0.5
	2604	Day 1 - 2 h PD	198.75	1	1.6	< 703.12	0	0.1	323.07	1	1.2
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	297.12	1	1.1
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	355.74	1	1.3

Appendix 16

Individual Cytokines Values

Females

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
2	2501	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	2502	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	2503	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	1494.69	1	2.1	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	2505	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	2506	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3

Appendix 16

Individual Cytokines Values

Females

Group 2 - mRNA-1893 10 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
2	2507	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	2508	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	2509	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	2510	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	2604	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3

Appendix 16

Individual Cytokines Values

Females

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
3	3501	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	153.28	0	0.6
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	164.42	0	0.6
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	228.63	0	0.9
	3502	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	189.96	0	0.7
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	186.07	0	0.7
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	280.02	0	1.0
	3503	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	58.60	0	0.2
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	127.26	0	0.5
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	123.92	0	0.5
	3504	Day 1 - 2 h PD	< 93.76	0	0.4	900.48	0	0.4	153.24	0	0.6
		Day 15 - 2 h PD	< 93.76	0	0.4	7554.22	1	3.0	155.83	0	0.6
		Day 29 - 2 h PD	< 93.76	0	0.4	3763.16	1	1.5	198.95	0	0.7
	3505	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	158.77	0	0.6
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	219.41	0	0.8
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	154.38	0	0.6

Appendix 16

Individual Cytokines Values

Females

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
3	3506	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	617.01	1	2.3
		Day 15 - 6 h PD	258.31	1	2.1	< 703.12	0	0.1	791.34	1	3.0
		Day 29 - 6 h PD	553.07	1	4.5	< 703.12	0	0.1	1197.07	1	4.5
	3507	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	217.14	0	0.8
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	237.61	0	0.9
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	218.16	0	0.8
	3508	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	395.65	1	1.5
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	359.61	1	1.3
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	497.04	1	1.9
	3509	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	256.26	0	1.0
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	344.16	1	1.3
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	203.79	0	0.8
	3510	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	434.09	1	1.6
		Day 15 - 6 h PD	125.02	0	1.0	< 703.12	0	0.1	1003.74	1	3.8
		Day 29 - 6 h PD	151.20	1	1.2	< 703.12	0	0.1	749.29	1	2.8

Appendix 16

Individual Cytokines Values

Females

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
3	3501	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	3502	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	3503	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	3504	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	3505	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3

Appendix 16

Individual Cytokines Values

Females

Group 3 - mRNA-1893 30 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
3	3506	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	3507	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	3508	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	3509	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	3510	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3

Appendix 16

Individual Cytokines Values

Females

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4506	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	608.18	1	2.3
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	648.89	1	2.4
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	846.58	1	3.2
	4507	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	267.35	0	1.0
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	296.00	1	1.1
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	583.22	1	2.2
	4508	Day 1 - 6 h PD	540.28	1	4.4	< 703.12	0	0.1	1598.15	1	6.0
		Day 15 - 6 h PD	1401.51	1	11.5	< 703.12	0	0.1	1820.80	1	6.8
		Day 29 - 6 h PD	605.78	1	5.0	< 703.12	0	0.1	2616.22	1	9.8
	4509	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	314.57	1	1.2
		Day 15 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	440.07	1	1.6
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	604.19	1	2.3
	4510	Day 1 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	602.25	1	2.3
		Day 15 - 6 h PD	< 93.76	0	0.4	754.35	0	0.3	558.84	1	2.1
		Day 29 - 6 h PD	< 93.76	0	0.4	< 703.12	0	0.1	1019.36	1	3.8

Appendix 16

Individual Cytokines Values

Females

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4511	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	133.20	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	190.54	0	0.7
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	129.78	0	0.5
		Day 43	< 93.76	0	0.4	< 703.12	0	0.1	121.76	0	0.5
	4512	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	122.33	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	187.22	0	0.7
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	177.16	0	0.7
		Day 43	< 93.76	0	0.4	< 703.12	0	0.1	153.41	0	0.6
	4513	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	151.08	0	0.6
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	209.15	0	0.8
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	242.27	0	0.9
		Day 43	< 93.76	0	0.4	< 703.12	0	0.1	147.66	0	0.6
	4514	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	160.29	0	0.6
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	167.76	0	0.6
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	144.45	0	0.5
		Day 43	< 93.76	0	0.4	< 703.12	0	0.1	< 117.20	0	0.2

Appendix 16

Individual Cytokines Values

Females

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	IL-1β pg/mL	Incidence	Fold Change	IL-6 pg/mL	Incidence	Fold Change	IP-10 pg/mL	Incidence	Fold Change
4	4515	Day 1 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	139.01	0	0.5
		Day 15 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	130.41	0	0.5
		Day 29 - 2 h PD	< 93.76	0	0.4	< 703.12	0	0.1	136.39	0	0.5
		Day 43	< 93.76	0	0.4	< 703.12	0	0.1	131.50	0	0.5

Appendix 16

Individual Cytokines Values

Females

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4506	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	2450.00	1	3.5	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	4507	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	4508	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	4509	Day 1 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	1551.98	1	2.2	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	8.92	0	1.0
	4510	Day 1 - 6 h PD	1446.27	1	2.1	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 6 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3

Appendix 16

Individual Cytokines Values

Females

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4511	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	4512	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	4513	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
	4514	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	14.89	1	1.7
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	25.16	1	2.8

Appendix 16

Individual Cytokines Values

Females

Group 4 - mRNA-1893 96 µg/dose

Group	Animal Number	Occasion	MCP-1 pg/mL	Incidence	Fold Change	MIP-1α pg/mL	Incidence	Fold Change	TNF-α pg/mL	Incidence	Fold Change
4	4515	Day 1 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 15 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 29 - 2 h PD	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3
		Day 43	< 1406.30	0	1.0	< 23.44	0	1.0	< 5.86	0	0.3

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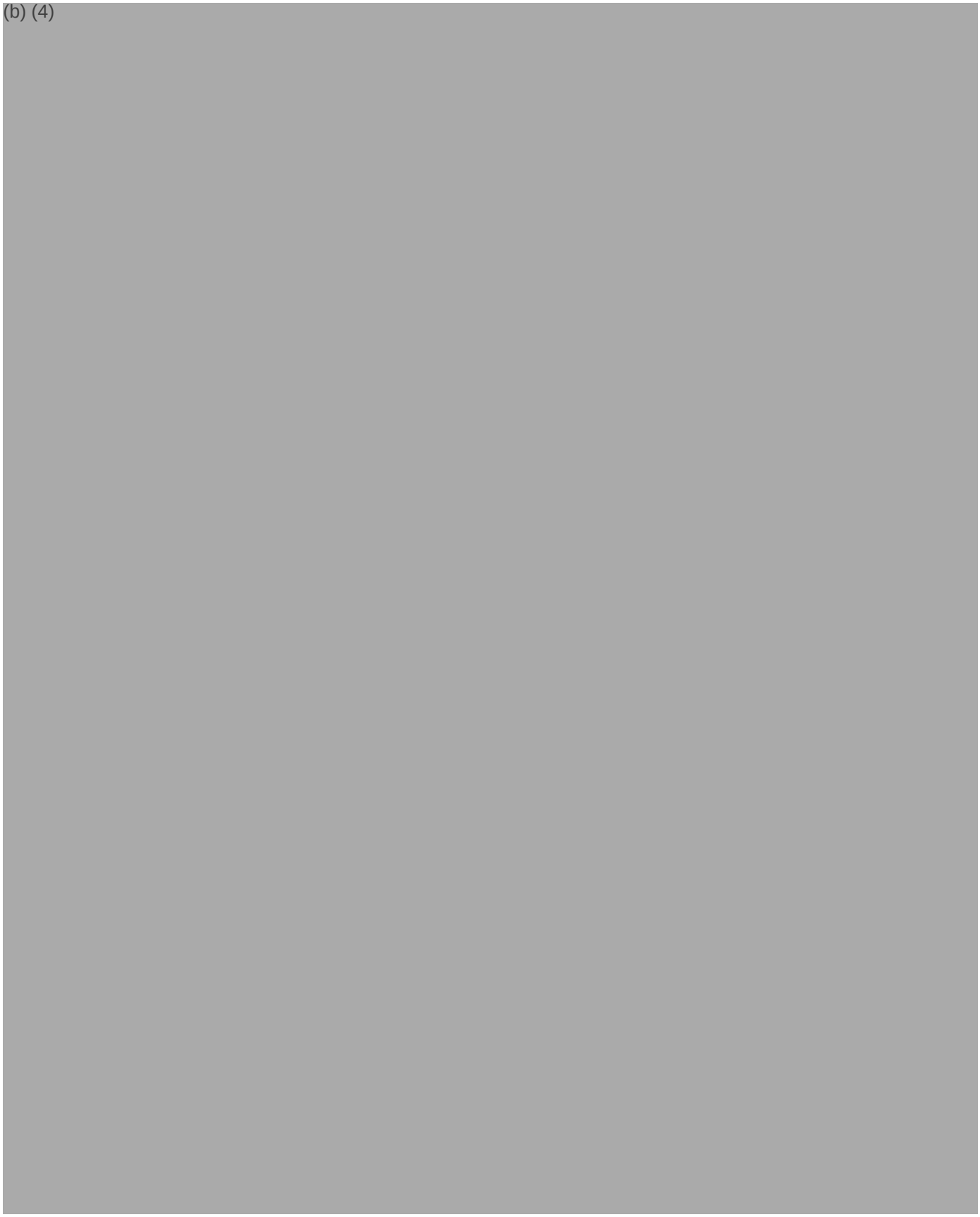

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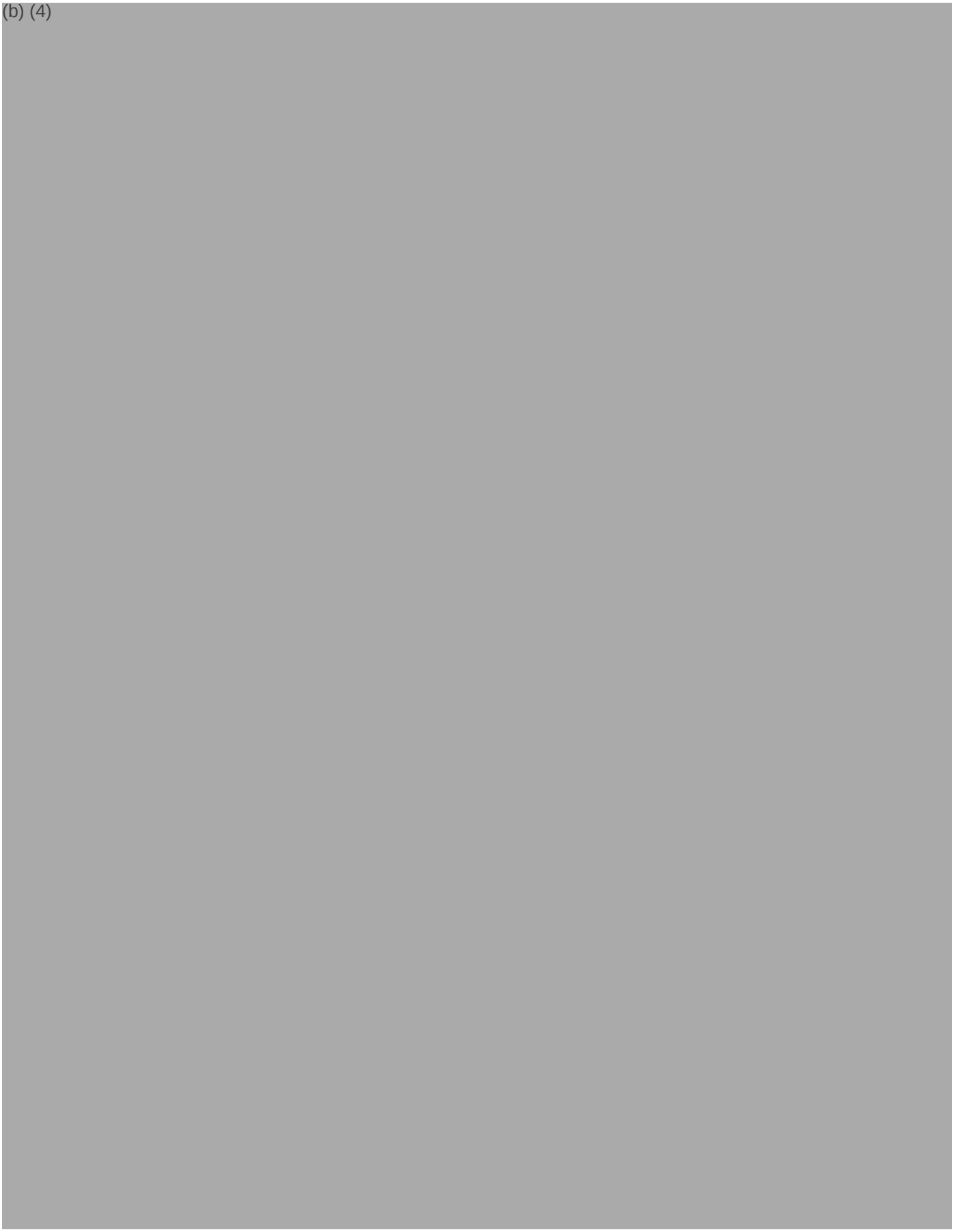

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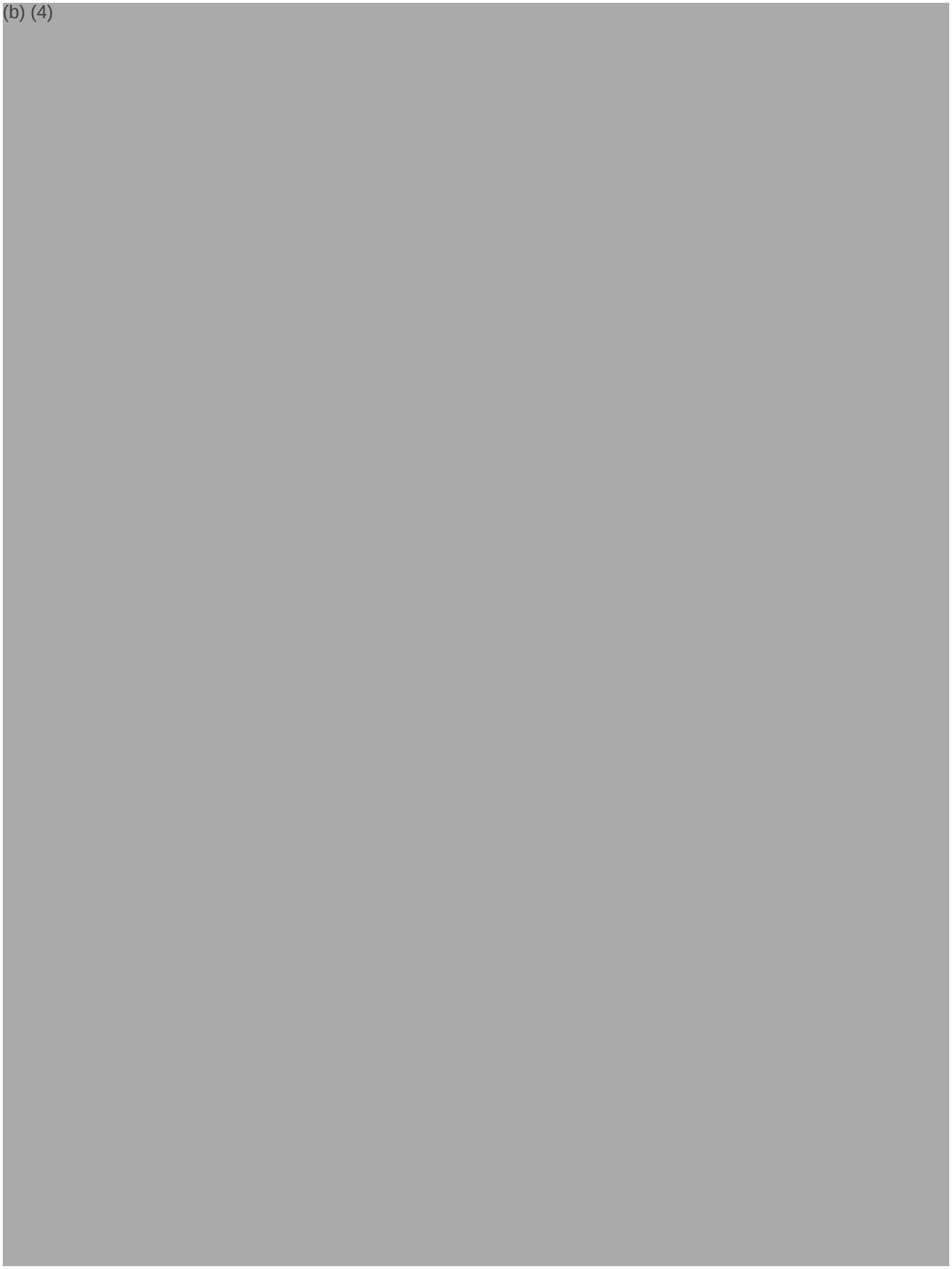

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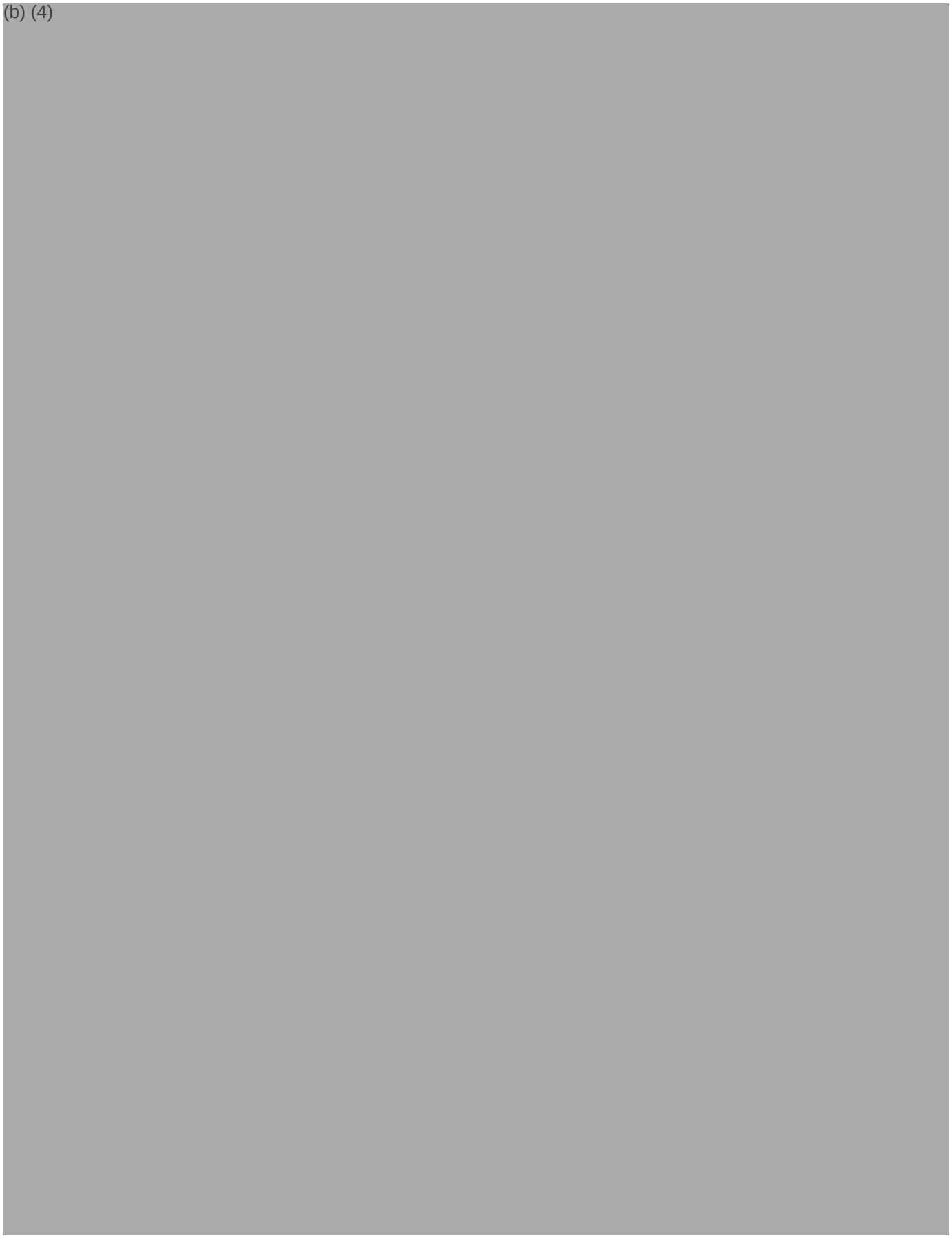

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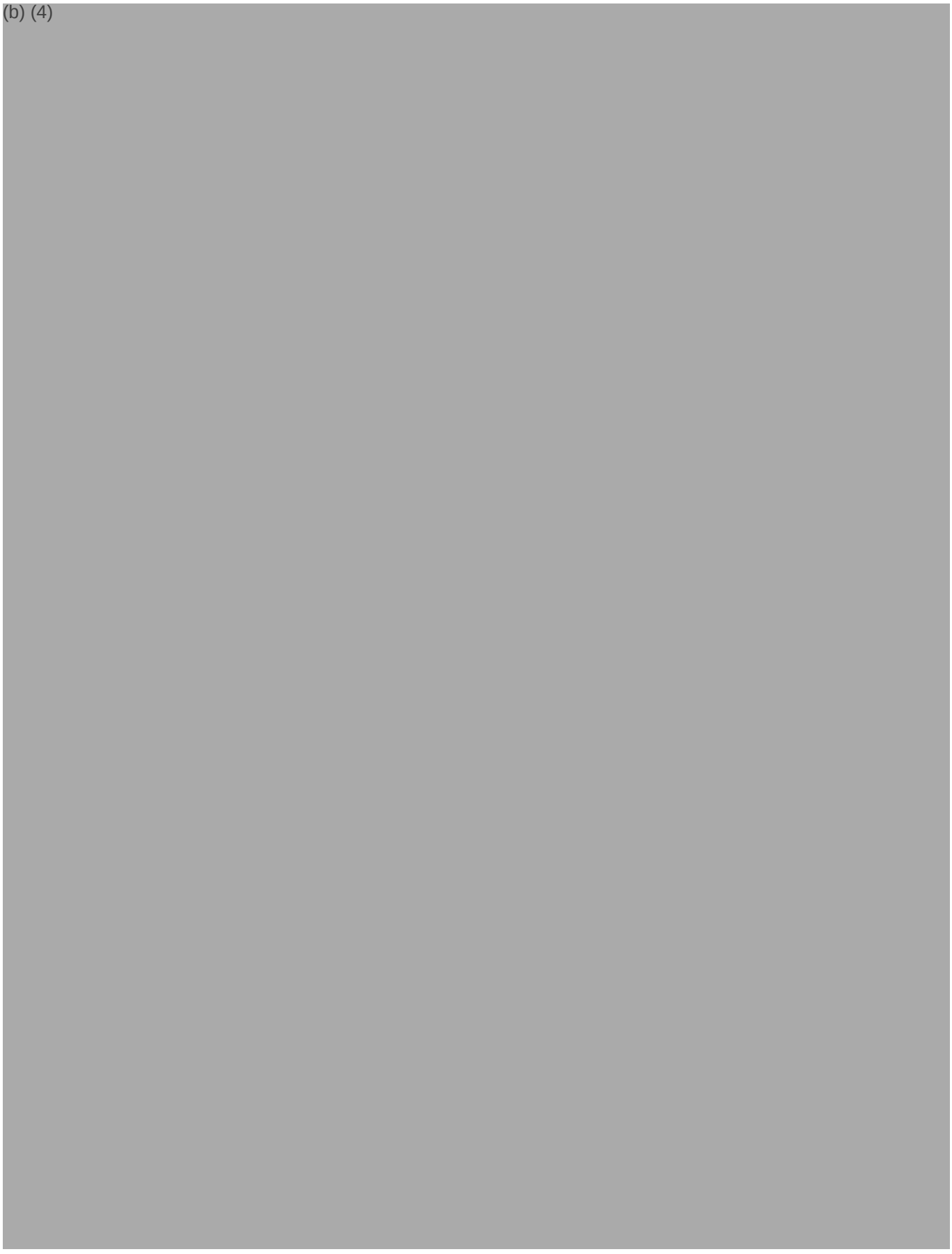
(b) (4)



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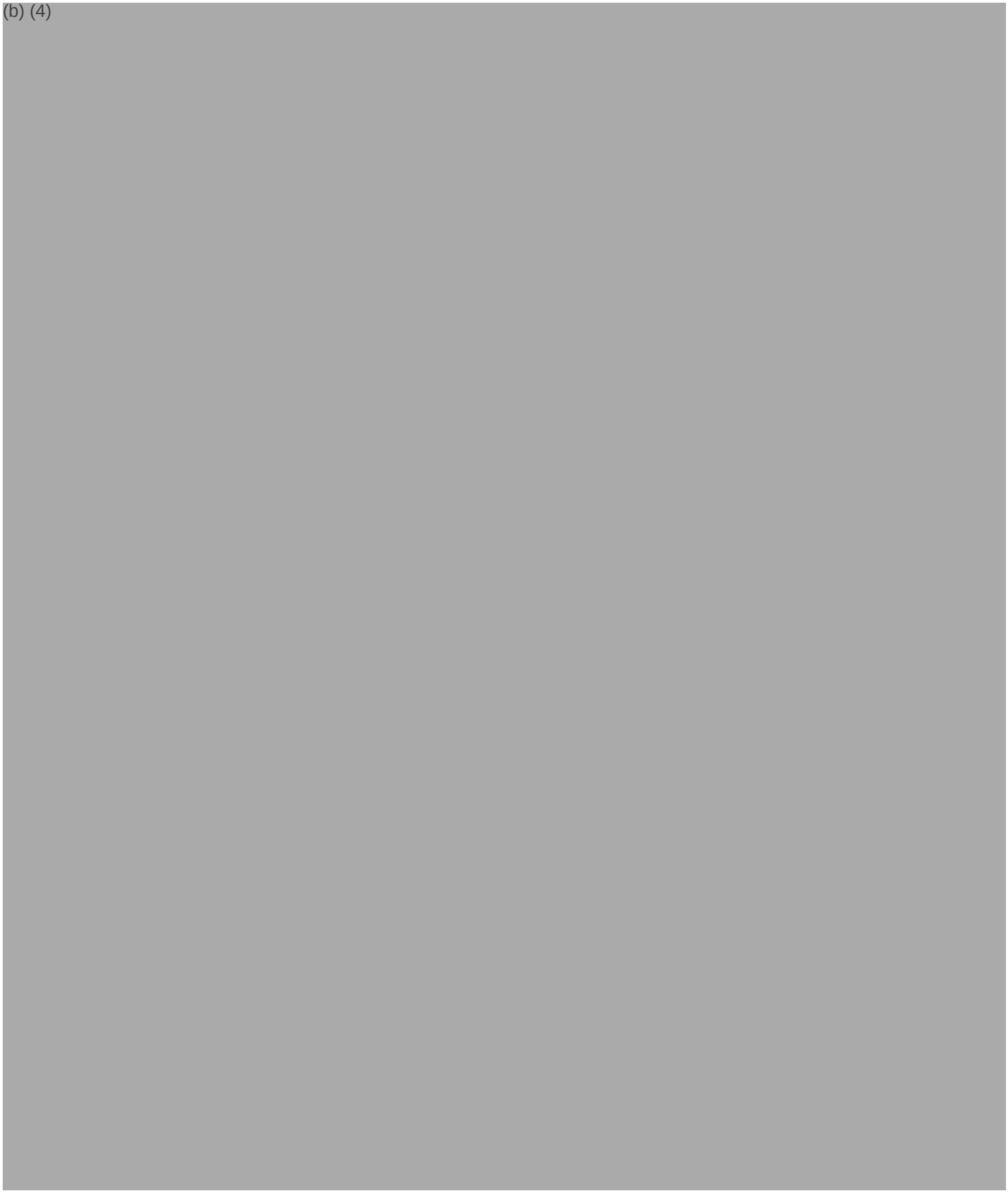

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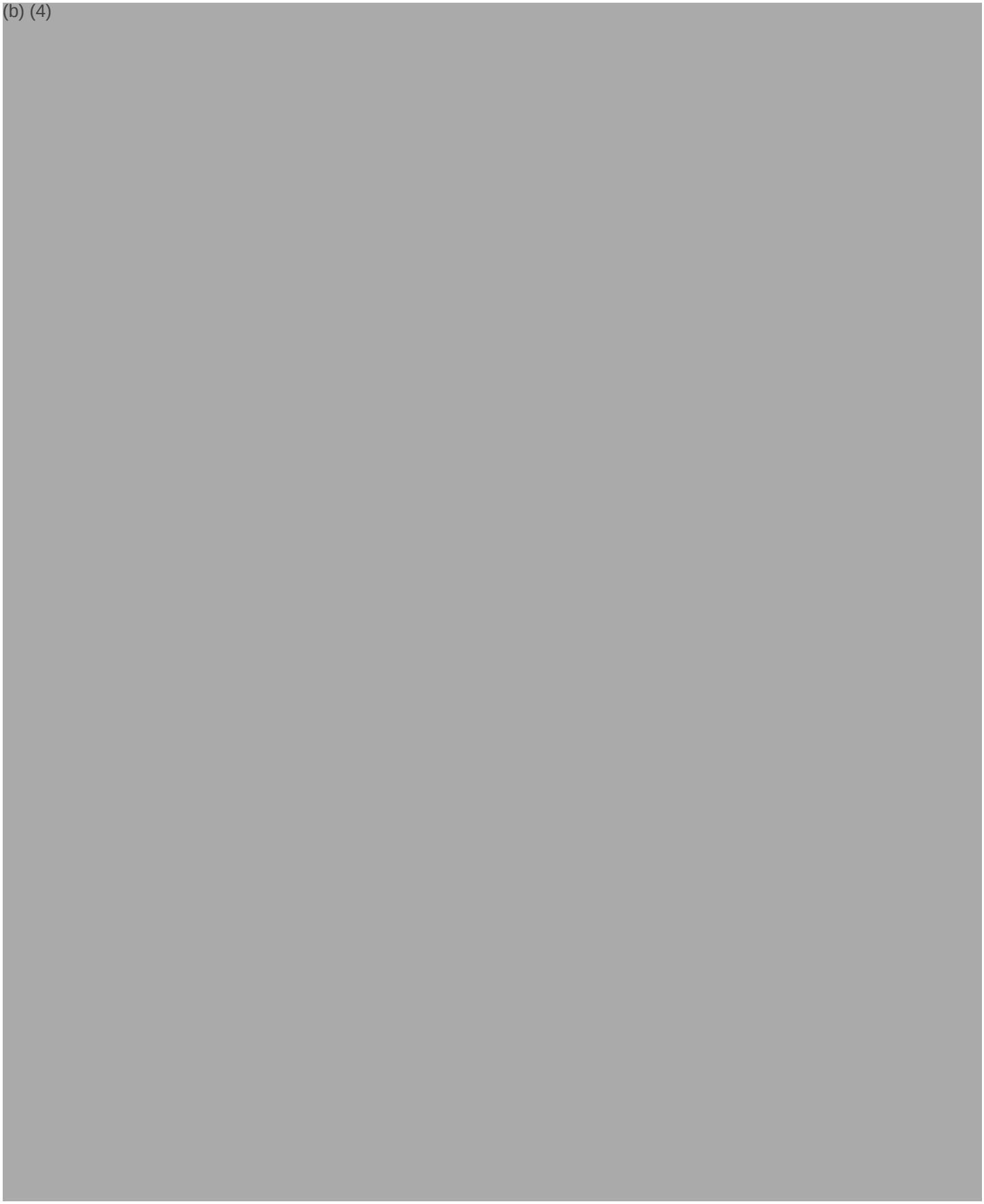

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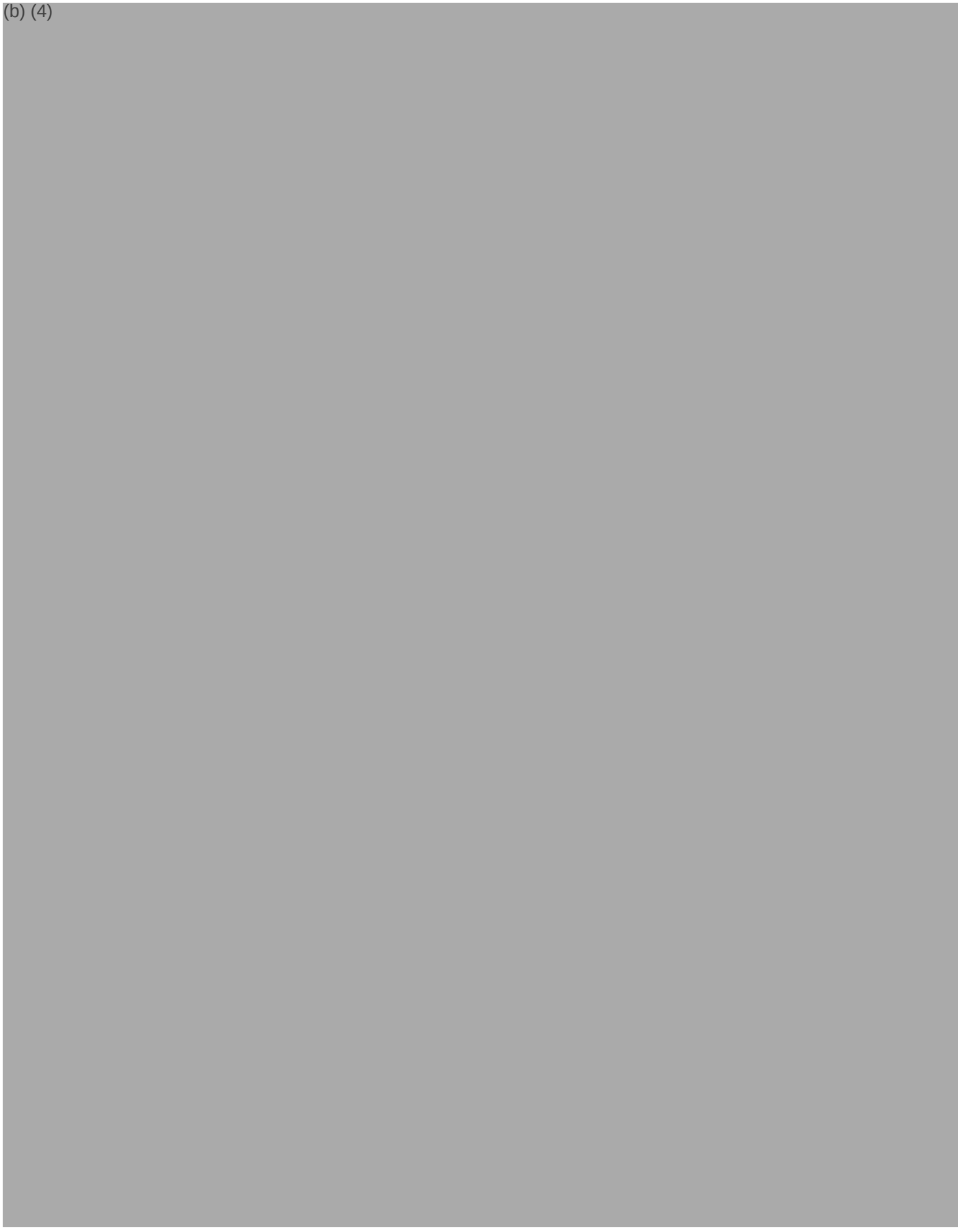

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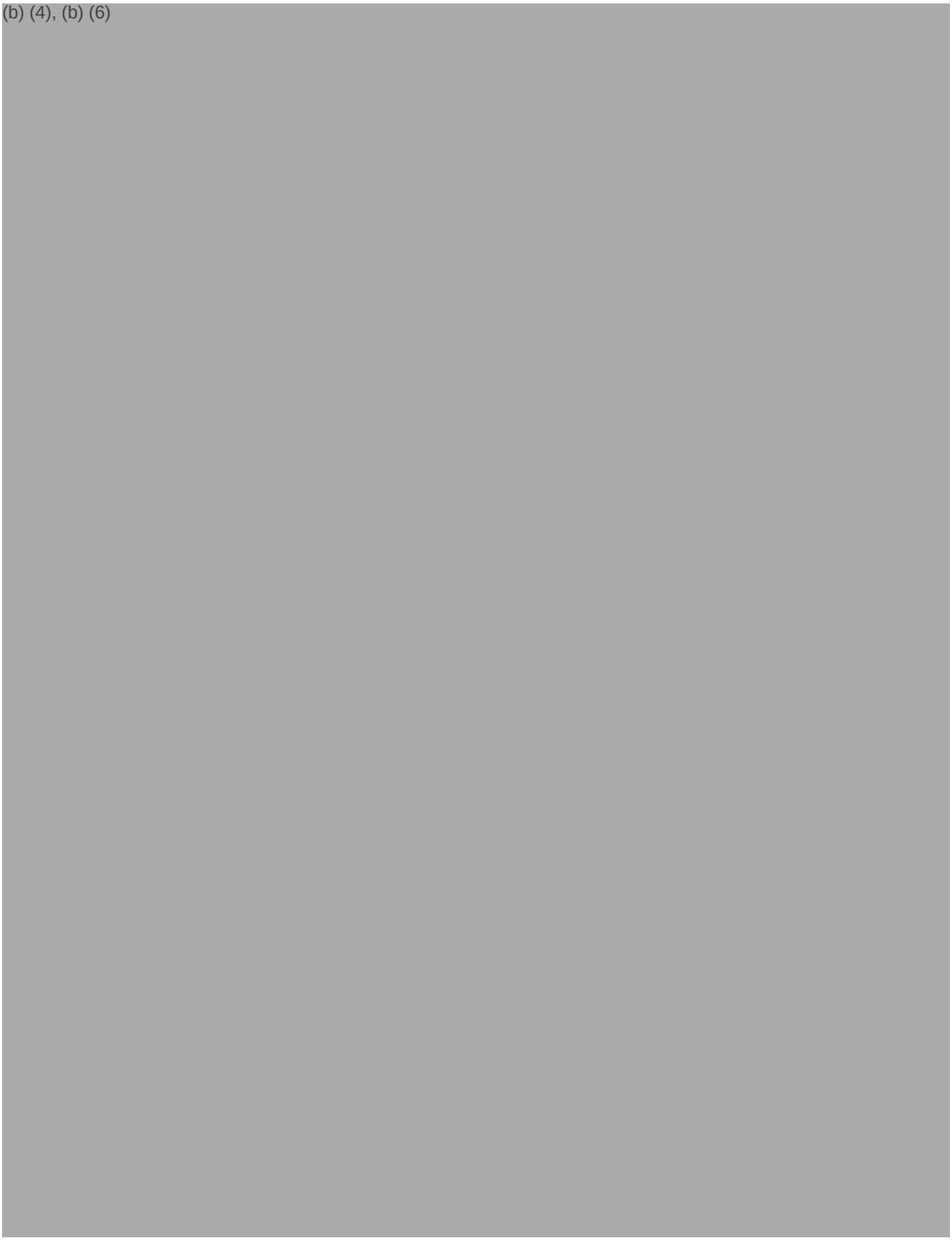

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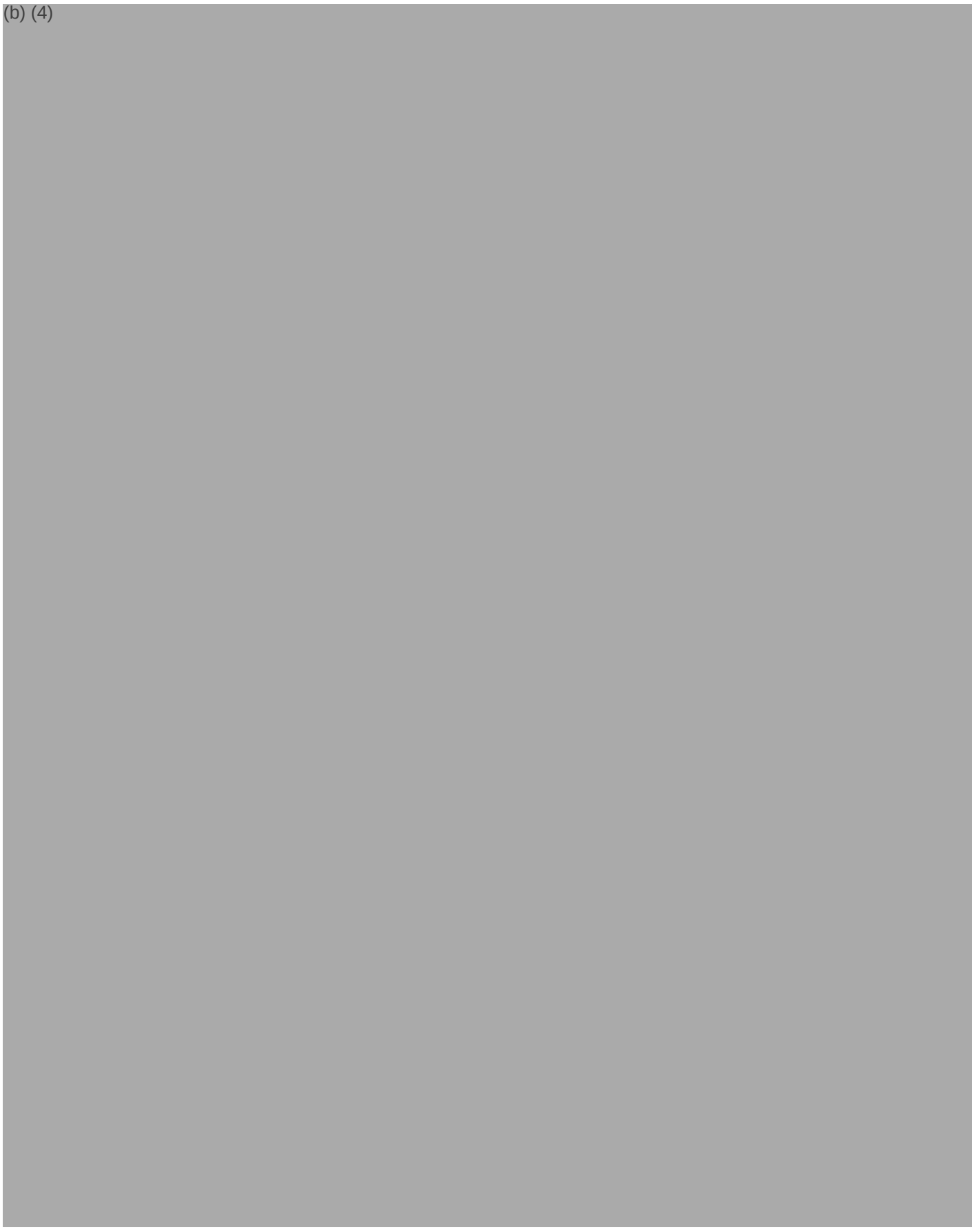

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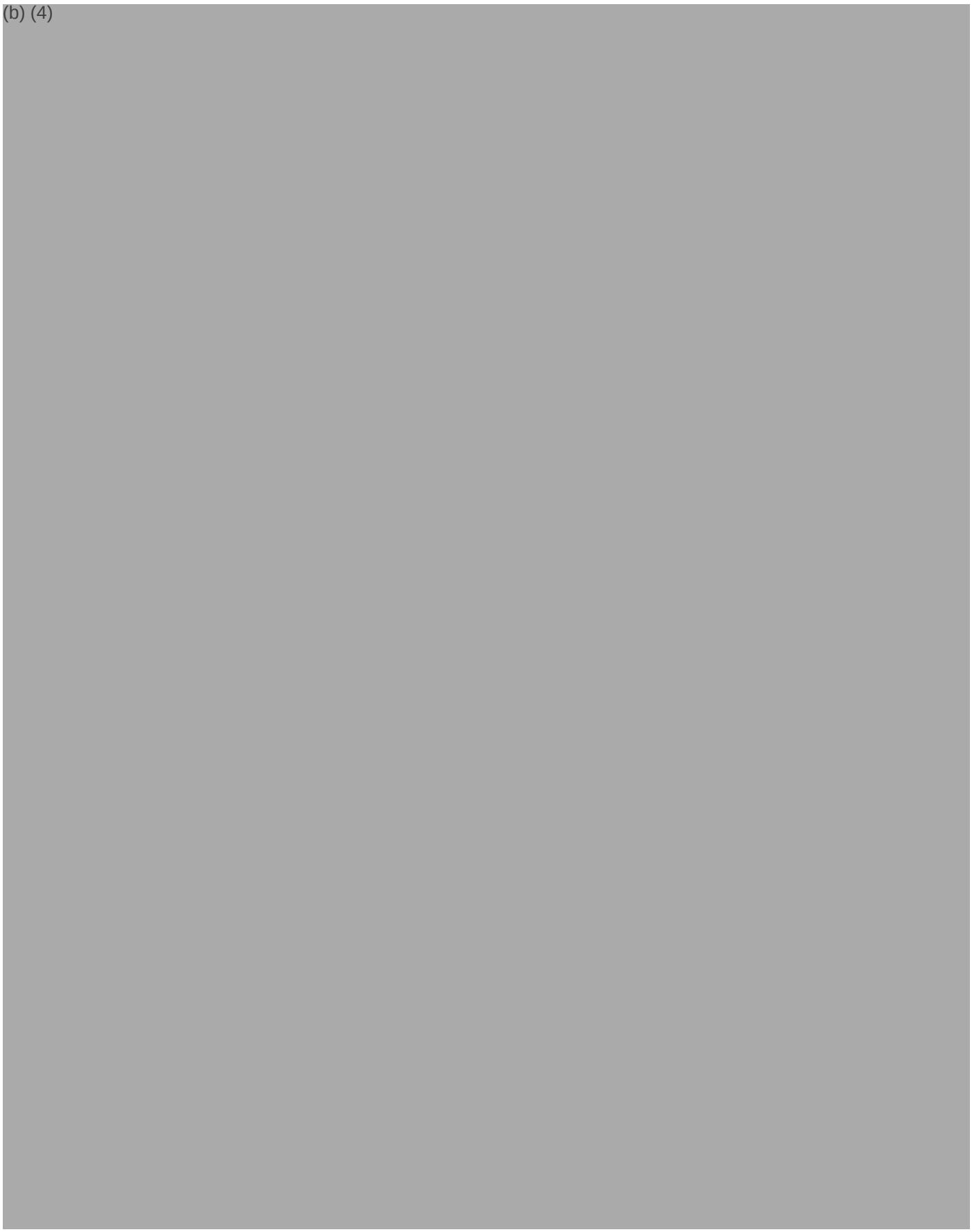

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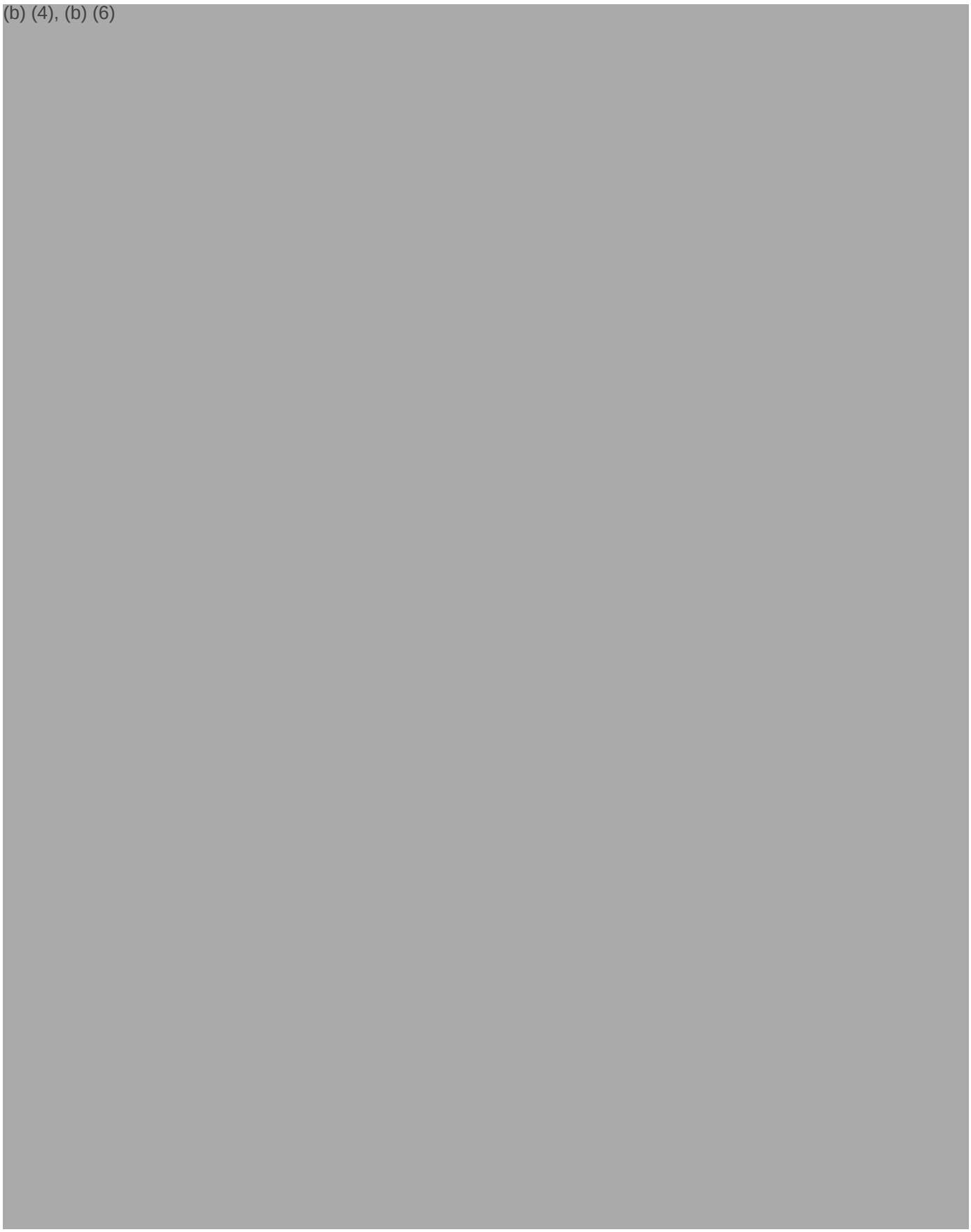

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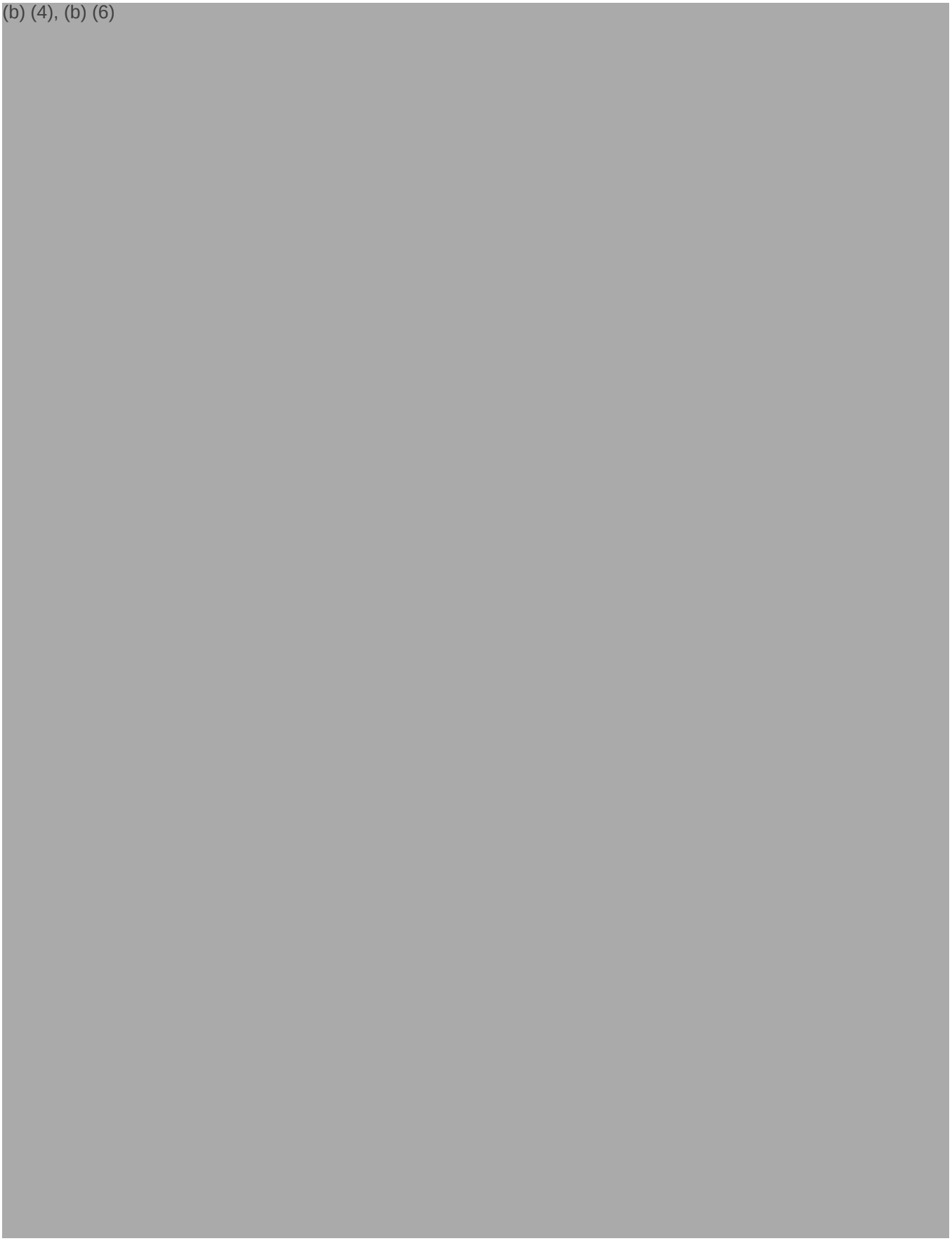

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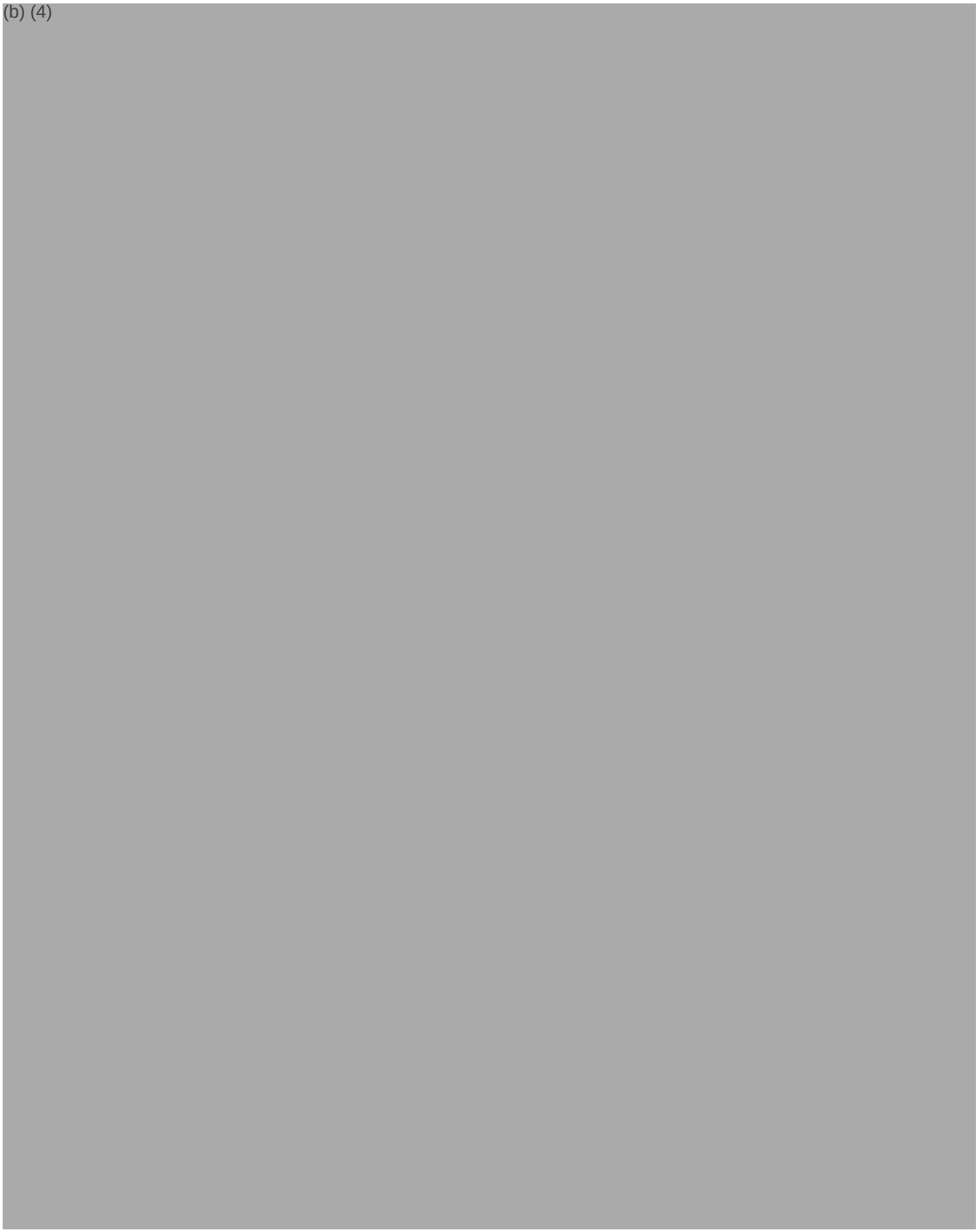

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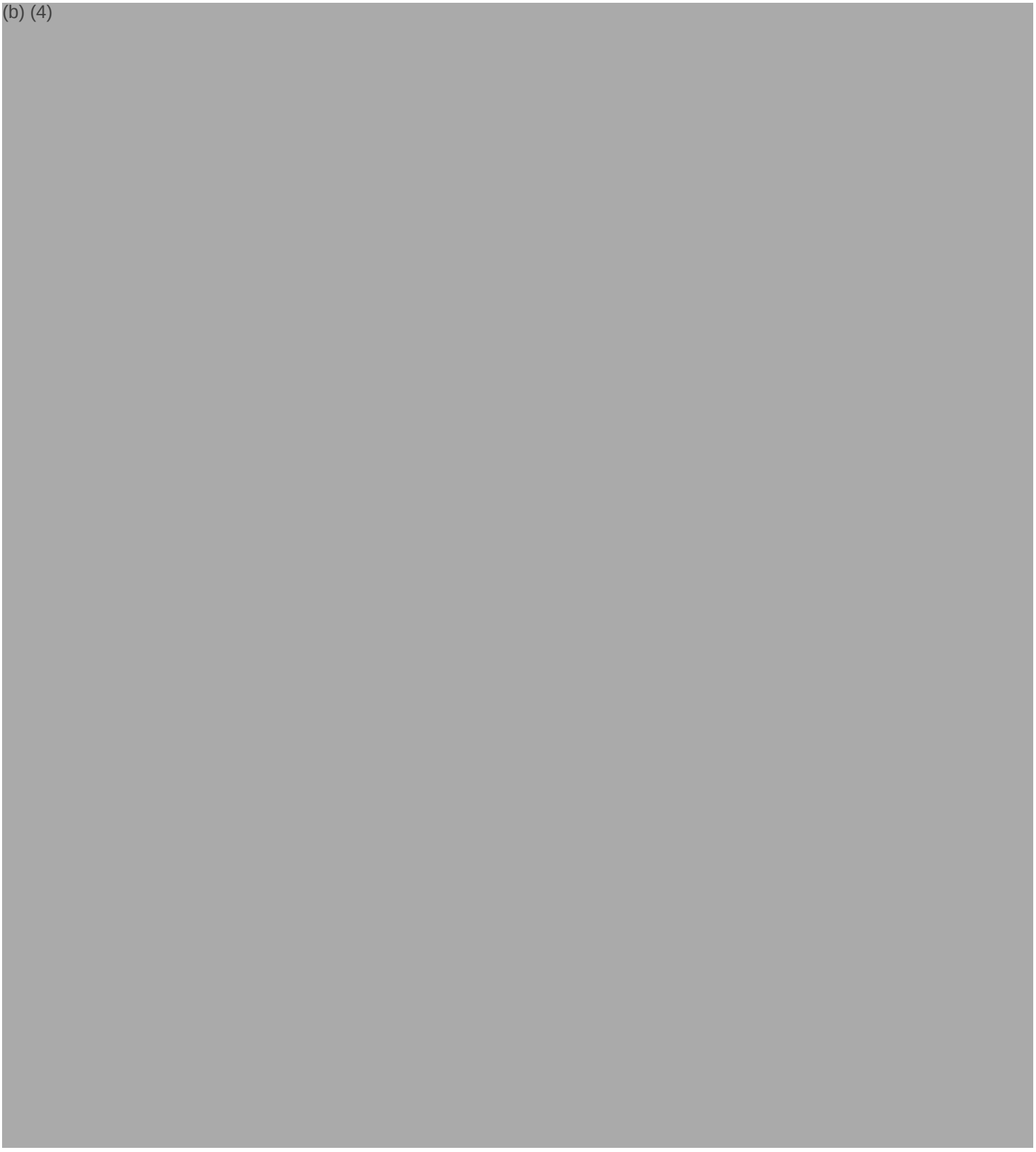

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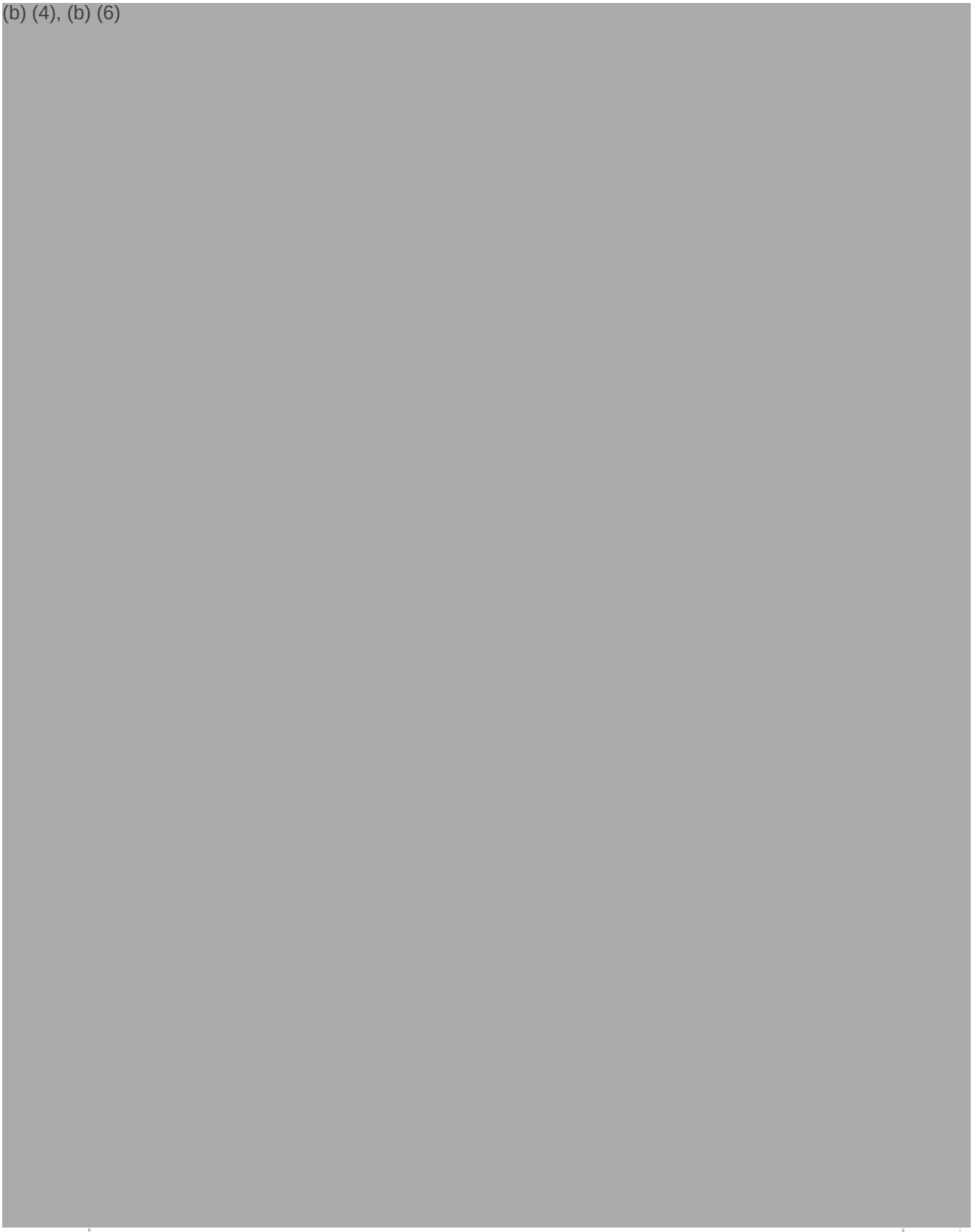

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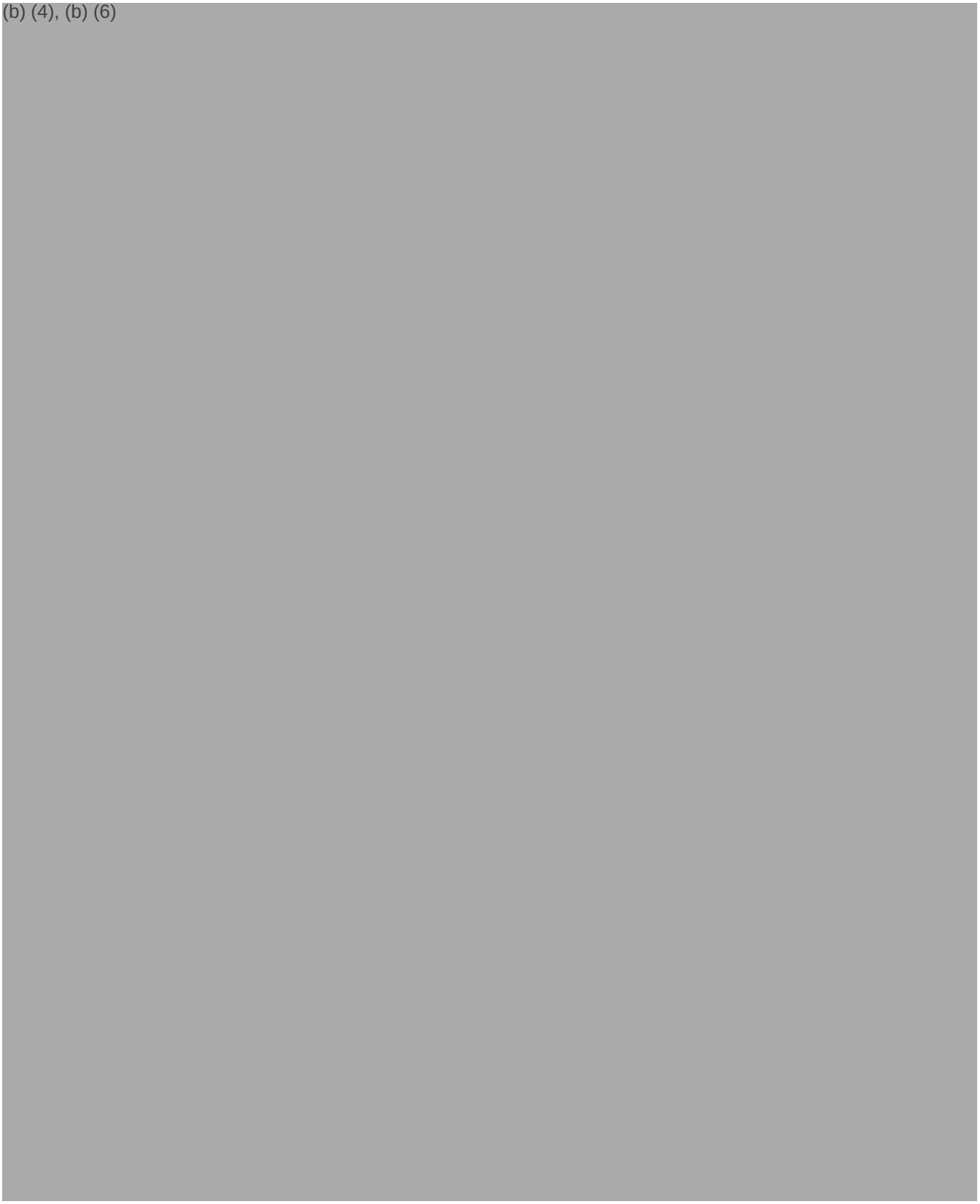

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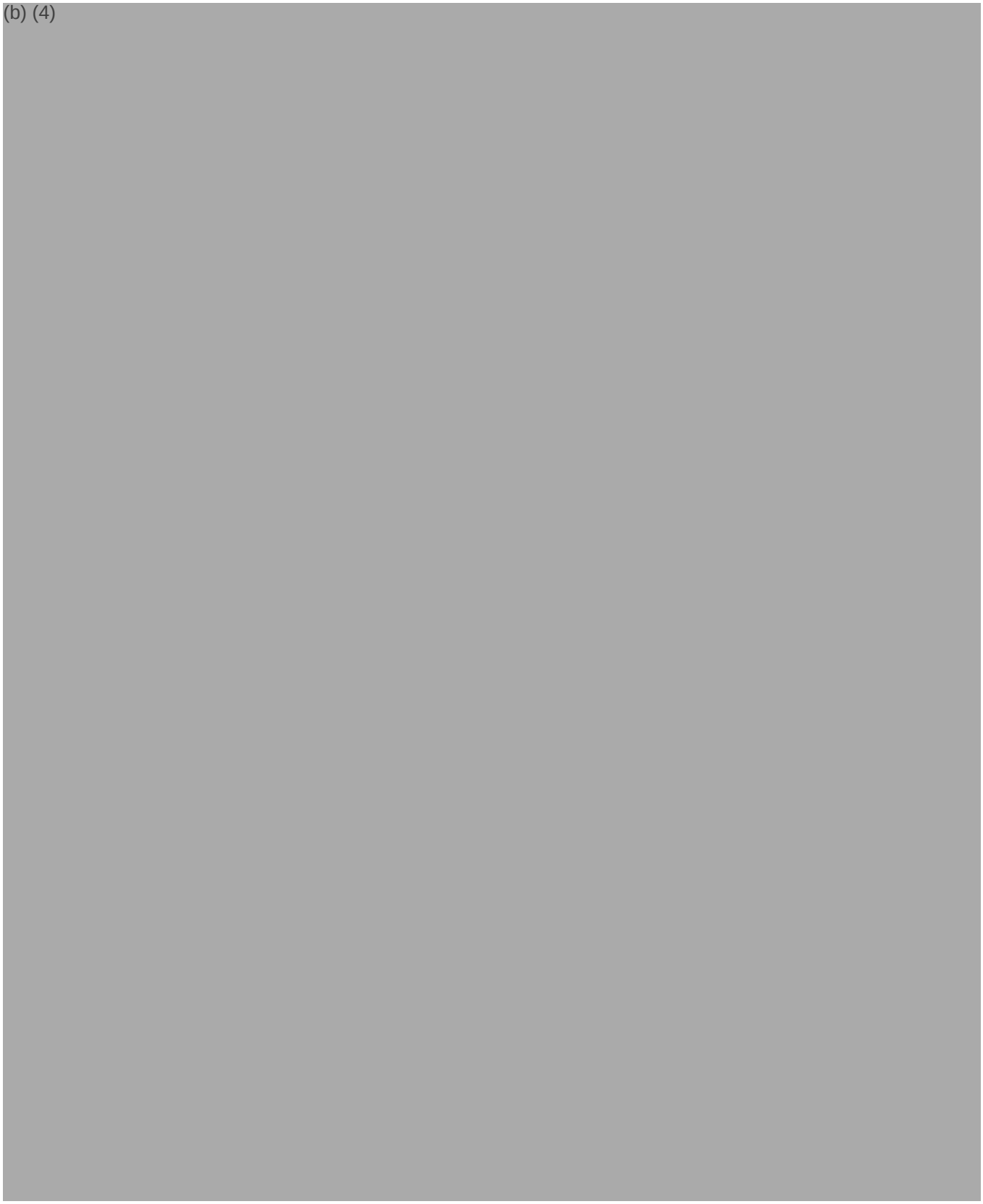

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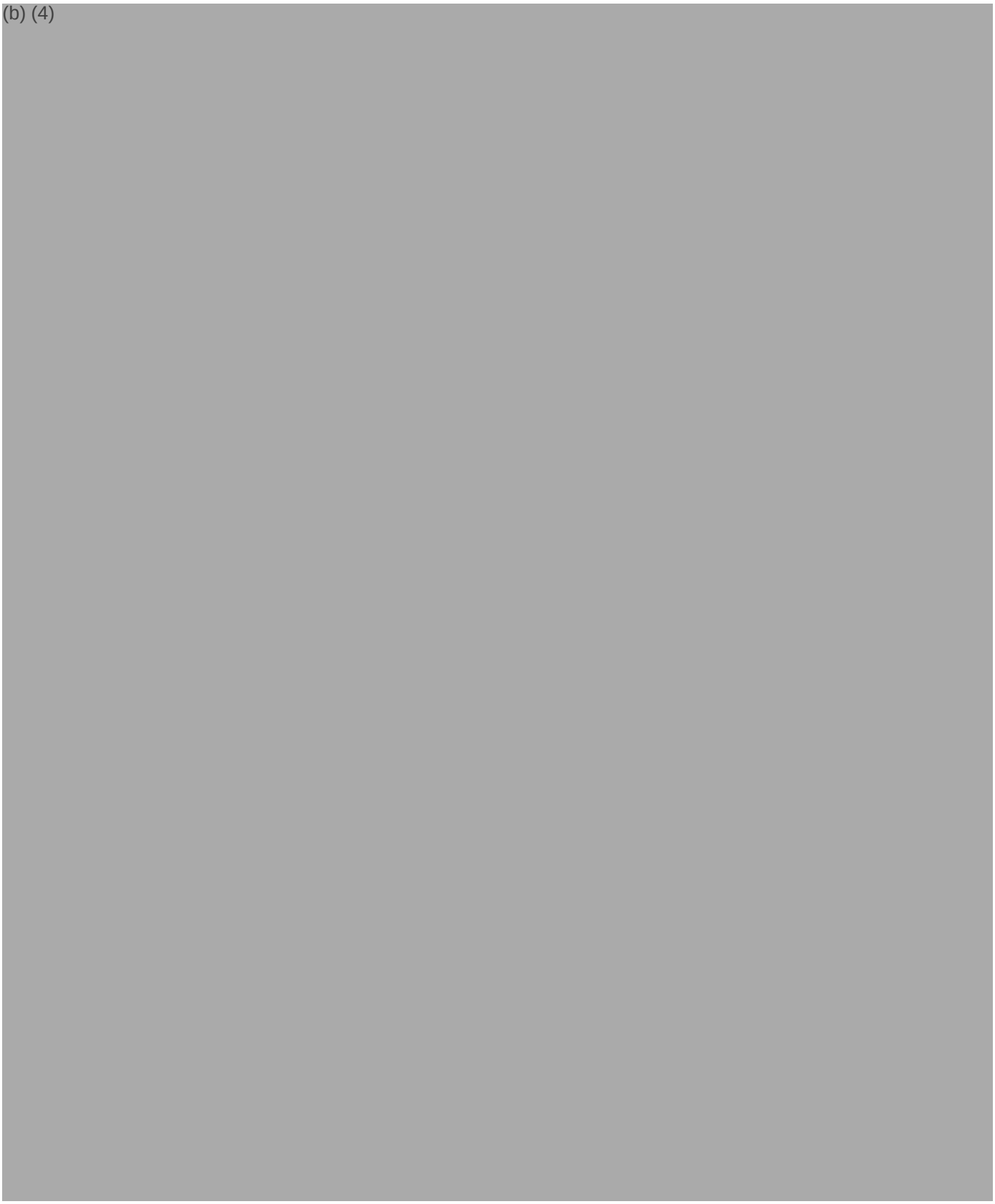

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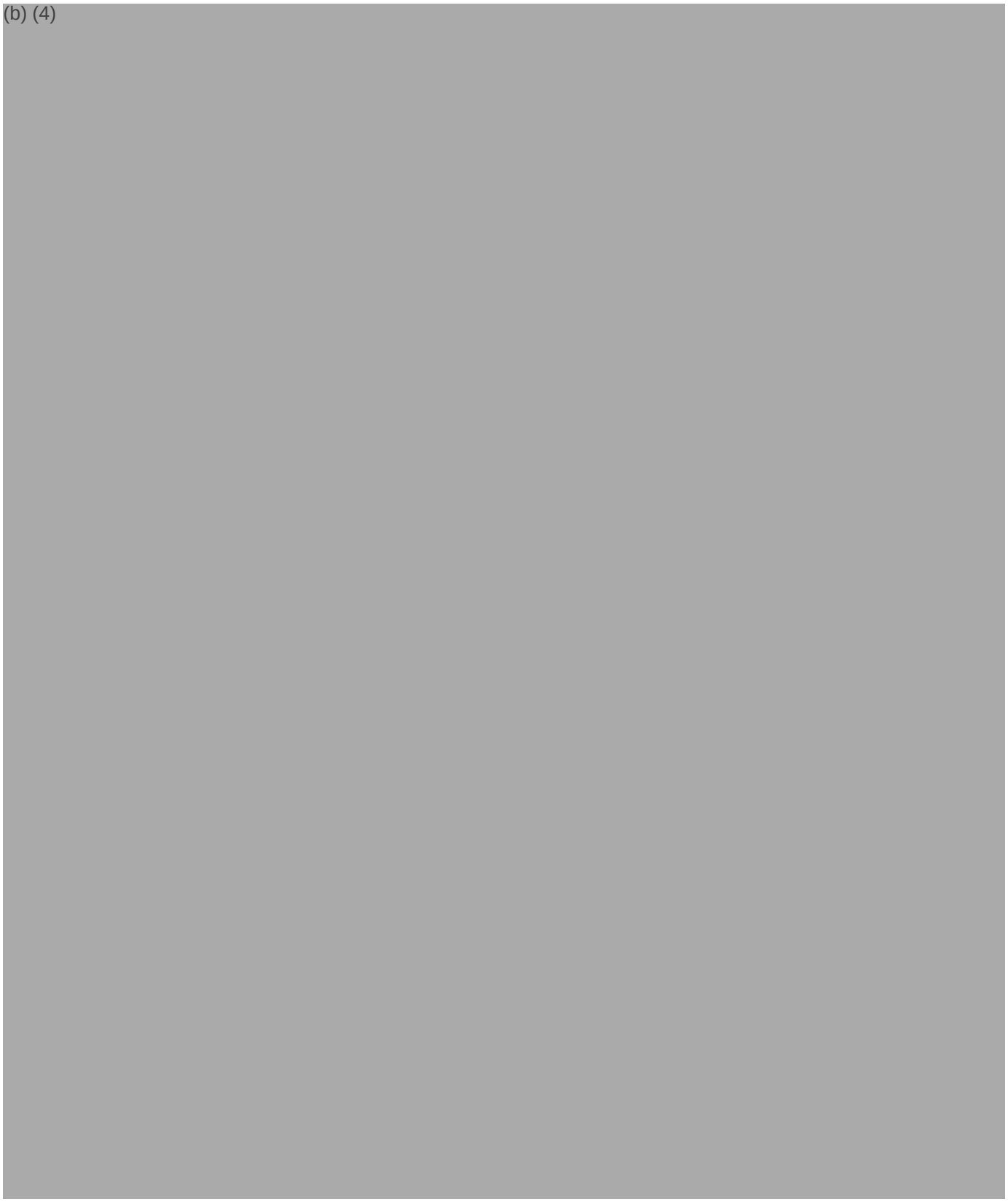

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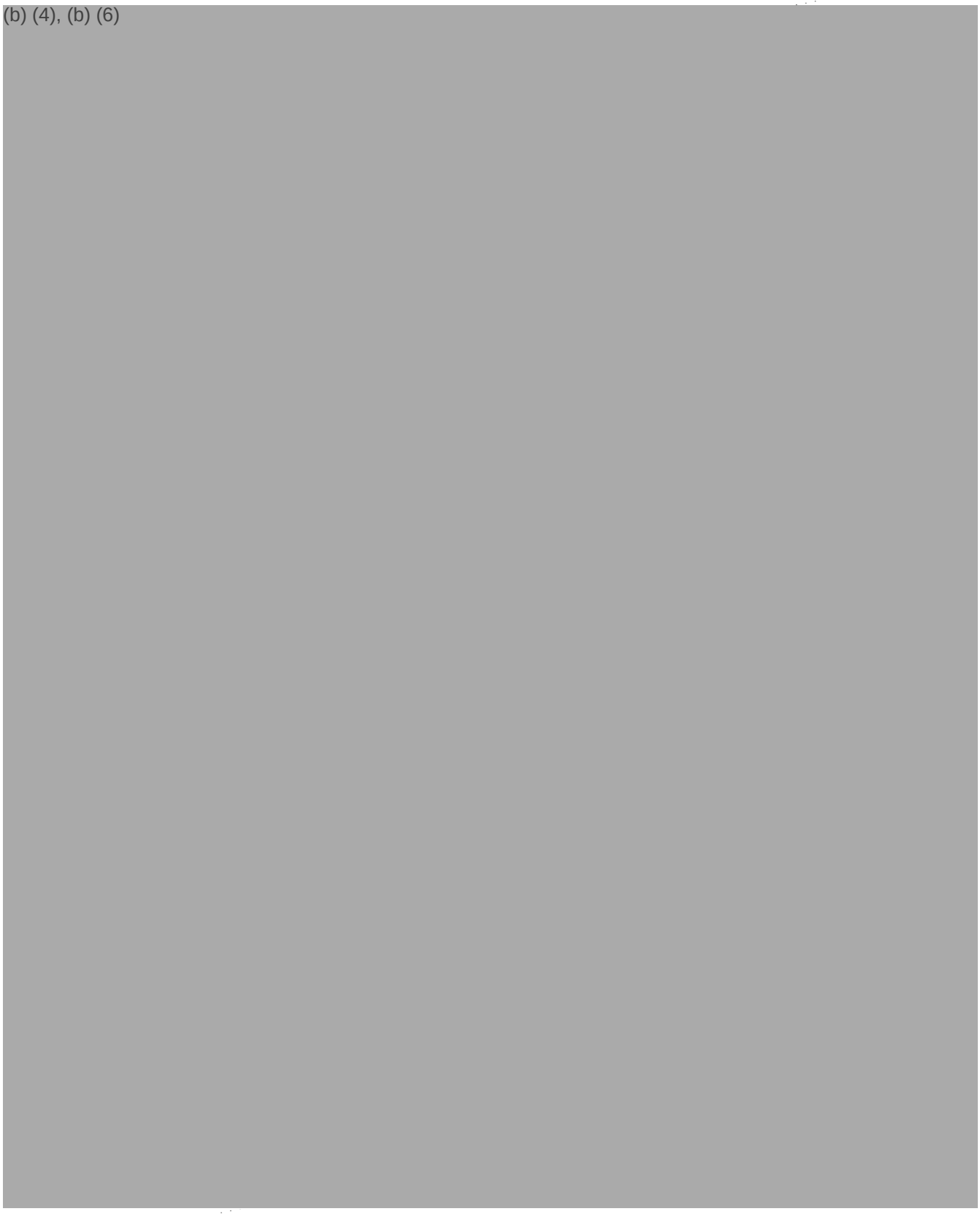

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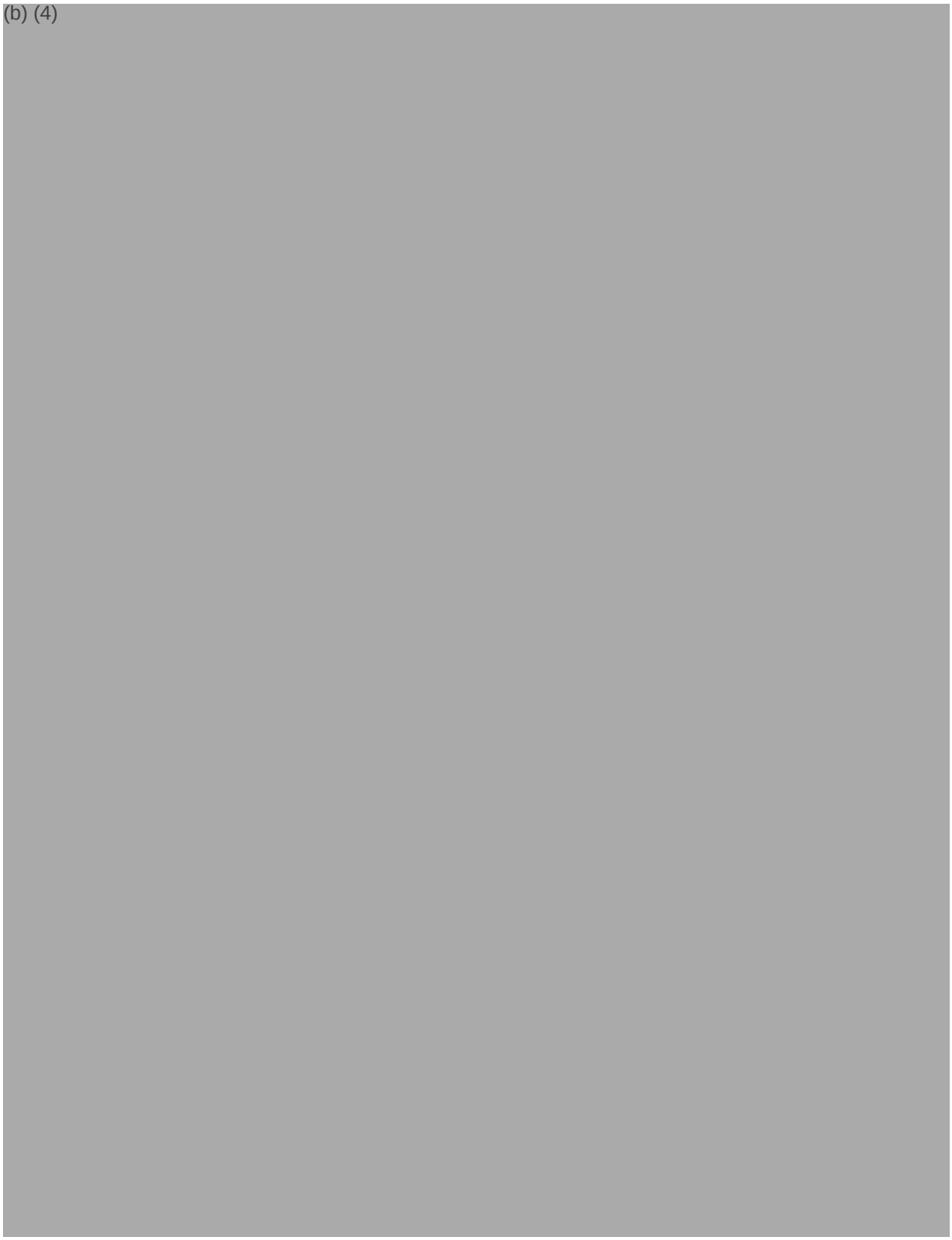

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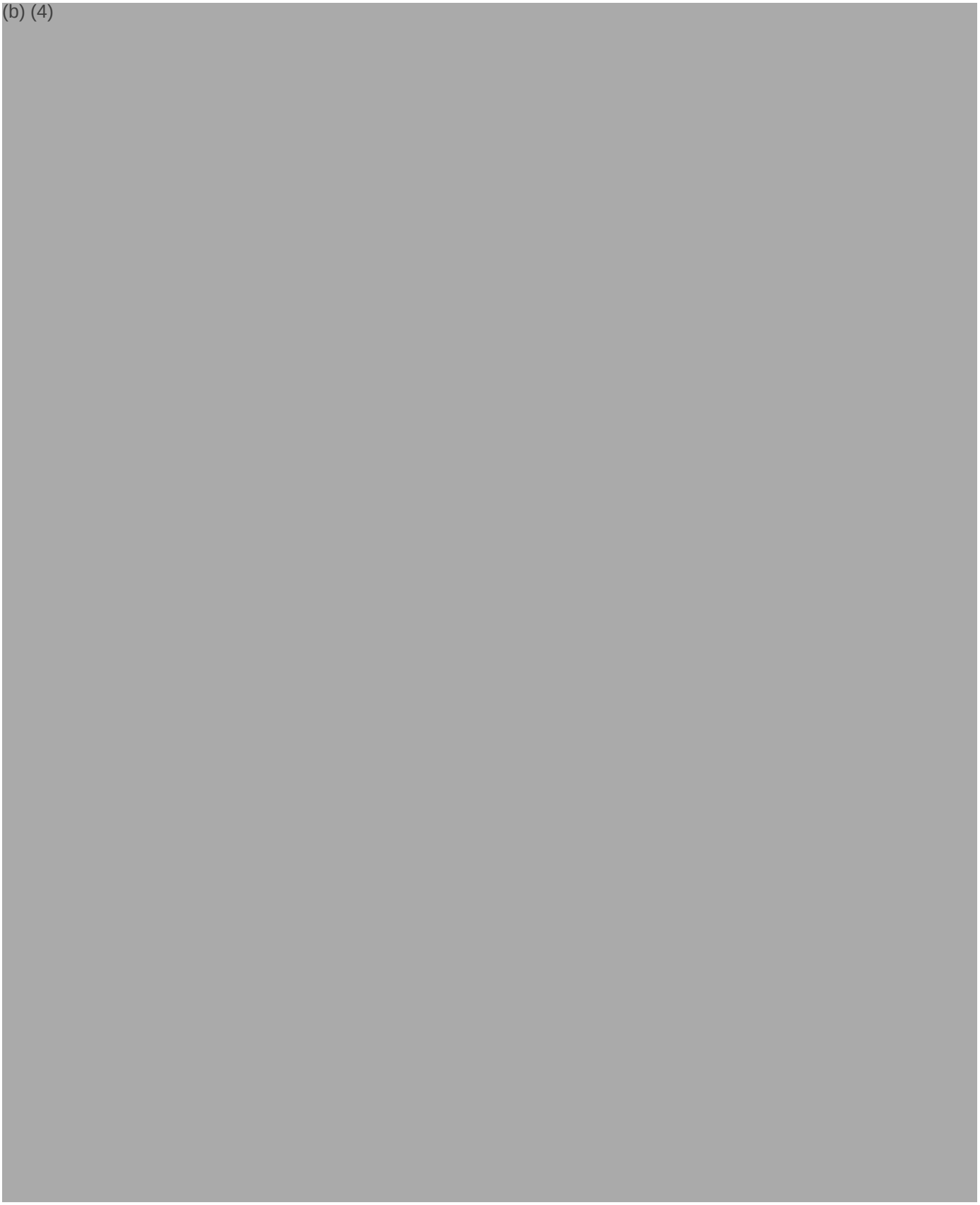

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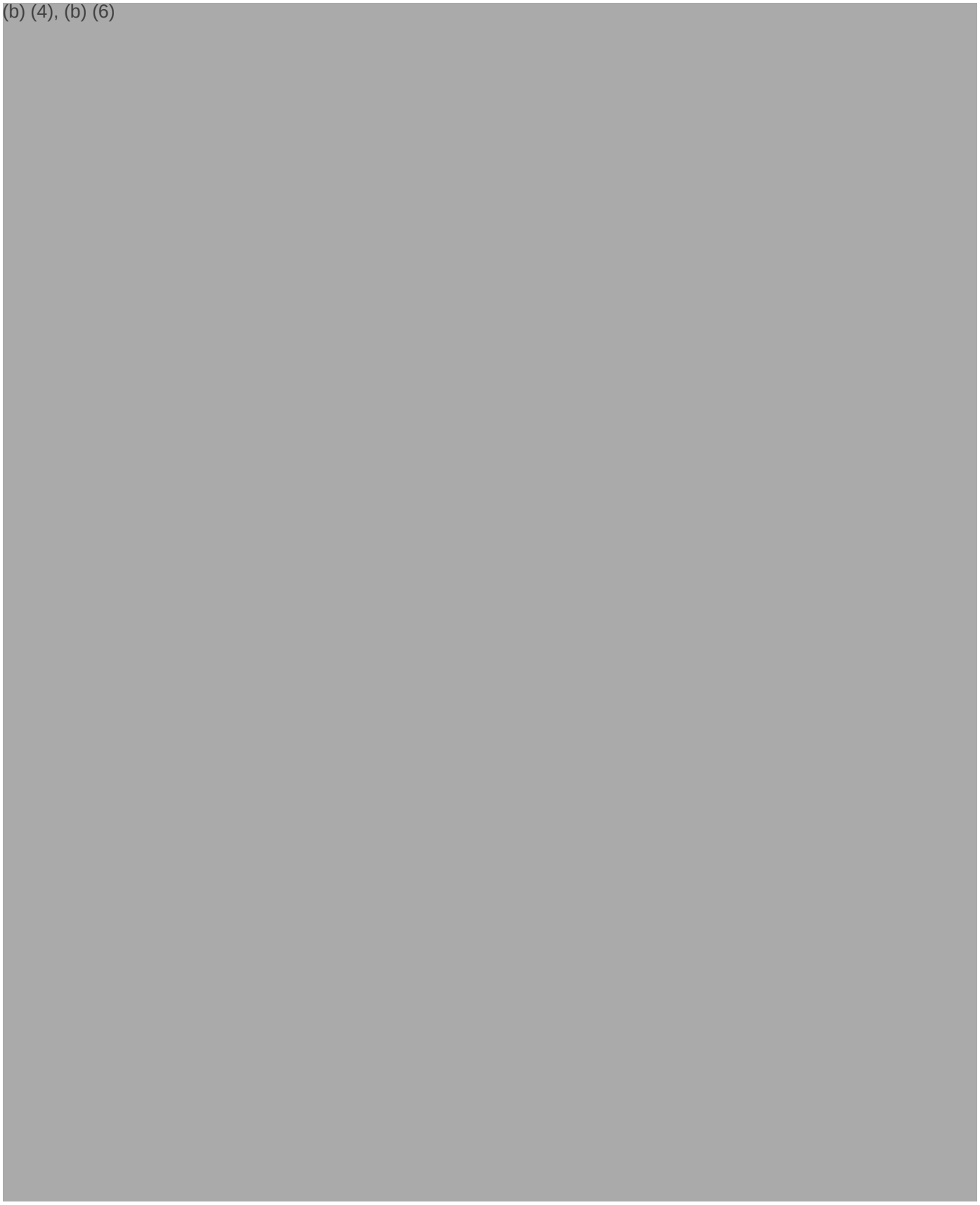

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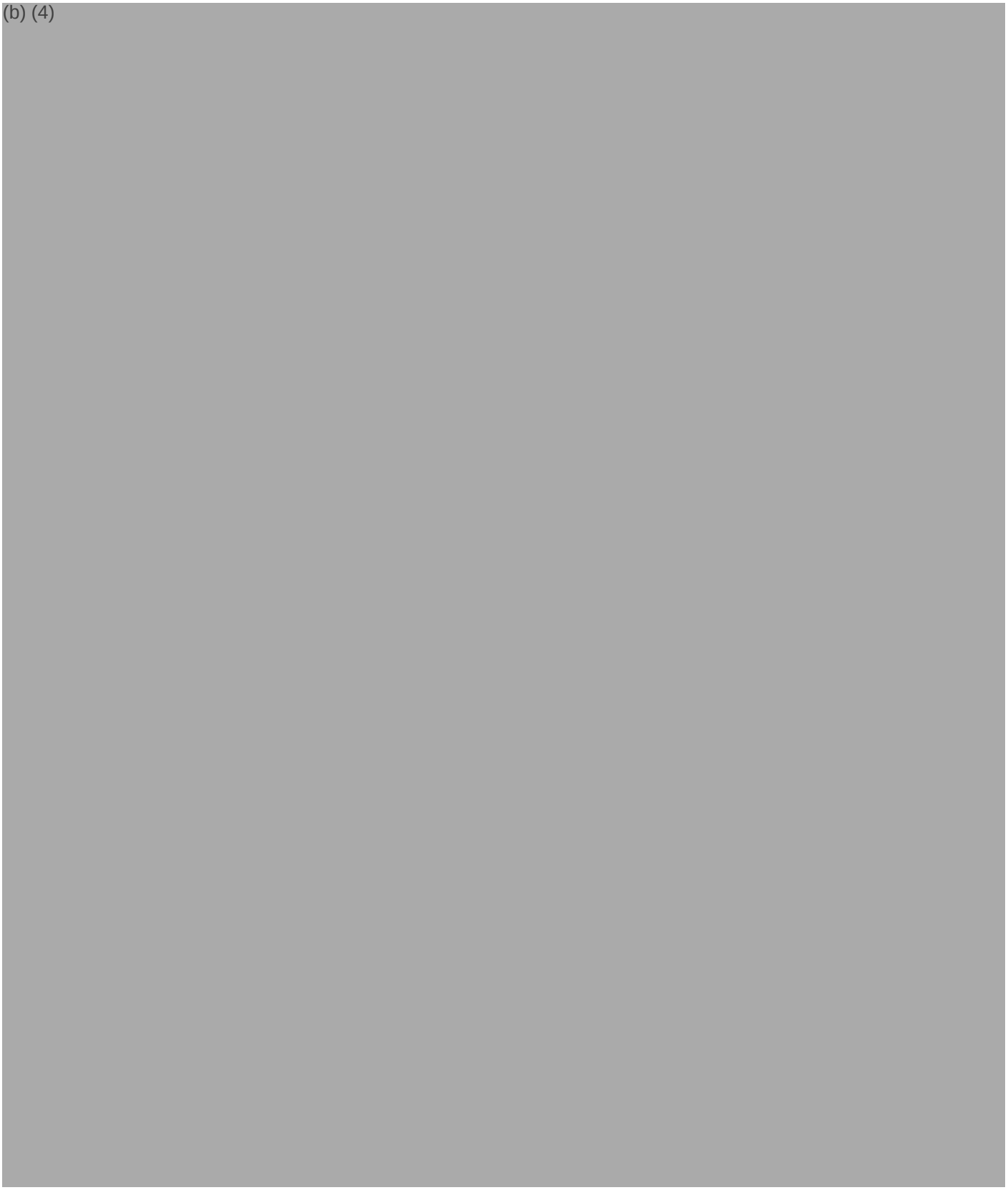

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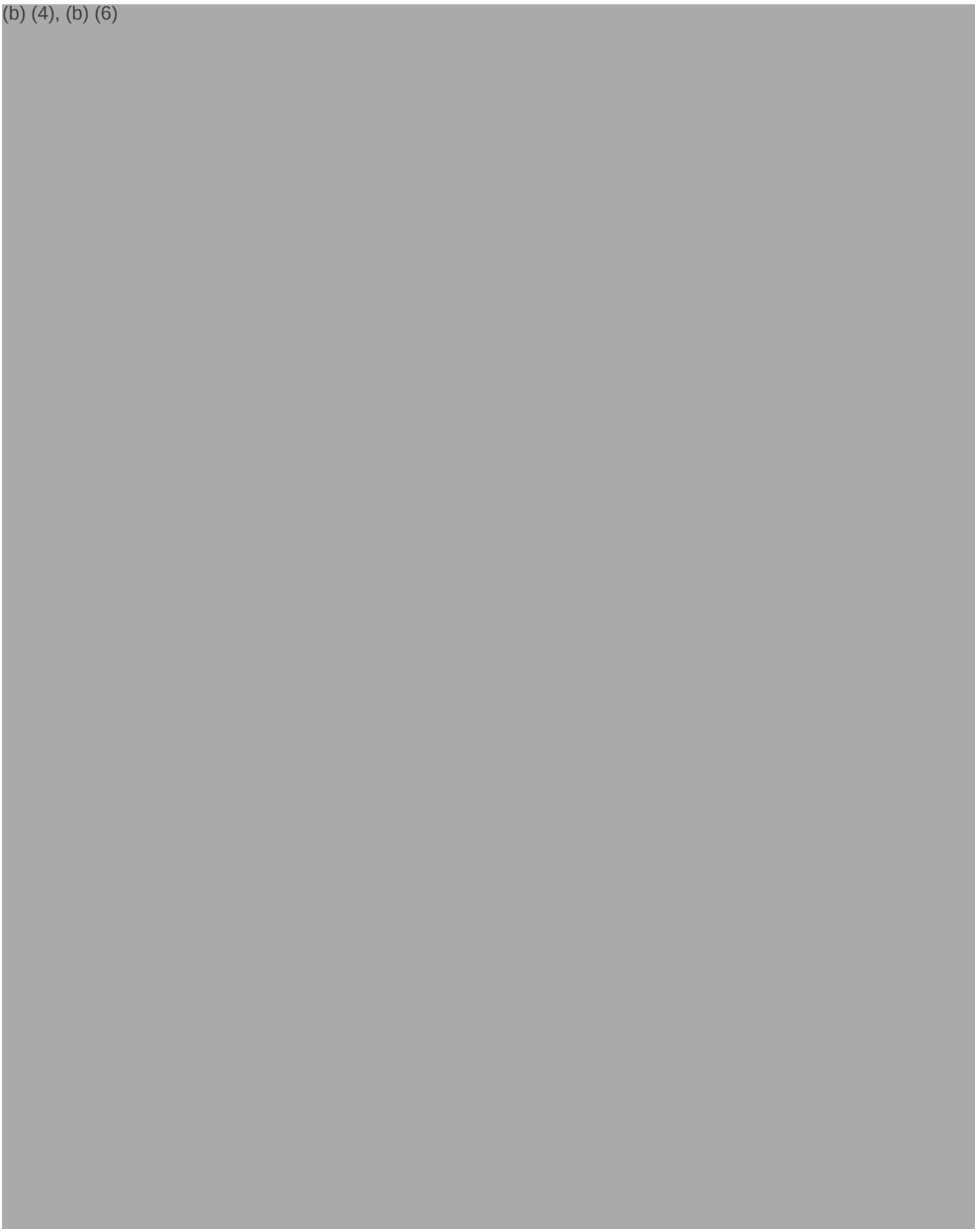

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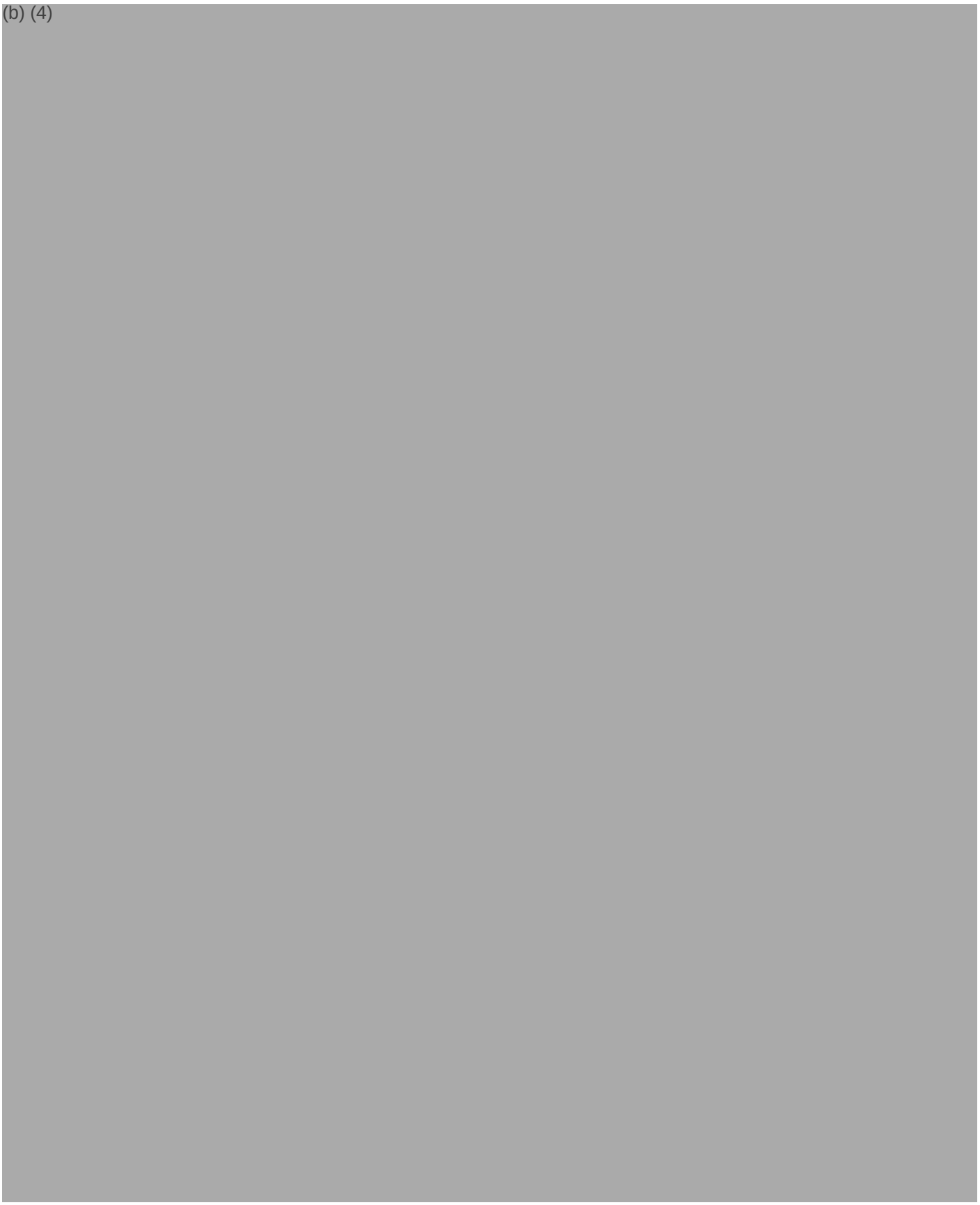

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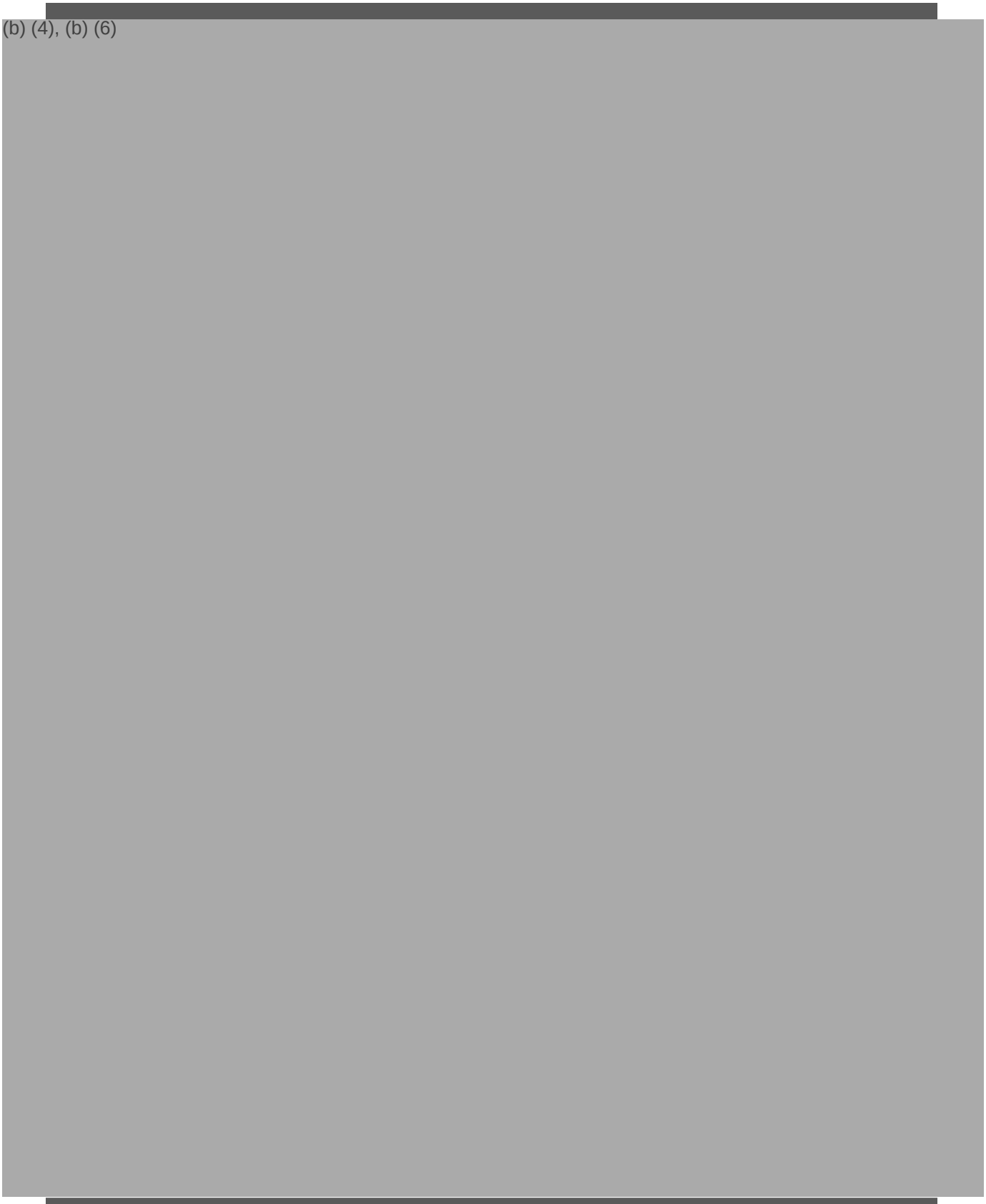

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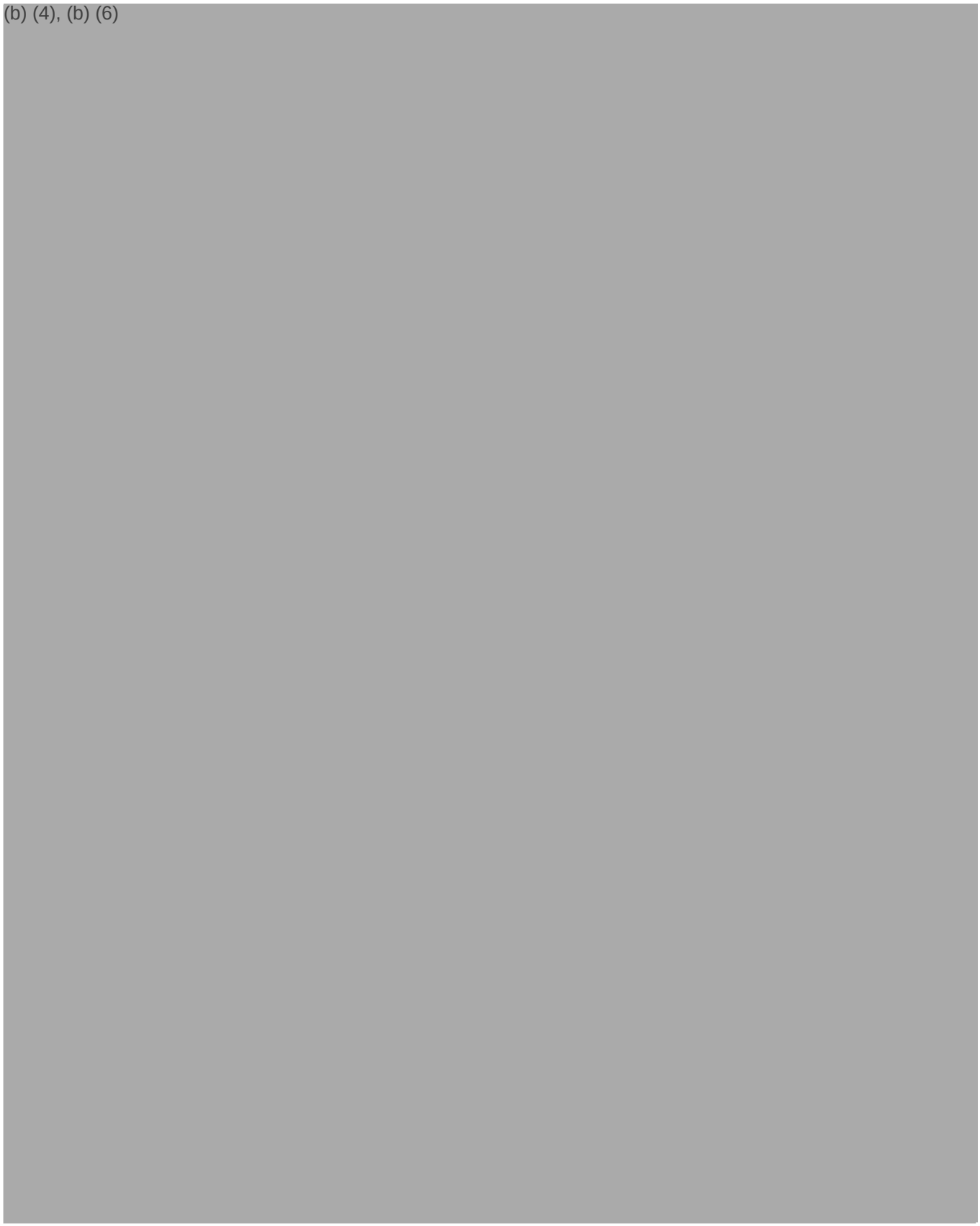

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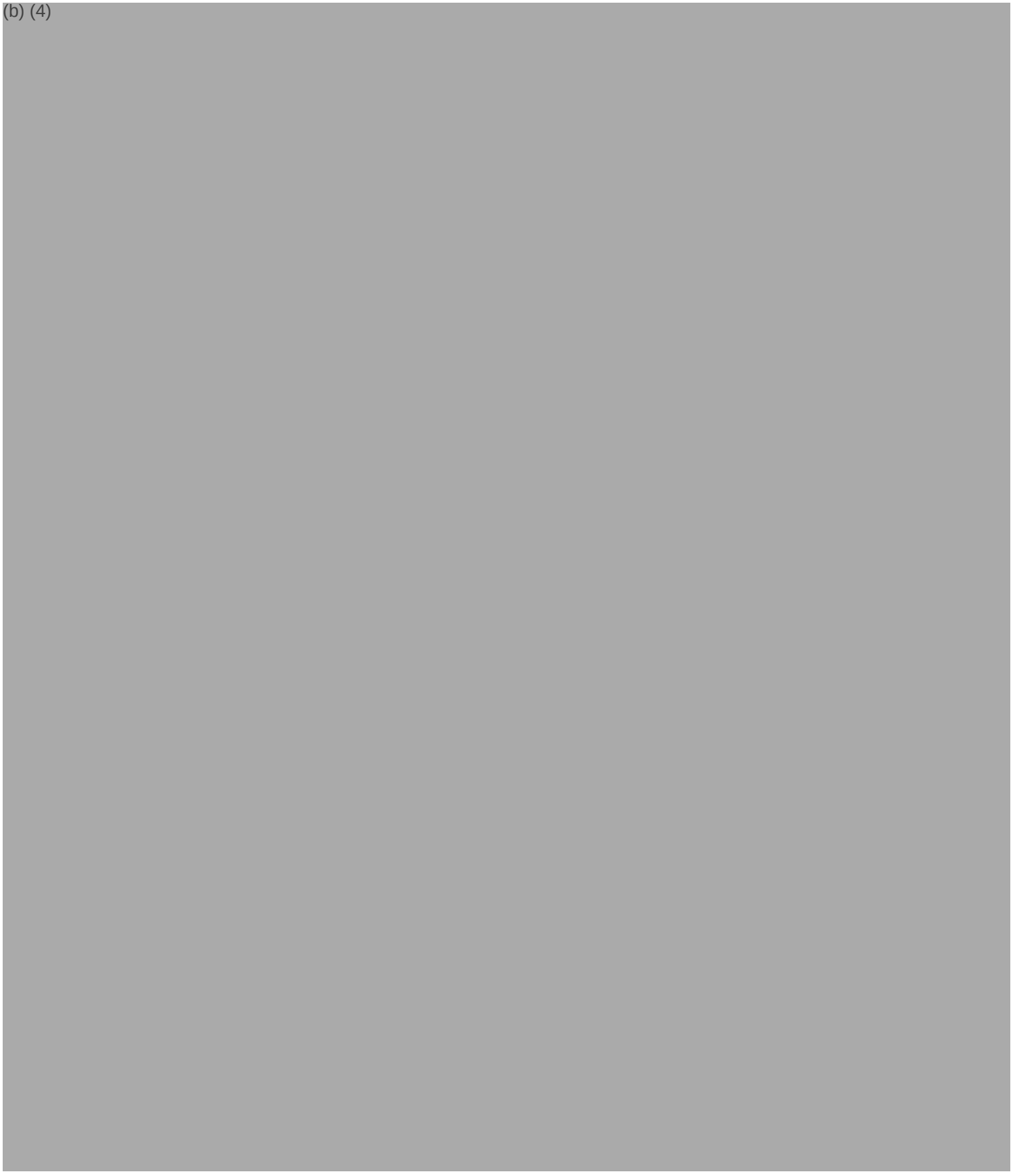

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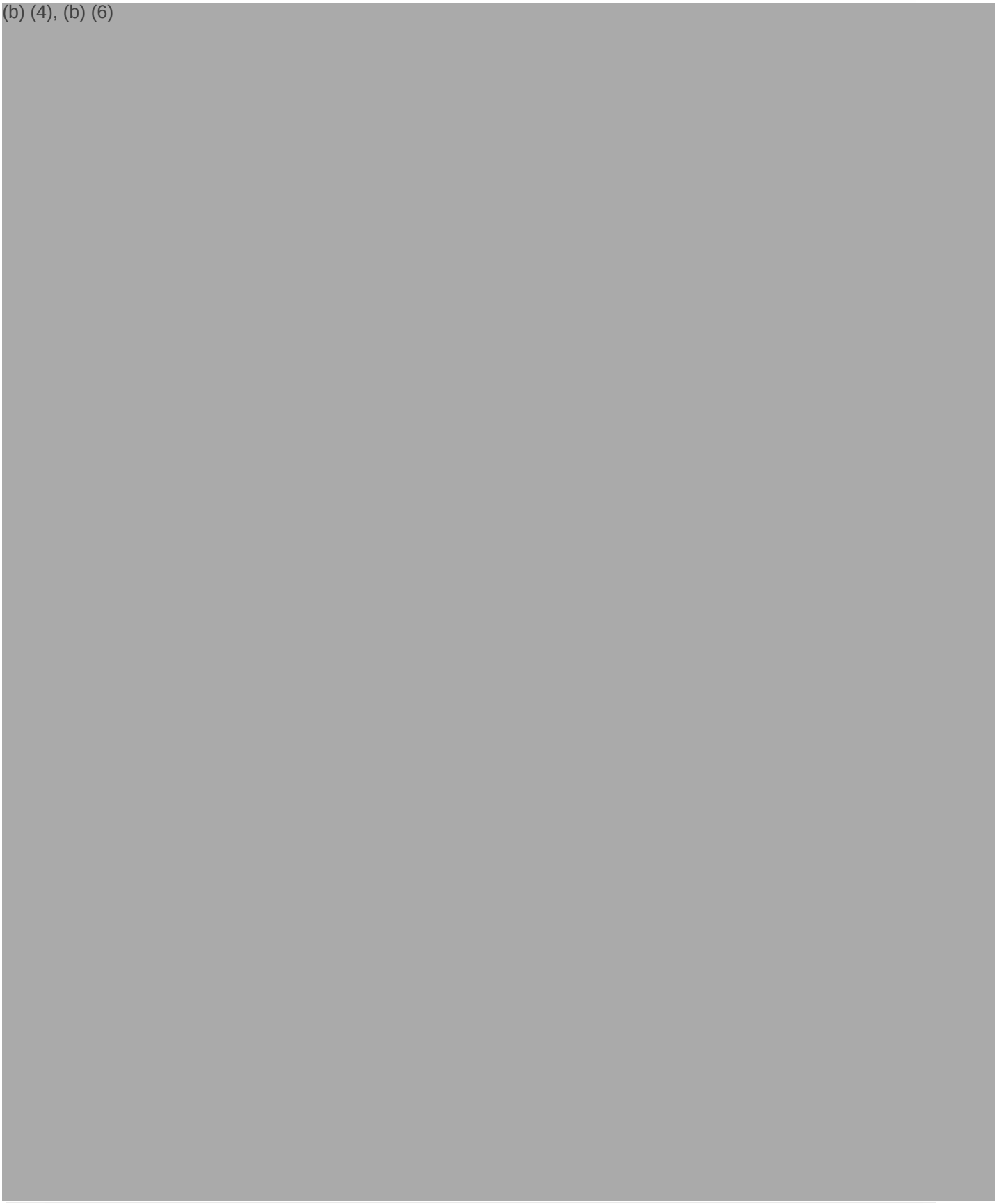

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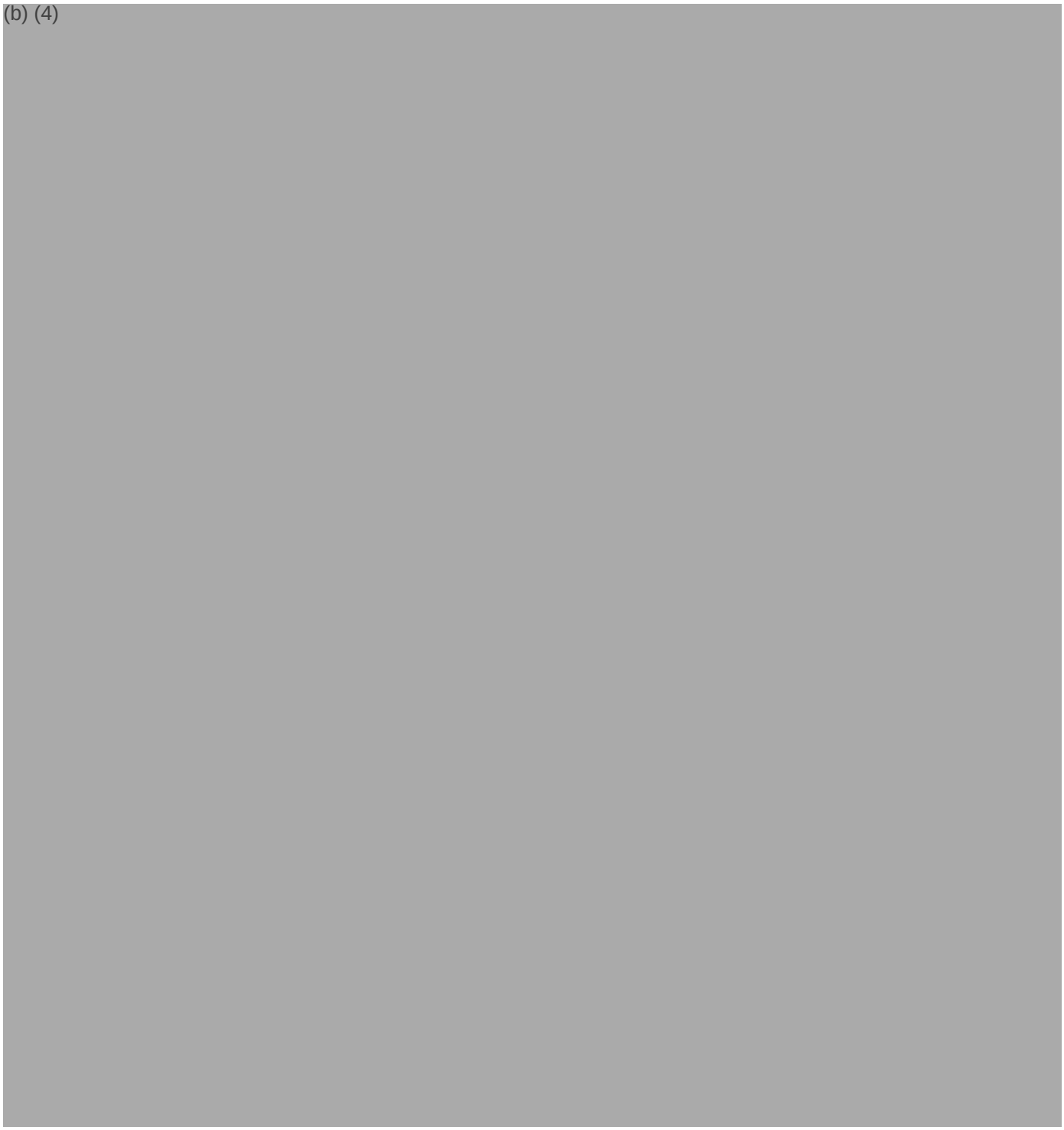

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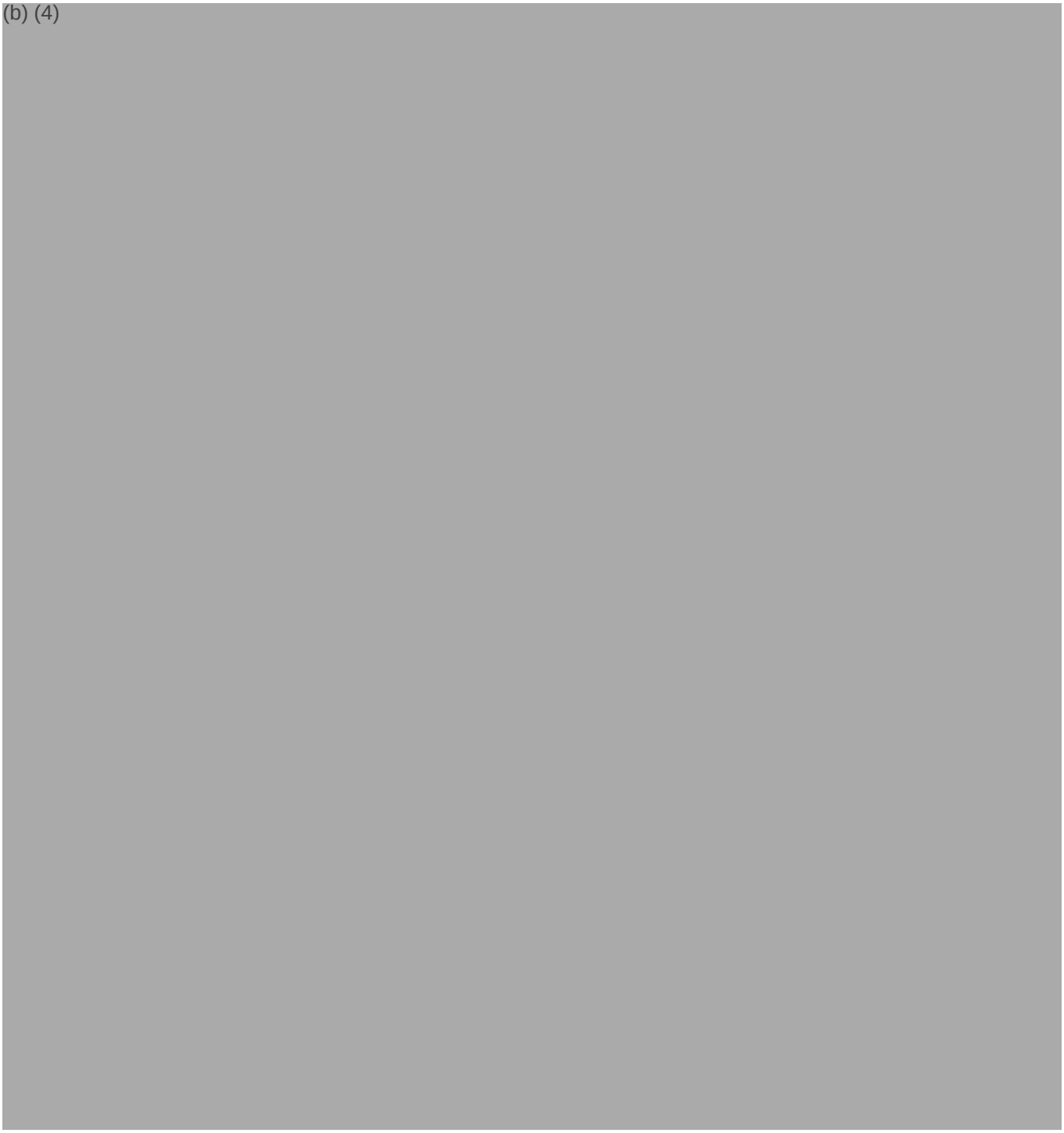

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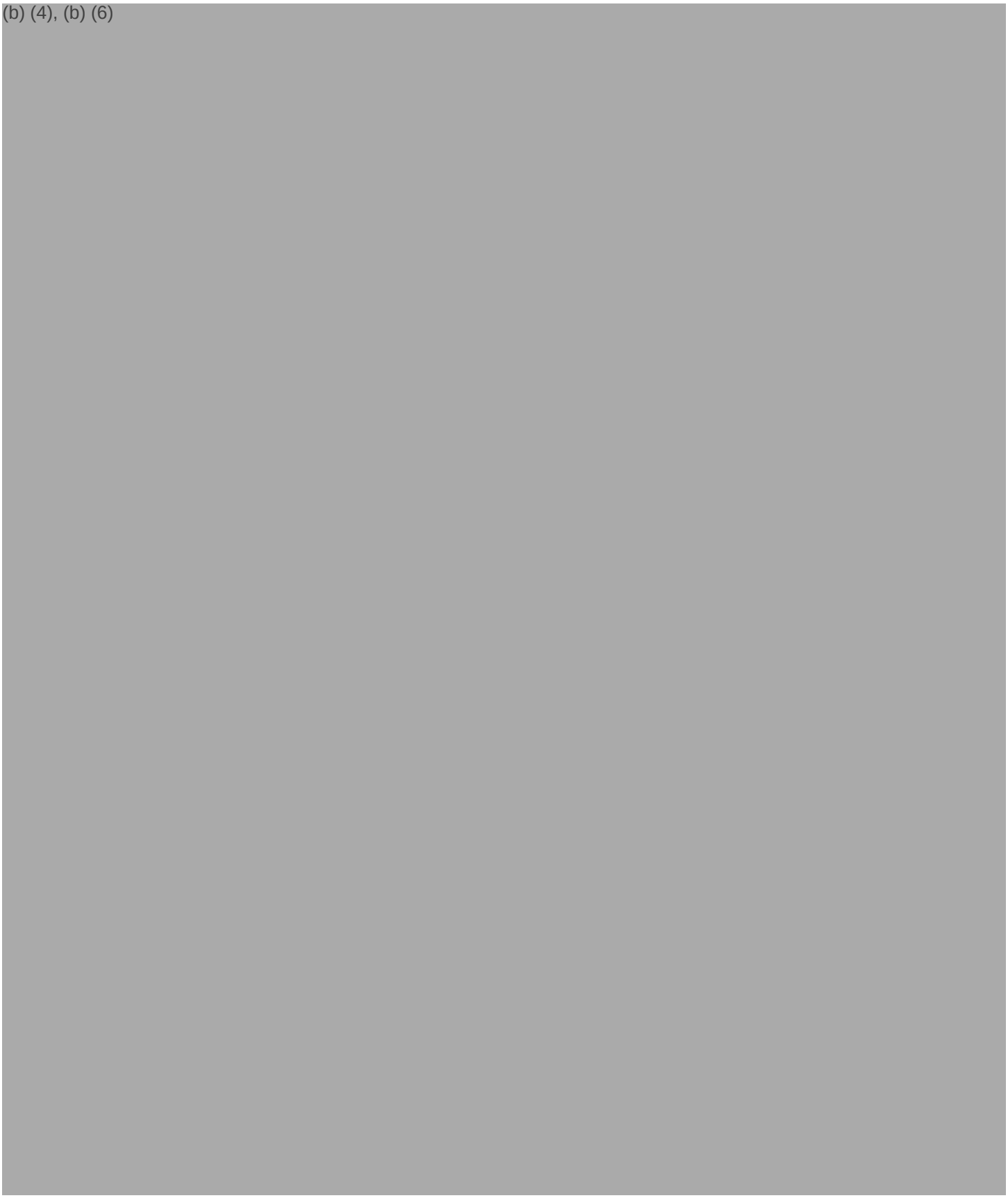

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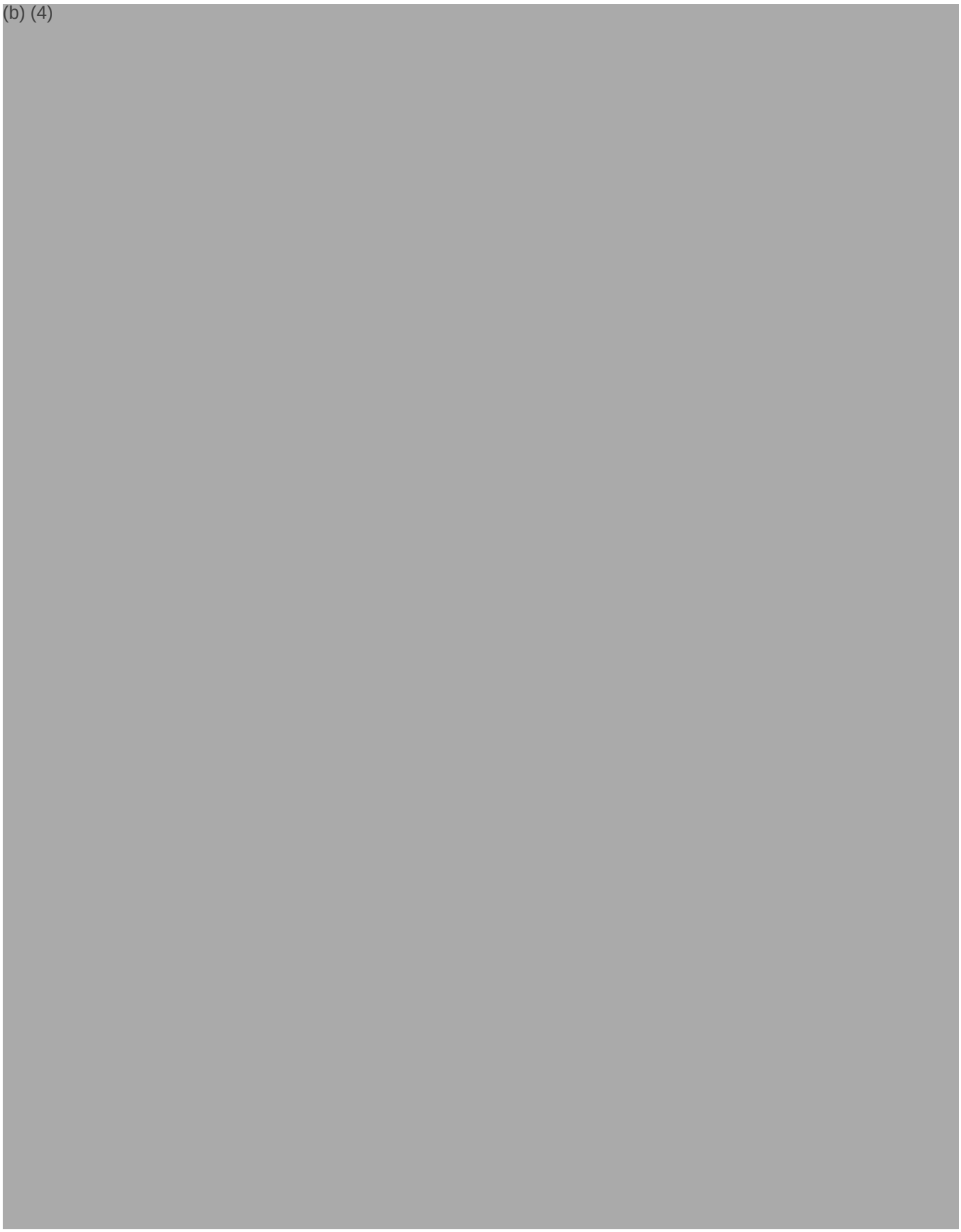

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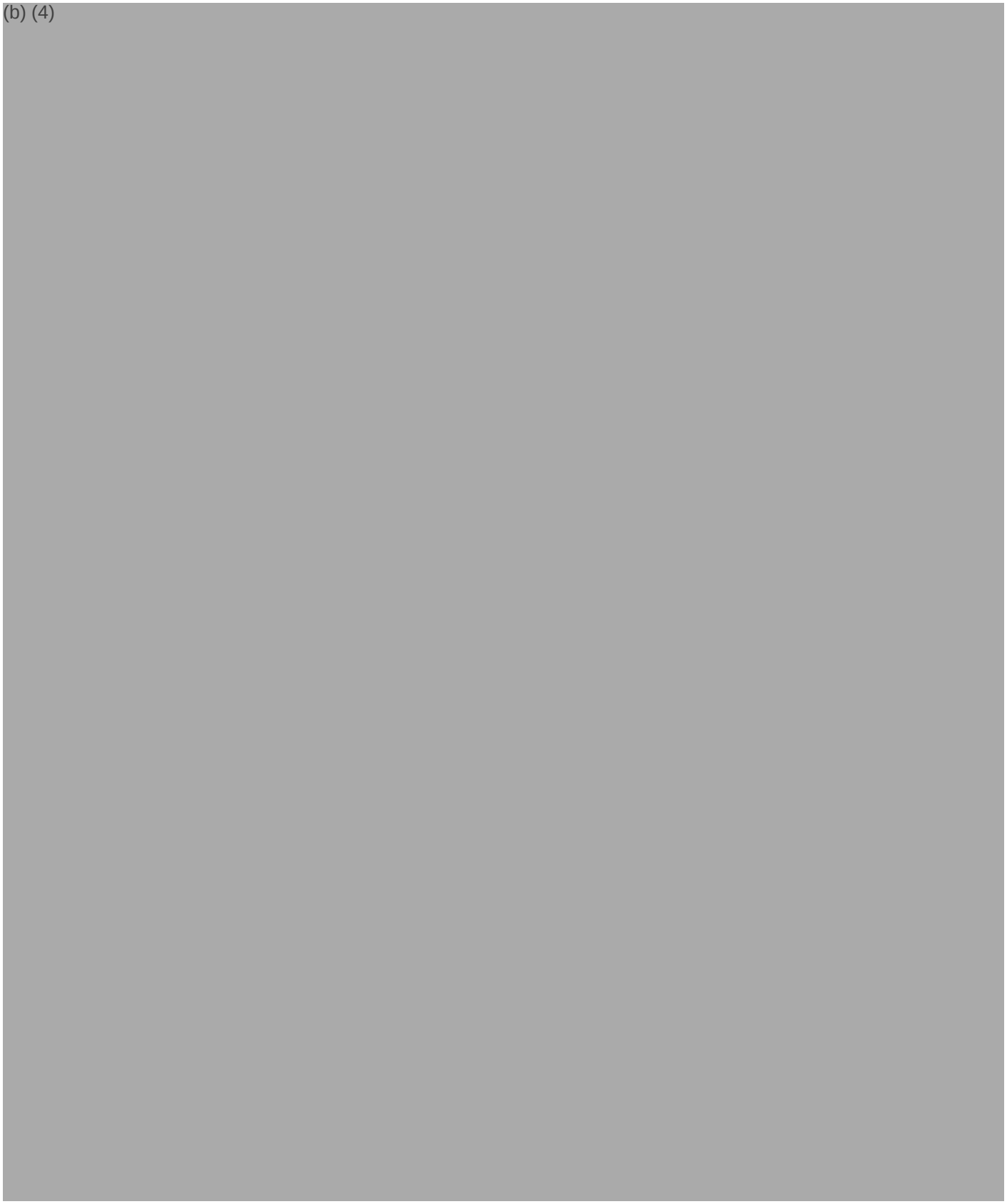

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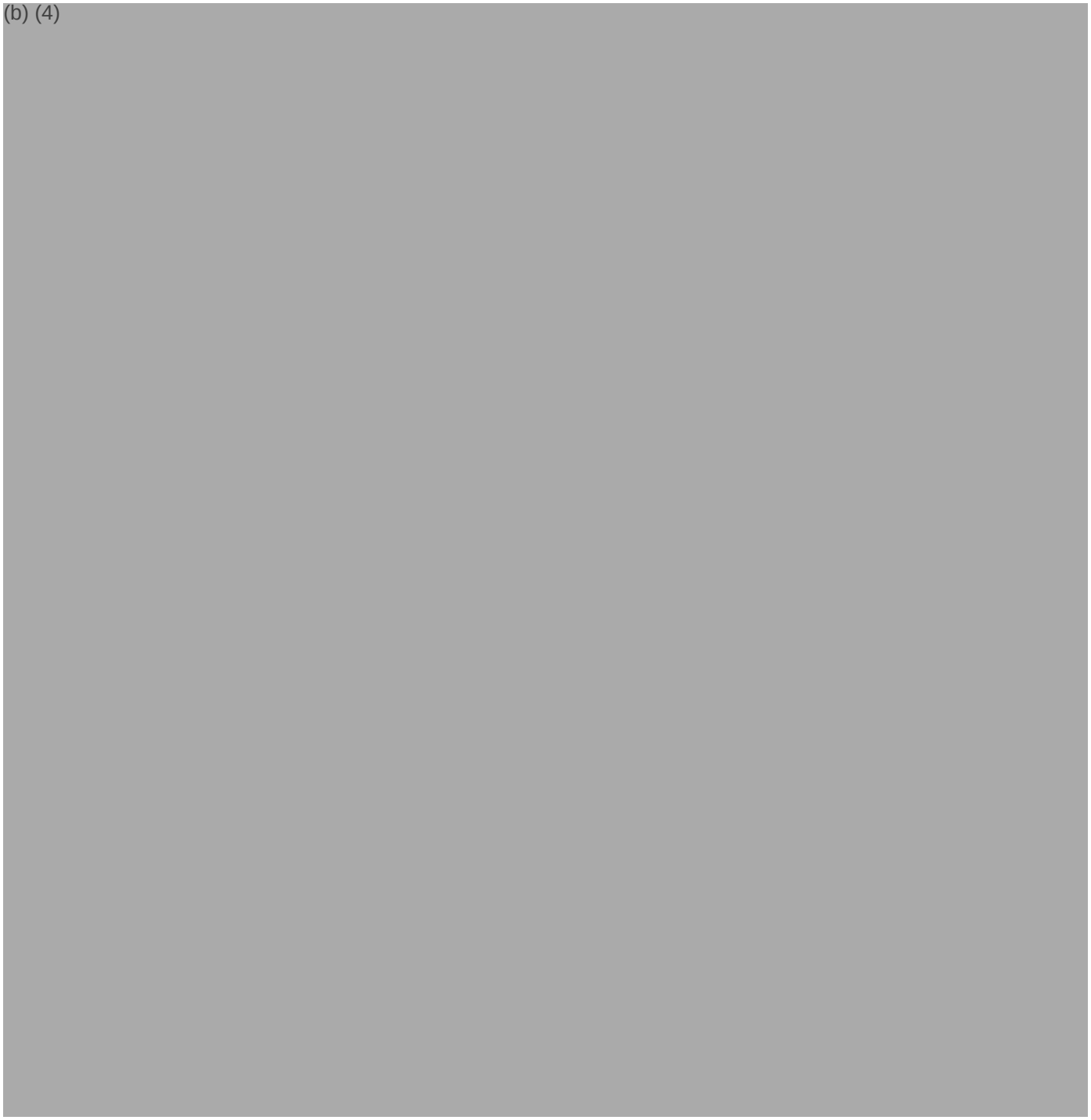

Appendix 18

FINAL REPORT

Study Phase: Pathology

Test Facility Study No. 5002400

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

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1. SUMMARY

This report presents the pathology findings in rats assigned to Study No.5002400. 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.

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

The intramuscular injection of mRNA-1893 to rats at dose of 0, 10, 30, and 96 µg/dose resulted in Test Item effects at the end of main study.

mRNA-1893-related organ weights changes were observed in the spleen (increased mean weights) of males at 96 µg/dose and females at ≥ 30 µg/dose. There were no gross and histologic correlates to these weight changes.

mRNA-1893-related macroscopic findings were observed in the injection site (firm consistency, swelling, thick and dark focus) and draining lymph nodes (iliac, inguinal and/or popliteal) of injections site (enlargement) of males and females at ≥ 10 µg/dose. These findings correlated with mixed cell inflammation in the injection site and increased lymphoid cellularity in the iliac, inguinal and/or popliteal lymph nodes seen histologically.

mRNA-1893-related microscopic findings were observed in the injection site (mixed cell inflammation and epidermal hyperplasia), sciatic nerve (perineurial mixed cell inflammation), draining lymph nodes (iliac, inguinal and/or popliteal) of injection site (perinodal mixed cell inflammation, increased lymphoid cellularity and neutrophilic inflammation), liver (periportal to midzonal hepatocellular vacuolation and Kupffer cell hypertrophy), spleen (decreased cellularity; periarteriolar lymphoid sheath, increased cellularity and neutrophilic infiltration; red pulp and increased extramedullary hematopoiesis) of males and/or females at ≥ 10 µg/dose; bone marrow (increased cellularity; myeloid) of males at ≥ 30 µg/dose and females at ≥ 10 µg/dose and seminal vesicle (increased single cell necrosis) of males at 96 µg/dose. The microscopic findings observed in the sciatic nerve, draining lymph nodes of injection site, bone marrow and spleen (increased extramedullary hematopoiesis) were considered to be secondary or a reactive response to the injection site inflammation.

Following the 2-week recovery period, a partial or complete recovery of all mRNA-1893-related effects was noted. Gross and/or microscopic findings were still present 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 injection site draining lymph nodes (perinodal mixed cell inflammation), in iliac and/or popliteal lymph nodes (enlargement, increased lymphoid cellularity) and liver (periportal to midzonal hepatocellular vacuolation). These remaining findings occurred with a decreased incidence and/or severity indicating partial recovery.

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

Appendix 18

2. INTRODUCTION

This report presents the pathology findings in rats assigned to Study No. 5002400. 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.

3. MATERIALS AND METHODS

Experimental procedures applicable to pathology investigations are summarized in Text Table 1.

Text Table 1
Experimental Design

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

A complete gross pathological examination was performed on all main study and recovery animals and organ weights were recorded, as specified in the Study Plan. A detailed microscopic evaluation of study plan-specified tissues was performed on all Group 1 and 4 animals. Histopathological evaluation was limited to all gross abnormalities and tissues with potential mRNA-1893-related findings on main study animals from Group 2 and 3 (bone marrow, sciatic nerve, liver, spleen, lymph nodes (iliac, inguinal and popliteal) and injection site in males and females and seminal vesicles in males. Tissues that were supposed to be microscopically evaluated per study plan but were not available on the slide (and therefore not evaluated) are listed in the Individual Animal Data of the pathology report as not present. These missing tissues did not affect the outcome or interpretation of the pathology portion of the study, because there were sufficient tissues present in each dose group for evaluation and interpretation. Additional details along with deviations from these procedures may be found in the main study report.

3.1. Computerized System

Critical computerized system used in this study phase is listed in Text Table 2.

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Text Table 2
Computerized System

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	10	Terminal body weight, organ weight data, gross pathology and histopathology.

4. RESULTS AND DISCUSSIONS

4.1. Mortality

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

4.2. Gross Pathology

4.2.1. Terminal Euthanasia Animals (Day 30)

(Table 1 and Appendix 4)

mRNA-1893-related gross pathology findings are summarized in Text Table 3.

Text Table 3
Summary of Gross Pathology Findings – Scheduled Euthanasia (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**10**	**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 control and treated animals and, therefore, were considered unrelated to administration of mRNA-1893.

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4.2.2. Recovery Euthanasia Animals (Day 43)

(Table 1 and Appendix 4)

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 4.

Text Table 4
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 control and treated animals and, therefore, were considered unrelated to administration of mRNA-1893.

4.3. Organ Weights

4.3.1. Terminal Euthanasia Animals (Day 30)

(Table 2, Table 3, Table 4, Appendix 1, Appendix 2, and Appendix 3)

mRNA-1893-related organ weight changes are summarized in Text Table 5.

Text Table 5
Summary of Organ Weight Data – Scheduled Euthanasia (Day 30)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**10**	**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.

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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.

4.3.2. Recovery Euthanasia Animals (Day 43)

(Table 2, Table 3, Table 4, Appendix 1, Appendix 2, and Appendix 3)

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.

4.4. Histopathology

4.4.1. Terminal Euthanasia Animals (Day 30)

(Table 5 and Appendix 4)

mRNA-1893-related microscopic findings are summarized in Text Table 6.

Text Table 6
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

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	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**
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
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

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	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**
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 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. In treated 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

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≥ 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 a higher incidence and/or severity of increased lymphoid cellularity in males and/or females at ≥ 10 µg/dose compared to control 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 control and treated animals and, therefore, were considered unrelated to administration of mRNA-1893.

4.4.2. Recovery Euthanasia Animals (Day 43)

(Table 5 and Appendix 4)

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 7.

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Text Table 7
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.

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

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5. CONCLUSIONS

The 1 month (3 doses administered every other weeks) intramuscular injection of mRNA-1893 to rats at dose of 0, 10, 30, and 96 µg/dose resulted in Test Item effects at the end of main study.

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

mRNA-1893-related organ weights changes were observed in the spleen (increased mean weights) in males at 96 µg/dose and in females at ≥ 30 µg/dose. There were no gross and histologic correlates to these weight changes.

mRNA-1893-related macroscopic findings were observed in the injection site (firm consistency, swelling, thick and dark focus) and draining lymph nodes (iliac, inguinal and/or popliteal) of injections site (enlargement) of males and females at ≥ 10 µg/dose. These findings correlated with mixed cell inflammation in the injection site and increased lymphoid cellularity in the iliac, inguinal and/or popliteal lymph nodes seen histologically.

mRNA-1893-related microscopic findings were observed in the injection site (mixed cell inflammation and epidermal hyperplasia), sciatic nerve (perineurial mixed cell inflammation), draining lymph nodes (iliac, inguinal and /or popliteal) of injection site (perinodal mixed cell inflammation, increased lymphoid cellularity and neutrophilic inflammation), liver (periportal to midzonal hepatocellular vacuolation and Kupffer cell hypertrophy), spleen (decreased cellularity; periarteriolar lymphoid sheath, increased cellularity and neutrophilic infiltration; red pulp and increased extramedullary hematopoiesis) of males and/or females at ≥ 10 µg/dose; bone marrow (increased cellularity; myeloid) of males at ≥ 30 µg/dose and females at ≥ 10 µg/dose and seminal vesicle (increased single cell necrosis) of males at 96 µg/dose. The microscopic findings observed in the sciatic nerve, draining lymph nodes (iliac, inguinal and popliteal) of injection site, bone marrow and spleen (increased extramedullary hematopoiesis) were considered to be secondary or a reactive response to the injection site inflammation.

Following the 2-week recovery period, a partial or complete recovery of all mRNA-1893-related effects was noted. Gross and/or microscopic findings were still present 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 injection site draining lymph nodes (perinodal mixed cell inflammation), in iliac and/or popliteal lymph nodes (enlargement, increased lymphoid cellularity) and liver (periportal to midzonal hepatocellular vacuolation). These remaining findings occurred with a decreased incidence and/or severity indicating partial recovery.

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

Appendix 18

6. REPORT APPROVAL

DocuSigned by:
(b) (6)
Signer Name: (b) (6)
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Appendix 18

Table 1
Summary of Macroscopic Pathology

Appendix 18

Summary of Macroscopic Pathology Explanation Page

Abbreviation	Description
GALT	Gut Associated Lymphoid Tissue

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE MARROW								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE, FEMUR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BONE, STERNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
BRAIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
CERVIX								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
EPIDIDYMIS								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
ESOPHAGUS								
Submitted	10	10	10	10	10	10	10	10

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Summary of Macroscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
ESOPHAGUS (Continued...)								
No Visible Lesions	10	10	10	10	10	10	10	10
EYE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GALT								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, ADRENAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	9	10	10
Focus, dark	0	0	0	0	0	1	0	0
GLAND, HARDERIAN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, MAMMARY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PARATHYROID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PITUITARY								
Submitted	10	10	10	10	10	10	10	10

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Summary of Macroscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, PITUITARY (Continued...)								
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, PROSTATE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
GLAND, SEMINAL VESICLE								
Submitted	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	10	.	.	.	.
GLAND, THYROID								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	9	10	10	10
Enlargement	0	0	0	0	1	0	0	0
HEART								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
KIDNEY								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	5	9	10	10	9	10
Dilatation; pelvis	0	1	5	1	0	0	1	0

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Summary of Macroscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
LARGE INTESTINE, CECUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, COLON								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARGE INTESTINE, RECTUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LARYNX								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
LIVER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	10	8	9	10	8	10
Focus, pale	0	1	0	2	1	0	2	0
LUNG								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	8	8	7	5	10	10	10	8
Focus, dark	2	2	3	5	0	0	0	2
LYMPH NODE								
Submitted	0	0	0	1	0	0	1	0

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Summary of Macroscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE (Continued...)								
Enlargement	.	.	.	1	.	.	0	.
Discoloration, mottled	.	.	.	0	.	.	1	.
Focus, dark	.	.	.	0	.	.	0	.
LYMPH NODE, ILIAC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	8	10	10	7	10	9	9	4
Focus, dark	2	0	0	0	0	0	0	0
Enlargement	0	0	0	3	0	1	1	6
LYMPH NODE, INGUINAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	9	10	10	10	8
Enlargement	0	0	0	1	0	0	0	2
Focus, dark	0	0	0	0	0	0	0	0
LYMPH NODE, MANDIBULAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	9	10	7	9	9	7	8
Enlargement	1	1	0	2	1	1	2	2
Focus, dark	1	0	0	1	0	0	1	0
Discoloration, mottled	0	0	0	0	0	0	0	0
LYMPH NODE, MESENTERIC								
Submitted	10	10	10	10	10	10	10	10

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, MESENTERIC (Continued...)								
No Visible Lesions	10	10	10	9	10	10	10	10
Enlargement	0	0	0	1	0	0	0	0
LYMPH NODE, POPLITEAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	9	10	10	10	10	9	8
Focus, dark	1	0	0	0	0	0	0	0
Enlargement	0	1	0	0	0	0	1	2
MUSCLE, SKELETAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, OPTIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
NERVE, SCIATIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
OVARY								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	9	10	10	10
Cyst, pale	.	.	.	.	1	0	0	0

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
OVIDUCT								
Submitted	.	.	.	.	0	0	0	0
PANCREAS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	10	10	10	10	10	10	10
Mass	1	0	0	0	0	0	0	0
SITE, INJECTION								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	6	1	0	10	3	0	0
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
SKIN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, DUODENUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SMALL INTESTINE, ILEUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
SMALL INTESTINE, JEJUNUM								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, CERVICAL								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, LUMBAR								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPINAL CORD, THORACIC								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
SPLEEN								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	9	10	10	9	10	10	10	9
Irregular surface	1	0	0	1	0	0	0	1
STOMACH								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	9	10	10	10	10
Thick	0	0	0	1	0	0	0	0
TESTIS								
Submitted	10	10	10	10	.	.	.	.

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
TESTIS (Continued...)								
No Visible Lesions	10	10	10	10	.	.	.	.
THYMUS								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	9	9	8	8	8	9	10
Focus, dark	0	1	1	2	2	2	1	0
TONGUE								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
TRACHEA								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
URINARY BLADDER								
Submitted	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	10	10	10	10	10	10
UTERUS								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10
VAGINA								
Submitted	.	.	.	.	10	10	10	10
No Visible Lesions	.	.	.	.	10	10	10	10

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
ARTERY, AORTA				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE MARROW				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, FEMUR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BONE, STERNUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
BRAIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
CERVIX				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
EPIDIDYMIS				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
ESOPHAGUS				
Submitted	5	5	5	5

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
ESOPHAGUS (Continued...)				
No Visible Lesions	5	5	5	5
EYE				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GALT				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, ADRENAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	4	4
Focus, dark	0	0	1	1
GLAND, HARDERIAN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, MAMMARY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PARATHYROID				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, PITUITARY				
Submitted	5	5	5	5

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, PITUITARY (Continued...)				
No Visible Lesions	5	5	5	5
GLAND, PROSTATE				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, SALIVARY, MANDIBULAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, SEMINAL VESICLE				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
GLAND, THYROID				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Enlargement	0	0	0	0
HEART				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
KIDNEY				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Dilatation; pelvis	0	0	0	0

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LARGE INTESTINE, CECUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, COLON				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, RECTUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LARYNX				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
LIVER				
Submitted	5	5	5	5
No Visible Lesions	5	2	4	3
Focus, pale	0	3	1	2
LUNG				
Submitted	5	5	5	5
No Visible Lesions	3	5	5	4
Focus, dark	2	0	0	1
LYMPH NODE				
Submitted	0	0	2	1

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE (Continued...)				
Enlargement	.	.	1	1
Discoloration, mottled	.	.	1	0
Focus, dark	.	.	1	1
LYMPH NODE, ILIAC				
Submitted	5	5	5	5
No Visible Lesions	5	4	5	5
Focus, dark	0	0	0	0
Enlargement	0	1	0	0
LYMPH NODE, INGUINAL				
Submitted	5	5	5	5
No Visible Lesions	5	4	5	4
Enlargement	0	0	0	0
Focus, dark	0	1	0	1
LYMPH NODE, MANDIBULAR				
Submitted	5	5	5	5
No Visible Lesions	3	2	3	3
Enlargement	1	2	2	2
Focus, dark	2	2	0	0
Discoloration, mottled	0	1	0	0
LYMPH NODE, MESENTERIC				
Submitted	5	5	5	5

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, MESENTERIC (Continued...)				
No Visible Lesions	5	5	5	5
Enlargement	0	0	0	0
LYMPH NODE, POPLITEAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Focus, dark	0	0	0	0
Enlargement	0	0	0	0
MUSCLE, SKELETAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, OPTIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, SCIATIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
OVARY				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
Cyst, pale	.	.	0	0

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
OVIDUCT				
Submitted	.	.	0	1
Cyst, pale	.	.	.	1
PANCREAS				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Mass	0	0	0	0
SITE, INJECTION				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Abnormal consistency; firm	0	0	0	0
Swelling	0	0	0	0
Thick	0	0	0	0
Focus, dark	0	0	0	0
SKIN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, DUODENUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, ILEUM				
Submitted	5	5	5	5

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
SMALL INTESTINE, ILEUM (Continued...)				
No Visible Lesions	5	5	5	5
SMALL INTESTINE, JEJUNUM				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, CERVICAL				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, LUMBAR				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, THORACIC				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
SPLEEN				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Irregular surface	0	0	0	0
STOMACH				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
Thick	0	0	0	0

Appendix 18

Summary of Macroscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
TESTIS				
Submitted	5	5	.	.
No Visible Lesions	5	5	.	.
THYMUS				
Submitted	5	5	5	5
No Visible Lesions	4	5	5	5
Focus, dark	1	0	0	0
TONGUE				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
TRACHEA				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
URINARY BLADDER				
Submitted	5	5	5	5
No Visible Lesions	5	5	5	5
UTERUS				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5
VAGINA				
Submitted	.	.	5	5
No Visible Lesions	.	.	5	5

Appendix 18

Table 2
Summary of Absolute Organ Weights

Appendix 18

Summary of Absolute Organ Weights Explanation Page

Abbreviation	Description
BW	Body weight

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 18

Summary of Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Terminal Body Weight (g) [G]	Mean	392.8	395.4	387.2	390.5
	SD	35.3	38.0	33.9	31.6
	N	10	10	10	10
	%Diff	-	0.7	-1.4	-0.6
Brain Weight (g) [G1]	Mean	1.9892	2.0126	2.0299	2.0077
	SD	0.0627	0.0836	0.0656	0.1295
	N	10	10	10	10
	%Diff	-	1.1764	2.0460	0.9300
Epididymis Weight (g) [G2]	Mean	1.0426	1.0454	0.9703	1.0022
	SD	0.0881	0.0922	0.0589	0.0601
	N	10	10	10	10
	%Diff	-	0.2686	-6.9346	-3.8749
Gland, Adrenal Weight (g) [G2]	Mean	0.05583	0.05715	0.05588	0.06093
	SD	0.00869	0.00712	0.00689	0.01142
	N	10	10	10	10
	%Diff	-	2.36432	0.08956	9.13487
Gland, Pituitary Weight (g) [G2]	Mean	0.01192	0.01137	0.01143	0.01273
	SD	0.00131	0.00196	0.00111	0.00232
	N	10	10	10	10
	%Diff	-	-4.61409	-4.11074	6.79530
Gland, Prostate Weight (g) [G2]	Mean	1.1434	1.1129	1.0283	1.0154
	SD	0.1272	0.1715	0.1090	0.1208
	N	10	10	10	10
	%Diff	-	-2.6675	-10.0665	-11.1947
Gland, Thyroid Weight (g) [G2]	Mean	0.01670	0.01670	0.01529	0.01628
	SD	0.00219	0.00309	0.00216	0.00256
	N	10	10	10	10
	%Diff	-	0.00000	-8.44311	-2.51497
Heart Weight (g) [G2]	Mean	1.3195	1.3166	1.3627	1.3924
	SD	0.0904	0.1412	0.1346	0.1206
	N	10	10	10	10
	%Diff	-	-0.2198	3.2740	5.5248

[G] - Anova & Dunnett
[G1] - Kruskal-Wallis & Dunn
[G2] - Anova & Dunnett

Appendix 18

Summary of Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Kidney Weight (g) [G]	Mean	2.5917	2.6315	2.5911	2.7099
	SD	0.2446	0.2672	0.2612	0.2203
	N	10	10	10	10
	%Diff	-	1.5357	-0.0232	4.5607
Liver Weight (g) [G]	Mean	11.9820	12.0380	12.1846	13.1913
	SD	1.2135	1.6392	1.4762	1.2388
	N	10	10	10	10
	%Diff	-	0.4674	1.6909	10.0926
Lung Weight (g) [G]	Mean	1.4076	1.4727	1.4605	1.5512
	SD	0.1032	0.0972	0.1413	0.0951
	N	10	10	10	10
	%Diff	-	4.6249	3.7582	10.2018
Spleen Weight (g) [G]	Mean	0.7680	0.7622	0.8164	0.8760
	SD	0.0896	0.1262	0.1139	0.1078
	N	10	10	10	10
	%Diff	-	-0.7552	6.3021	14.0625
Testis Weight (g) [G]	Mean	3.6431	3.8541	3.6483	3.7772
	SD	0.2464	0.2893	0.3116	0.2141
	N	10	10	10	10
	%Diff	-	5.7918	0.1427	3.6809
Thymus Weight (g) [G]	Mean	0.4375	0.4233	0.4386	0.4960
	SD	0.1218	0.1052	0.1292	0.1051
	N	10	10	10	10
	%Diff	-	-3.2457	0.2514	13.3714

[G] - Anova & Dunnett

Appendix 18

Summary of Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Terminal Body Weight (g) [G]	Mean	247.3	240.6	233.6	237.6
	SD	9.9	15.4	10.5	27.4
	N	10	10	10	10
	%Diff	-	-2.7	-5.5	-3.9
Brain Weight (g) [G1]	Mean	1.9231	1.8608	1.8427	1.8633
	SD	0.1626	0.0765	0.0721	0.0895
	N	10	10	10	10
	%Diff	-	-3.2396	-4.1807	-3.1096
Gland, Adrenal Weight (g) [G1]	Mean	0.06328	0.05686	0.06163	0.07049
	SD	0.00529	0.00902	0.00721	0.00629
	N	10	10	10	10
	%Diff	-	-10.14539	-2.60746	11.39381
Gland, Pituitary Weight (g) [G1]	Mean	0.01583	0.01561	0.01409	0.01444
	SD	0.00180	0.00186	0.00123	0.00199
	N	10	10	10	10
	%Diff	-	-1.38977	-10.99179	-8.78080
Gland, Thyroid Weight (g) [G1]	Mean	0.01381	0.01303	0.01336	0.01357
	SD	0.00294	0.00166	0.00245	0.00315
	N	10	10	10	10
	%Diff	-	-5.64808	-3.25851	-1.73787
Heart Weight (g) [G1]	Mean	1.0025	0.9668	0.9458	1.0022
	SD	0.0642	0.0880	0.0522	0.0927
	N	10	10	10	10
	%Diff	-	-3.5611	-5.6559	-0.0299
Kidney Weight (g) [G1]	Mean	1.7451	1.6519	1.6339	1.6989
	SD	0.0823	0.1466	0.0880	0.1660
	N	10	10	10	10
	%Diff	-	-5.3407	-6.3721	-2.6474
Liver Weight (g) [G1]	Mean	7.5762	7.5530	7.3966	7.8640
	SD	0.4330	0.6152	0.7571	0.8581
	N	10	10	10	10
	%Diff	-	-0.3062	-2.3706	3.7987

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

Appendix 18

Summary of Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Lung Weight (g) [G]	Mean	1.1201	1.1511	1.1540	1.1480
	SD	0.0479	0.0968	0.0996	0.1257
	N	10	10	10	10
	%Diff	-	2.7676	3.0265	2.4908
Ovary Weight (g) [G1]	Mean	0.1155	0.0940	0.1077	0.0985
	SD	0.0475	0.0148	0.0169	0.0132
	N	10	10	10	10
	%Diff	-	-18.6147	-6.7532	-14.7186
Spleen Weight (g) [G1]	Mean	0.5604	0.5568	0.6027	0.6192
	SD	0.0587	0.0435	0.0950	0.0586
	N	10	10	10	10
	%Diff	-	-0.6424	7.5482	10.4925
Thymus Weight (g) [G1]	Mean	0.3775	0.3571	0.3673	0.3277
	SD	0.0390	0.0831	0.0720	0.0972
	N	10	10	10	10
	%Diff	-	-5.4040	-2.7020	-13.1921
Uterus Weight (g) [G]	Mean	0.7021	0.5563	0.6382	0.6650
	SD	0.3061	0.1756	0.1383	0.2150
	N	10	10	10	10
	%Diff	-	-20.7663	-9.1013	-5.2841

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

Appendix 18

Summary of Absolute Organ Weights: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Terminal Body Weight (g) [G]	Mean	431.0	414.8
	SD	63.0	23.0
	N	5	5
	%Diff	-	-3.8
Brain Weight (g) [G1]	Mean	2.0966	2.0608
	SD	0.0279	0.1272
	N	5	5
	%Diff	-	-1.7075
Epididymis Weight (g) [G2]	Mean	1.2054	1.2122
	SD	0.0593	0.0141
	N	5	5
	%Diff	-	0.5641
Gland, Adrenal Weight (g) [G1]	Mean	0.05808	0.05256
	SD	0.00486	0.00515
	N	5	5
	%Diff	-	-9.50413
Gland, Pituitary Weight (g) [G1]	Mean	0.01386	0.01262
	SD	0.00213	0.00143
	N	5	5
	%Diff	-	-8.94661
Gland, Prostate Weight (g) [G2]	Mean	1.0672	0.9576
	SD	0.1664	0.0678
	N	5	5
	%Diff	-	-10.2699
Gland, Thyroid Weight (g) [G1]	Mean	0.01448	0.01540
	SD	0.00371	0.00350
	N	5	5
	%Diff	-	6.35359
Heart Weight (g) [G1]	Mean	1.5358	1.4208
	SD	0.2941	0.1686
	N	5	5
	%Diff	-	-7.4880

[G] - Anova & Dunnett
[G1] - Anova & Dunnett
[G2] - Kruskal-Wallis & Dunn

Appendix 18

Summary of Absolute Organ Weights: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Kidney Weight (g) [G]	Mean	2.6544	2.7592
	SD	0.4151	0.2231
	N	5	5
	%Diff	-	3.9482
Liver Weight (g) [G]	Mean	12.8276	11.9704
	SD	2.7029	1.1539
	N	5	5
	%Diff	-	-6.6825
Lung Weight (g) [G]	Mean	1.4082	1.4738
	SD	0.2013	0.1776
	N	5	5
	%Diff	-	4.6584
Spleen Weight (g) [G]	Mean	0.7418	0.7694
	SD	0.1563	0.1150
	N	5	5
	%Diff	-	3.7207
Testis Weight (g) [G]	Mean	3.7510	3.7340
	SD	0.2049	0.1871
	N	5	5
	%Diff	-	-0.4532
Thymus Weight (g) [G]	Mean	0.4220	0.3722
	SD	0.0762	0.0798
	N	5	5
	%Diff	-	-11.8009

[G] - Anova & Dunnett

Appendix 18

Summary of Absolute Organ Weights: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Terminal Body Weight (g) [G]	Mean	255.2	248.4
	SD	12.8	2.4
	N	5	5
	%Diff	-	-2.7
Brain Weight (g) [G1]	Mean	1.8986	1.8318
	SD	0.1160	0.0753
	N	5	5
	%Diff	-	-3.5184
Gland, Adrenal Weight (g) [G1]	Mean	0.05920	0.06304
	SD	0.00989	0.00334
	N	5	5
	%Diff	-	6.48649
Gland, Pituitary Weight (g) [G1]	Mean	0.01602	0.01700
	SD	0.00207	0.00154
	N	5	5
	%Diff	-	6.11735
Gland, Thyroid Weight (g) [G1]	Mean	0.01308	0.01272
	SD	0.00210	0.00182
	N	5	5
	%Diff	-	-2.75229
Heart Weight (g) [G1]	Mean	1.0494	1.0718
	SD	0.0703	0.1810
	N	5	5
	%Diff	-	2.1346
Kidney Weight (g) [G1]	Mean	1.7030	1.6498
	SD	0.1338	0.1340
	N	5	5
	%Diff	-	-3.1239
Liver Weight (g) [G1]	Mean	7.7722	7.3750
	SD	0.5581	0.4582
	N	5	5
	%Diff	-	-5.1105

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

Appendix 18

Summary of Absolute Organ Weights: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Lung Weight (g) [G]	Mean	1.1322	1.1252
	SD	0.0593	0.0737
	N	5	5
	%Diff	-	-0.6183
Ovary Weight (g) [G]	Mean	0.1020	0.1036
	SD	0.0117	0.0189
	N	5	5
	%Diff	-	1.5686
Spleen Weight (g) [G]	Mean	0.5166	0.4954
	SD	0.0695	0.0340
	N	5	5
	%Diff	-	-4.1038
Thymus Weight (g) [G]	Mean	0.3608	0.3526
	SD	0.0551	0.0712
	N	5	5
	%Diff	-	-2.2727
Uterus Weight (g) [G]	Mean	0.5894	0.5722
	SD	0.3222	0.2559
	N	5	5
	%Diff	-	-2.9182

[G] - Anova & Dunnett

Appendix 18

Table 3
Summary of Organ Weights Relative to Body Weight

Appendix 18

Summary of Organ Weights Relative to Body Weight Explanation Page

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 18

Summary of Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Brain (%) [G]	Mean	0.50937	0.51240	0.52705	0.51547
	SD	0.03912	0.04481	0.03767	0.03025
	N	10	10	10	10
	%Diff	-	0.59493	3.47052	1.19594
Epididymis (%) [G]	Mean	0.26660	0.26565	0.25244	0.25779
	SD	0.02522	0.02648	0.02774	0.02218
	N	10	10	10	10
	%Diff	-	-0.35539	-5.31193	-3.30546
Gland, Adrenal (%) [G]	Mean	0.01420	0.01446	0.01447	0.01555
	SD	0.00157	0.00123	0.00161	0.00221
	N	10	10	10	10
	%Diff	-	1.86691	1.90038	9.55117
Gland, Pituitary (%) [G]	Mean	0.00304	0.00287	0.00296	0.00325
	SD	0.00025	0.00032	0.00028	0.00044
	N	10	10	10	10
	%Diff	-	-5.62956	-2.47579	6.86989
Gland, Prostate (%) [G]	Mean	0.29285	0.28404	0.26706	0.26048
	SD	0.04061	0.05529	0.03236	0.02735
	N	10	10	10	10
	%Diff	-	-3.00802	-8.80608	-11.05356
Gland, Thyroid (%) [G]	Mean	0.00426	0.00422	0.00396	0.00419
	SD	0.00047	0.00068	0.00057	0.00068
	N	10	10	10	10
	%Diff	-	-0.87246	-6.89216	-1.66373
Heart (%) [G]	Mean	0.33758	0.33376	0.35238	0.35681
	SD	0.02991	0.02871	0.02632	0.01759
	N	10	10	10	10
	%Diff	-	-1.13271	4.38386	5.69421
Kidney (%) [G]	Mean	0.66114	0.66582	0.66882	0.69463
	SD	0.04748	0.03306	0.02592	0.03520
	N	10	10	10	10
	%Diff	-	0.70921	1.16296	5.06588

[G] - Anova & Dunnett

Appendix 18

Summary of Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Liver (%) [G]	Mean	3.05495	3.03733	3.14259	3.38416**
	SD	0.22186	0.19996	0.19540	0.26686
	N	10	10	10	10
	%Diff	-	-0.57681	2.86895	10.77638
Lung (%) [G]	Mean	0.36001	0.37360	0.37756	0.39816**
	SD	0.03163	0.01753	0.02289	0.02031
	N	10	10	10	10
	%Diff	-	3.77349	4.87431	10.59675
Spleen (%) [G]	Mean	0.19581	0.19212	0.21073	0.22457**
	SD	0.01799	0.01916	0.02014	0.02288
	N	10	10	10	10
	%Diff	-	-1.88364	7.62303	14.68763
Testis (%) [G]	Mean	0.93172	0.97889	0.94591	0.97029
	SD	0.07948	0.07513	0.08655	0.05831
	N	10	10	10	10
	%Diff	-	5.06245	1.52273	4.13949
Thymus (%) [G]	Mean	0.11059	0.10608	0.11273	0.12657
	SD	0.02513	0.02039	0.03026	0.02494
	N	10	10	10	10
	%Diff	-	-4.08183	1.93519	14.44386

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

Appendix 18

Summary of Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Brain (%) [G]	Mean	0.77767	0.77590	0.78968	0.79261
	SD	0.05717	0.05297	0.03421	0.08608
	N	10	10	10	10
	%Diff	-	-0.22797	1.54414	1.92019
Gland, Adrenal (%) [G]	Mean	0.02562	0.02368	0.02648	0.03004 *
	SD	0.00225	0.00374	0.00366	0.00455
	N	10	10	10	10
	%Diff	-	-7.55676	3.37485	17.27971
Gland, Pituitary (%) [G]	Mean	0.00640	0.00650	0.00605	0.00612
	SD	0.00069	0.00081	0.00073	0.00089
	N	10	10	10	10
	%Diff	-	1.56357	-5.40256	-4.44288
Gland, Thyroid (%) [G]	Mean	0.00558	0.00544	0.00574	0.00576
	SD	0.00114	0.00079	0.00118	0.00140
	N	10	10	10	10
	%Diff	-	-2.49760	2.97252	3.22318
Heart (%) [G]	Mean	0.40569	0.40150	0.40546	0.42505
	SD	0.02639	0.01992	0.02601	0.05072
	N	10	10	10	10
	%Diff	-	-1.03323	-0.05690	4.77276
Kidney (%) [G]	Mean	0.70635	0.68665	0.69973	0.71783
	SD	0.03726	0.04156	0.03034	0.05419
	N	10	10	10	10
	%Diff	-	-2.78885	-0.93750	1.62461
Liver (%) [G]	Mean	3.06861	3.14352	3.16741	3.31423
	SD	0.22319	0.24554	0.30667	0.14103
	N	10	10	10	10
	%Diff	-	2.44119	3.21974	8.00430
Lung (%) [G]	Mean	0.45304	0.47823	0.49396	0.48640
	SD	0.01261	0.02245	0.03671	0.06098
	N	10	10	10	10
	%Diff	-	5.56183	9.03380	7.36468

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

Appendix 18

Summary of Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Ovary (%) [G]	Mean	0.04660	0.03919	0.04615	0.04197
	SD	0.01856	0.00630	0.00719	0.00773
	N	10	10	10	10
	%Diff	-	-15.89554	-0.96437	-9.94249
Spleen (%) [G]	Mean	0.22661	0.23192	0.25768*	0.26246*
	SD	0.02228	0.01921	0.03745	0.02904
	N	10	10	10	10
	%Diff	-	2.34641	13.71379	15.82386
Thymus (%) [G]	Mean	0.15274	0.14873	0.15761	0.13675
	SD	0.01558	0.03544	0.03194	0.03079
	N	10	10	10	10
	%Diff	-	-2.62647	3.18930	-10.46916
Uterus (%) [G1]	Mean	0.28489	0.23078	0.27264	0.28396
	SD	0.12598	0.06570	0.05514	0.10076
	N	10	10	10	10
	%Diff	-	-18.99446	-4.29978	-0.32502

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

Appendix 18

Summary of Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Brain (%) [G]	Mean	0.49517	0.49712
	SD	0.07488	0.02427
	N	5	5
	%Diff	-	0.39399
Epididymis (%) [G]	Mean	0.28438	0.29291
	SD	0.04142	0.01571
	N	5	5
	%Diff	-	3.00117
Gland, Adrenal (%) [G]	Mean	0.01360	0.01270
	SD	0.00113	0.00139
	N	5	5
	%Diff	-	-6.62953
Gland, Pituitary (%) [G]	Mean	0.00322	0.00304
	SD	0.00028	0.00025
	N	5	5
	%Diff	-	-5.63788
Gland, Prostate (%) [G1]	Mean	0.24938	0.23117
	SD	0.03426	0.01638
	N	5	5
	%Diff	-	-7.30143
Gland, Thyroid (%) [G]	Mean	0.00332	0.00370
	SD	0.00056	0.00077
	N	5	5
	%Diff	-	11.42467
Heart (%) [G]	Mean	0.35590	0.34210
	SD	0.04445	0.02913
	N	5	5
	%Diff	-	-3.87621
Kidney (%) [G]	Mean	0.61543	0.66486*
	SD	0.03100	0.03118
	N	5	5
	%Diff	-	8.03169

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

Appendix 18

Summary of Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Liver (%) [G]	Mean	2.96317	2.88421
	SD	0.40033	0.19792
	N	5	5
	%Diff	-	-2.66489
Lung (%) [G]	Mean	0.32723	0.35435
	SD	0.01347	0.02430
	N	5	5
	%Diff	-	8.28950
Spleen (%) [G]	Mean	0.17363	0.18517
	SD	0.03601	0.02215
	N	5	5
	%Diff	-	6.64716
Testis (%) [G]	Mean	0.88903	0.90201
	SD	0.16346	0.06030
	N	5	5
	%Diff	-	1.46051
Thymus (%) [G]	Mean	0.09821	0.08934
	SD	0.01413	0.01563
	N	5	5
	%Diff	-	-9.03840

[G] - Anova & Dunnett

Appendix 18

Summary of Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Brain (%) [G]	Mean	0.74476	0.73755
	SD	0.04735	0.03274
	N	5	5
	%Diff	-	-0.96817
Gland, Adrenal (%) [G]	Mean	0.02312	0.02537
	SD	0.00296	0.00113
	N	5	5
	%Diff	-	9.72591
Gland, Pituitary (%) [G]	Mean	0.00628	0.00684
	SD	0.00080	0.00057
	N	5	5
	%Diff	-	8.91548
Gland, Thyroid (%) [G]	Mean	0.00511	0.00512
	SD	0.00062	0.00069
	N	5	5
	%Diff	-	0.17846
Heart (%) [G]	Mean	0.41110	0.43155
	SD	0.01473	0.07386
	N	5	5
	%Diff	-	4.97565
Kidney (%) [G]	Mean	0.66700	0.66437
	SD	0.03290	0.05613
	N	5	5
	%Diff	-	-0.39421
Liver (%) [G]	Mean	3.05532	2.96950
	SD	0.31331	0.19089
	N	5	5
	%Diff	-	-2.80872
Lung (%) [G]	Mean	0.44384	0.45309
	SD	0.01588	0.03149
	N	5	5
	%Diff	-	2.08306

[G] - Anova & Dunnett

Appendix 18

Summary of Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Ovary (%) [G]	Mean	0.04014	0.04174
	SD	0.00592	0.00783
	N	5	5
	%Diff	-	3.97435
Spleen (%) [G]	Mean	0.20283	0.19951
	SD	0.02970	0.01485
	N	5	5
	%Diff	-	-1.63798
Thymus (%) [G]	Mean	0.14100	0.14182
	SD	0.01681	0.02774
	N	5	5
	%Diff	-	0.58108
Uterus (%) [G]	Mean	0.22755	0.23071
	SD	0.11123	0.10432
	N	5	5
	%Diff	-	1.38707

[G] - Anova & Dunnett

Appendix 18

Table 4
Summary of Organ Weights Relative to Brain Weight

Appendix 18

Summary of Organ Weights Relative to Brain Weight Explanation Page

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 18

Summary of Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Epididymis (%) [G]	Mean	52.39133	51.97209	47.87773*	49.96946
	SD	3.82196	4.45785	3.85378	2.17070
	N	10	10	10	10
	%Diff	-	-0.80021	-8.61518	-4.62265
Gland, Adrenal (%) [G]	Mean	2.80622	2.83818	2.75012	3.03201
	SD	0.42222	0.30841	0.30138	0.51460
	N	10	10	10	10
	%Diff	-	1.13913	-1.99890	8.04611
Gland, Pituitary (%) [G1]	Mean	0.59895	0.56391	0.56323	0.63401
	SD	0.05897	0.08402	0.05320	0.10938
	N	10	10	10	10
	%Diff	-	-5.85023	-5.96348	5.85440
Gland, Prostate (%) [G]	Mean	57.43023	55.36714	50.69470	50.66205
	SD	5.71309	8.62169	5.48373	6.00427
	N	10	10	10	10
	%Diff	-	-3.59235	-11.72820	-11.78505
Gland, Thyroid (%) [G]	Mean	0.83915	0.83109	0.75157	0.81397
	SD	0.10434	0.15722	0.09057	0.13944
	N	10	10	10	10
	%Diff	-	-0.96090	-10.43774	-3.00070
Heart (%) [G]	Mean	66.35599	65.38315	67.15501	69.46320
	SD	4.43758	5.87043	6.77248	5.78383
	N	10	10	10	10
	%Diff	-	-1.46609	1.20415	4.68264
Kidney (%) [G]	Mean	130.19372	130.75991	127.52173	135.15617
	SD	10.22934	11.97139	10.78003	10.27013
	N	10	10	10	10
	%Diff	-	0.43488	-2.05232	3.81159
Liver (%) [G]	Mean	602.67564	598.30372	599.92529	658.09621
	SD	61.37180	77.89450	67.27060	57.86693
	N	10	10	10	10
	%Diff	-	-0.72542	-0.45636	9.19575

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

Appendix 18

Summary of Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Lung (%) [G]	Mean	70.78700	73.20619	71.85374	77.46642*
	SD	5.06224	4.32357	5.25492	5.88228
	N	10	10	10	10
	%Diff	-	3.41756	1.50697	9.43594
Spleen (%) [G]	Mean	38.60257	37.85988	40.17258	43.55612
	SD	4.29133	5.81933	4.95565	3.46376
	N	10	10	10	10
	%Diff	-	-1.92392	4.06712	12.83219
Testis (%) [G]	Mean	183.26933	191.80300	179.64787	188.53226
	SD	13.07775	16.65058	13.12123	11.61615
	N	10	10	10	10
	%Diff	-	4.65636	-1.97603	2.87170
Thymus (%) [G]	Mean	21.98611	21.06309	21.52258	24.80556
	SD	6.03017	5.26431	5.94860	5.81431
	N	10	10	10	10
	%Diff	-	-4.19822	-2.10832	12.82375

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

Appendix 18

Summary of Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Gland, Adrenal (%) [G]	Mean	3.31683	3.04758	3.34598	3.79544 *
	SD	0.44199	0.41266	0.37147	0.43905
	N	10	10	10	10
	%Diff	-	-8.11769	0.87888	14.42970
Gland, Pituitary (%) [G]	Mean	0.82766	0.83884	0.76611	0.77434
	SD	0.11086	0.09288	0.07749	0.09572
	N	10	10	10	10
	%Diff	-	1.35072	-7.43631	-6.44212
Gland, Thyroid (%) [G]	Mean	0.72420	0.70252	0.72697	0.73072
	SD	0.16845	0.10257	0.14509	0.17441
	N	10	10	10	10
	%Diff	-	-2.99319	0.38318	0.90034
Heart (%) [G]	Mean	52.45874	52.00585	51.32423	53.96065
	SD	5.66347	4.83076	1.88466	6.40323
	N	10	10	10	10
	%Diff	-	-0.86333	-2.16267	2.86302
Kidney (%) [G]	Mean	91.32536	88.78599	88.71418	91.28293
	SD	8.73210	7.07296	4.49463	9.23617
	N	10	10	10	10
	%Diff	-	-2.78058	-2.85921	-0.04647
Liver (%) [G]	Mean	396.34442	406.59608	401.41174	422.85996
	SD	40.19150	38.42205	38.15963	51.64817
	N	10	10	10	10
	%Diff	-	2.58655	1.27851	6.69003
Lung (%) [G]	Mean	58.57588	61.92521	62.58375	61.85279
	SD	5.03862	5.42027	4.25048	8.60370
	N	10	10	10	10
	%Diff	-	5.71793	6.84219	5.59430
Ovary (%) [G]	Mean	6.04835	5.03786	5.83983	5.32169
	SD	2.55276	0.66489	0.85076	0.92441
	N	10	10	10	10
	%Diff	-	-16.70687	-3.44744	-12.01414

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

Appendix 18

Summary of Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	10 ug/dose Group 2	30 ug/dose Group 3	96 ug/dose Group 4
Spleen (%) [G]	Mean	29.28032	29.90949	32.63563	33.39635
	SD	3.69955	1.72782	4.48920	4.53152
	N	10	10	10	10
	%Diff	-	2.14876	11.45926	14.05730
Thymus (%) [G]	Mean	19.74397	19.20484	19.88431	17.61179
	SD	2.49376	4.40494	3.49787	5.24093
	N	10	10	10	10
	%Diff	-	-2.73057	0.71081	-10.79915
Uterus (%) [G1]	Mean	37.10374	29.92488	34.58949	35.68513
	SD	17.54940	9.31645	7.26367	11.21048
	N	10	10	10	10
	%Diff	-	-19.34808	-6.77629	-3.82338

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

Appendix 18

Summary of Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Epididymis (%) [G]	Mean	57.47921	59.01973
	SD	2.31782	4.04457
	N	5	5
	%Diff	-	2.68013
Gland, Adrenal (%) [G]	Mean	2.76841	2.55522
	SD	0.20175	0.25603
	N	5	5
	%Diff	-	-7.70084
Gland, Pituitary (%) [G]	Mean	0.66016	0.61421
	SD	0.09491	0.07772
	N	5	5
	%Diff	-	-6.95938
Gland, Prostate (%) [G1]	Mean	50.86652	46.51383
	SD	7.61356	2.67012
	N	5	5
	%Diff	-	-8.55709
Gland, Thyroid (%) [G]	Mean	0.68890	0.74388
	SD	0.17032	0.14627
	N	5	5
	%Diff	-	7.98101
Heart (%) [G]	Mean	73.15500	69.11140
	SD	13.52277	8.63681
	N	5	5
	%Diff	-	-5.52743
Kidney (%) [G]	Mean	126.44215	134.08543
	SD	18.66370	10.48339
	N	5	5
	%Diff	-	6.04489
Liver (%) [G]	Mean	610.78113	582.53017
	SD	123.97092	64.89462
	N	5	5
	%Diff	-	-4.62538

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

Appendix 18

Summary of Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Lung (%) [G]	Mean	67.10347	71.44464
	SD	9.09061	6.51206
	N	5	5
	%Diff	-	6.46938
Spleen (%) [G]	Mean	35.36481	37.43329
	SD	7.35106	5.81525
	N	5	5
	%Diff	-	5.84898
Testis (%) [G]	Mean	178.93846	181.62603
	SD	10.08541	11.93706
	N	5	5
	%Diff	-	1.50195
Thymus (%) [G]	Mean	20.09669	18.04195
	SD	3.44652	3.60009
	N	5	5
	%Diff	-	-10.22425

[G] - Anova & Dunnett

Appendix 18

Summary of Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Gland, Adrenal (%) [G]	Mean	3.11871	3.44589
	SD	0.46276	0.22722
	N	5	5
	%Diff	-	10.49069
Gland, Pituitary (%) [G]	Mean	0.84102	0.92899
	SD	0.06320	0.08997
	N	5	5
	%Diff	-	10.45981
Gland, Thyroid (%) [G]	Mean	0.69106	0.69597
	SD	0.11405	0.10698
	N	5	5
	%Diff	-	0.71017
Heart (%) [G]	Mean	55.37723	58.62084
	SD	3.93421	10.25115
	N	5	5
	%Diff	-	5.85730
Kidney (%) [G]	Mean	89.93282	90.04848
	SD	8.54535	6.16065
	N	5	5
	%Diff	-	0.12861
Liver (%) [G]	Mean	411.46870	403.05668
	SD	49.71612	28.84545
	N	5	5
	%Diff	-	-2.04439
Lung (%) [G]	Mean	59.79842	61.54343
	SD	4.57557	5.17207
	N	5	5
	%Diff	-	2.91816
Ovary (%) [G]	Mean	5.37735	5.68906
	SD	0.58137	1.22079
	N	5	5
	%Diff	-	5.79678

[G] - Anova & Dunnett

Appendix 18

Summary of Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date		0 ug/dose Group 1	96 ug/dose Group 4
Spleen (%) [G]	Mean	27.39913	27.03664
	SD	5.09697	1.31739
	N	5	5
	%Diff	-	-1.32302
Thymus (%) [G]	Mean	19.07050	19.32259
	SD	3.22016	4.31522
	N	5	5
	%Diff	-	1.32188
Uterus (%) [G]	Mean	30.63446	30.91150
	SD	15.12199	12.50629
	N	5	5
	%Diff	-	0.90433

[G] - Anova & Dunnett

Appendix 18

Table 5
Summary of Microscopic Pathology

Appendix 18

Summary of Microscopic Pathology Explanation Page

Abbreviation	Description
GALT	Gut Associated Lymphoid Tissue
SS	Special Stain

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study.

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
ARTERY, AORTA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BONE MARROW								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	8	2	10	9	9	0
Increased cellularity; myeloid	0	0	2	8	0	1	1	10
.... minimal	0	0	2	8	0	1	1	10
BONE, FEMUR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	9	10	.	.	10
Inflammation, mixed cell; joint	0	.	.	1	0	.	.	0
.... minimal	0	.	.	1	0	.	.	0
Inflammation; periosteal	0	.	.	0	0	.	.	0
.... minimal	0	.	.	0	0	.	.	0
BONE, STERNUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
BRAIN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	10	10	.	.	10
Hemorrhage; ventricular	1	.	.	0	0	.	.	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
BRAIN (Continued...)								
.... mild	1	.	.	0	0	.	.	0
CERVIX								
Examined	.	.	.	.	10	0	0	9
No Visible Lesions	.	.	.	.	10	.	.	9
Not Examined: Not Present In Wet Tissues.	.	.	.	.	0	0	0	1
EPIDIDYMIS								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	10	.	.	10	.	.	.	.
ESOPHAGUS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
EYE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	7	10	.	.	10
Rosette; retina	1	.	.	3	0	.	.	0
.... minimal	0	.	.	3	0	.	.	0
.... mild	1	.	.	0	0	.	.	0
GALT								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, ADRENAL								
Examined	10	0	0	10	10	1	0	10
No Visible Lesions	10	.	.	10	10	1	.	10
GLAND, HARDERIAN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Infiltration, mononuclear cell	0	.	.	0	0	.	.	0
.... minimal	0	.	.	0	0	.	.	0
GLAND, MAMMARY								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Not Examined: Not Present In Section.	.	.	.	.	0	0	0	0
GLAND, PARATHYROID								
Examined	9	0	0	10	10	0	0	9
No Visible Lesions	9	.	.	10	10	.	.	9
Not Examined: Not Present In Section.	1	0	0	0	0	0	0	1
GLAND, PITUITARY								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	9	.	.	10
Cyst	0	.	.	0	1	.	.	0
.... minimal	0	.	.	0	1	.	.	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
GLAND, PROSTATE								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	7	.	.	10	.	.	.	.
Inflammation	2	.	.	0	.	.	.	.
.... minimal	2	.	.	0	.	.	.	.
Infiltration, mononuclear cell	1	.	.	0	.	.	.	.
.... minimal	1	.	.	0	.	.	.	.
.... mild	0	.	.	0	.	.	.	.
GLAND, SALIVARY, MANDIBULAR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
GLAND, SEMINAL VESICLE								
Examined	10	10	10	10	.	.	.	.
No Visible Lesions	10	10	10	6	.	.	.	.
Single cell necrosis; increased	0	0	0	4	.	.	.	.
.... minimal	0	0	0	4	.	.	.	.
GLAND, THYROID								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Inflammation	0	.	.	0	0	.	.	0
.... mild	0	.	.	0	0	.	.	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
HEART								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	8	.	.	8	8	.	.	10
Infiltration, mononuclear cell	2	.	.	2	2	.	.	0
.... minimal	2	.	.	2	2	.	.	0
Inflammation, perivascular	0	.	.	0	0	.	.	0
.... minimal	0	.	.	0	0	.	.	0
KIDNEY								
Examined	10	1	5	10	10	0	1	10
No Visible Lesions	3	0	0	2	4	.	0	2
Cast; hyaline	2	0	1	1	0	.	0	0
.... minimal	2	0	1	1	0	.	0	0
Hemorrhage; tubular	0	0	0	1	0	.	0	1
.... minimal	0	0	0	1	0	.	0	1
Basophilia; tubular	7	1	3	7	4	.	0	7
.... minimal	7	1	3	7	4	.	0	7
Cyst	1	0	0	3	2	.	0	4
.... minimal	1	0	0	3	2	.	0	1
.... mild	0	0	0	0	0	.	0	3
Dilatation; pelvis	1	1	5	1	0	.	1	0
.... minimal	1	0	1	0	0	.	0	0
.... mild	0	1	3	1	0	.	1	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
KIDNEY (Continued...)								
.... moderate	0	0	1	0	0	.	0	0
Inflammation	0	0	0	1	2	.	0	0
.... minimal	0	0	0	1	2	.	0	0
Inflammation; pelvis	0	0	0	0	0	.	0	1
.... minimal	0	0	0	0	0	.	0	1
LARGE INTESTINE, CECUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
LARGE INTESTINE, COLON								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
LARGE INTESTINE, RECTUM								
Examined	10	0	0	10	10	0	0	9
No Visible Lesions	10	.	.	8	10	.	.	8
Not Examined: Not Present In Wet Tissues.	.	.	.	.	0	0	0	1
Inflammation	0	.	.	2	0	.	.	1
.... minimal	0	.	.	2	0	.	.	1
LIVER								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	3	7	4	2	7	6	2	0
Hypertrophy; kupffer cell	0	0	2	4	0	2	6	7

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
LIVER (Continued...)								
.... minimal	0	0	2	4	0	2	4	6
.... mild	0	0	0	0	0	0	2	1
Necrosis; hepatocellular	1	1	2	0	0	0	1	1
.... minimal	1	1	2	0	0	0	1	1
Vacuolation; hepatocellular	2	0	0	1	2	0	0	0
.... minimal	2	0	0	0	2	0	0	0
.... mild	0	0	0	1	0	0	0	0
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
Extramedullary hematopoiesis	2	0	4	2	0	1	0	0
.... minimal	2	0	4	2	0	1	0	0
Infiltration, mononuclear cell	2	0	1	0	0	0	0	0
.... minimal	2	0	1	0	0	0	0	0
Tension lipidosis	0	1	0	1	0	0	2	0
.... minimal	0	1	0	1	0	0	2	0
LUNG								
Examined	10	2	3	10	10	0	0	10
No Visible Lesions	3	1	2	5	5	.	.	1
Fibrosis; pleural	1	0	0	0	0	.	.	0
.... minimal	1	0	0	0	0	.	.	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
LUNG (Continued...)								
Hemorrhage	4	1	1	3	0	.	.	4
.... minimal	4	0	1	3	0	.	.	3
.... mild	0	1	0	0	0	.	.	0
.... moderate	0	0	0	0	0	.	.	1
Macrophage aggregation; alveolar	5	1	0	4	5	.	.	6
.... minimal	5	1	0	4	5	.	.	6
Thrombus	0	0	0	0	0	.	.	0
.... minimal	0	0	0	0	0	.	.	0
LYMPH NODE								
Examined	0	0	0	1	0	0	1	0
Increased cellularity; lymphoid	.	.	.	1	.	.	0	.
.... mild	.	.	.	1	.	.	0	.
Erythrocytosis	.	.	.	0	.	.	1	.
.... minimal	.	.	.	0	.	.	0	.
.... mild	.	.	.	0	.	.	1	.
LYMPH NODE, ILIAC								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	8	6	5	1	7	4	0	0
Erythrocytosis	1	3	3	1	0	1	2	1
.... minimal	0	2	3	1	0	1	2	1
.... mild	1	1	0	0	0	0	0	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, ILIAC (Continued...)								
Hemorrhage; perinodal	1	0	0	0	0	0	0	0
.... mild	1	0	0	0	0	0	0	0
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								
Examined	10	10	10	10	10	10	10	9
No Visible Lesions	10	9	8	1	10	10	8	4
Not Examined: Not Present In Wet Tissues.	.	.	.	.	0	0	0	1
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

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, INGUINAL (Continued...)								
Erythrocytosis	0	1	0	1	0	0	2	0
.... minimal	0	1	0	1	0	0	2	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, MANDIBULAR								
Examined	10	1	0	10	10	1	3	10
No Visible Lesions	7	0	.	8	8	0	2	8
Plasmacytosis	2	0	.	2	1	1	0	1
.... minimal	1	0	.	1	0	0	0	0
.... mild	1	0	.	1	0	1	0	0
.... moderate	0	0	.	0	1	0	0	1
Increased cellularity; lymphoid	3	1	.	2	2	1	1	2
.... minimal	1	0	.	0	0	0	1	0
.... mild	2	1	.	1	1	1	0	1
.... moderate	0	0	.	1	1	0	0	1
Erythrocytosis	0	0	.	0	0	0	0	0
.... minimal	0	0	.	0	0	0	0	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
LYMPH NODE, MESENTERIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
LYMPH NODE, POPLITEAL								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	9	1	0	1	10	0	0	0
Erythrocytosis	1	0	0	0	0	0	0	0
.... mild	1	0	0	0	0	0	0	0
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
MUSCLE, SKELETAL								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	9	7	.	.	5
Degeneration/necrosis; myofiber	1	.	.	0	1	.	.	2
.... minimal	1	.	.	0	1	.	.	2
Infiltration, mononuclear cell	0	.	.	1	2	.	.	5
.... minimal	0	.	.	1	2	.	.	5

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
NERVE, OPTIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
NERVE, SCIATIC								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	9	0	0	1	9	0	0	0
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
OVARY								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	9	.	.	10
Dilatation; bursal	.	.	.	.	1	.	.	0
.... minimal	.	.	.	.	1	.	.	0
OVIDUCT								
Examined	.	.	.	.	0	0	0	0
PANCREAS								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	9	.	.	9	9	.	.	9
Atrophy; acinar	0	.	.	1	1	.	.	1
.... minimal	0	.	.	1	1	.	.	1

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Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
PANCREAS (Continued...)								
Dilatation; ductular	1	.	.	0	0	.	.	0
.... marked	1	.	.	0	0	.	.	0
Inflammation; islet of langerhans	0	.	.	0	0	.	.	0
.... minimal	0	.	.	0	0	.	.	0
SITE, INJECTION								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	5	0	0	0	1	0	0	0
Degeneration/necrosis; myofiber	4	4	2	7	7	8	5	7
.... minimal	4	4	2	7	7	7	5	7
.... mild	0	0	0	0	0	1	0	0
Inflammation, mixed cell; dermal	0	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
Infiltration, mononuclear cell; muscular	2	3	0	0	3	0	0	0

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Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
SITE, INJECTION (Continued...)								
.... minimal	2	3	0	0	3	0	0	0
.... mild	0	0	0	0	0	0	0	0
Granuloma; muscular	1	0	0	0	0	0	0	0
.... minimal	1	0	0	0	0	0	0	0
Hyperplasia; epidermal	0	0	0	3	0	2	2	7
.... minimal	0	0	0	3	0	2	2	7
Inflammation; dermal	0	0	0	0	0	0	0	0
.... minimal	0	0	0	0	0	0	0	0
SKIN								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
Inflammation; dermal	0	.	.	0	0	.	.	0
.... minimal	0	.	.	0	0	.	.	0
SMALL INTESTINE, DUODENUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, ILEUM								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SMALL INTESTINE, JEJUNUM								
Examined	10	0	0	10	10	0	0	10

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Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
SMALL INTESTINE, JEJUNUM (Continued...)								
No Visible Lesions	10	.	.	10	10	.	.	10
SPINAL CORD, CERVICAL								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPINAL CORD, LUMBAR								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPINAL CORD, THORACIC								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
SPLEEN								
Examined	10	10	10	10	10	10	10	10
No Visible Lesions	10	10	0	0	10	3	0	0
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

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Summary of Microscopic Pathology

5002400

Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
SPLEEN (Continued...)								
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
STOMACH								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
TESTIS								
Examined	10	0	0	10	.	.	.	.
No Visible Lesions	9	.	.	9	.	.	.	.
Atrophy; tubular	0	.	.	1	.	.	.	.
.... minimal	0	.	.	1	.	.	.	.
Dilatation; rete testis	1	.	.	0	.	.	.	.
.... minimal	1	.	.	0	.	.	.	.
THYMUS								
Examined	10	1	1	10	10	2	1	10
No Visible Lesions	10	1	0	8	8	2	0	9
Hemorrhage	0	0	1	2	2	0	1	0
.... minimal	0	0	1	1	2	0	1	0
.... mild	0	0	0	1	0	0	0	0
Tingible body macrophages; increased	0	0	0	0	0	0	0	1
.... minimal	0	0	0	0	0	0	0	1

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Summary of Microscopic Pathology

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Removal Reason(s): TERMINAL EUTHANASIA	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
Number of Animals:	10	10	10	10	10	10	10	10
TONGUE								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	9	.	.	10
Infiltration, mononuclear cell	0	.	.	0	1	.	.	0
.... minimal	0	.	.	0	1	.	.	0
TRACHEA								
Examined	10	0	0	10	10	0	0	10
No Visible Lesions	10	.	.	10	10	.	.	10
URINARY BLADDER								
Examined	10	0	0	10	10	0	0	9
No Visible Lesions	10	.	.	10	10	.	.	9
Not Examined: Not Present In Wet Tissues.	.	.	.	.	0	0	0	1
UTERUS								
Examined	.	.	.	.	10	0	0	10
No Visible Lesions	.	.	.	.	10	.	.	10
VAGINA								
Examined	.	.	.	.	10	0	0	9
No Visible Lesions	.	.	.	.	10	.	.	9
Not Examined: Not Present In Wet Tissues.	.	.	.	.	0	0	0	1
NO CORRELATE								
Examined	3	2	2	5	1	3	3	4
No correlating lesion	3	2	2	5	1	3	3	4

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
ARTERY, AORTA				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BONE MARROW				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Increased cellularity; myeloid	0	0	0	0
.... minimal	0	0	0	0
BONE, FEMUR				
Examined	5	5	5	5
No Visible Lesions	4	5	5	5
Inflammation, mixed cell; joint	0	0	0	0
.... minimal	0	0	0	0
Inflammation; periosteal	1	0	0	0
.... minimal	1	0	0	0
BONE, STERNUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
BRAIN				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Hemorrhage; ventricular	0	0	0	0

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
BRAIN (Continued...)				
.... mild	0	0	0	0
CERVIX				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
Not Examined: Not Present In Wet Tissues.	.	.	0	0
EPIDIDYMIS				
Examined	5	5	.	.
No Visible Lesions	5	5	.	.
ESOPHAGUS				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
EYE				
Examined	5	5	5	5
No Visible Lesions	5	4	3	5
Rosette; retina	0	1	2	0
.... minimal	0	1	0	0
.... mild	0	0	2	0
GALT				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, ADRENAL				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, HARDERIAN				
Examined	5	5	5	5
No Visible Lesions	5	5	4	5
Infiltration, mononuclear cell	0	0	1	0
.... minimal	0	0	1	0
GLAND, MAMMARY				
Examined	5	5	5	4
No Visible Lesions	5	5	5	4
Not Examined: Not Present In Section.	.	.	0	1
GLAND, PARATHYROID				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Not Examined: Not Present In Section.	0	0	0	0
GLAND, PITUITARY				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Cyst	0	0	0	0
.... minimal	0	0	0	0

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
GLAND, PROSTATE				
Examined	5	5	.	.
No Visible Lesions	2	3	.	.
Inflammation	0	0	.	.
.... minimal	0	0	.	.
Infiltration, mononuclear cell	3	2	.	.
.... minimal	3	1	.	.
.... mild	0	1	.	.
GLAND, SALIVARY, MANDIBULAR				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
GLAND, SEMINAL VESICLE				
Examined	5	5	.	.
No Visible Lesions	5	5	.	.
Single cell necrosis; increased	0	0	.	.
.... minimal	0	0	.	.
GLAND, THYROID				
Examined	5	5	5	5
No Visible Lesions	5	4	5	5
Inflammation	0	1	0	0
.... mild	0	1	0	0

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5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
HEART				
Examined	5	5	5	5
No Visible Lesions	3	3	5	5
Infiltration, mononuclear cell	1	2	0	0
.... minimal	1	2	0	0
Inflammation, perivascular	1	0	0	0
.... minimal	1	0	0	0
KIDNEY				
Examined	5	5	5	5
No Visible Lesions	0	1	3	1
Cast; hyaline	0	1	0	2
.... minimal	0	1	0	2
Hemorrhage; tubular	0	0	0	0
.... minimal	0	0	0	0
Basophilia; tubular	5	3	2	2
.... minimal	5	3	2	2
Cyst	2	0	1	1
.... minimal	2	0	0	0
.... mild	0	0	1	1
Dilatation; pelvis	0	1	0	0
.... minimal	0	1	0	0
.... mild	0	0	0	0

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
KIDNEY (Continued...)				
.... moderate	0	0	0	0
Inflammation	0	0	1	1
.... minimal	0	0	1	1
Inflammation; pelvis	0	0	0	0
.... minimal	0	0	0	0
LARGE INTESTINE, CECUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, COLON				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
LARGE INTESTINE, RECTUM				
Examined	5	5	5	5
No Visible Lesions	5	4	5	5
Not Examined: Not Present In Wet Tissues.	.	.	0	0
Inflammation	0	1	0	0
.... minimal	0	1	0	0
LIVER				
Examined	5	5	5	5
No Visible Lesions	4	4	3	1
Hypertrophy; kupffer cell	0	0	0	0

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Summary of Microscopic Pathology

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Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LIVER (Continued...)				
.... minimal	0	0	0	0
.... mild	0	0	0	0
Necrosis; hepatocellular	0	0	0	0
.... minimal	0	0	0	0
Vacuolation; hepatocellular	0	0	1	0
.... minimal	0	0	1	0
.... mild	0	0	0	0
Vacuolation; hepatocellular, periportal to midzonal	0	1	0	3
.... minimal	0	1	0	3
.... mild	0	0	0	0
Extramedullary hematopoiesis	1	0	0	1
.... minimal	1	0	0	1
Infiltration, mononuclear cell	0	1	0	1
.... minimal	0	1	0	1
Tension lipidosis	0	0	1	1
.... minimal	0	0	1	1
LUNG				
Examined	5	5	5	5
No Visible Lesions	1	1	0	0
Fibrosis; pleural	0	0	0	0
.... minimal	0	0	0	0

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LUNG (Continued...)				
Hemorrhage	1	0	2	1
.... minimal	1	0	2	1
.... mild	0	0	0	0
.... moderate	0	0	0	0
Macrophage aggregation; alveolar	3	4	4	4
.... minimal	3	4	4	4
Thrombus	0	1	0	0
.... minimal	0	1	0	0
LYMPH NODE				
Examined	0	0	2	1
Increased cellularity; lymphoid	.	.	0	0
.... mild	.	.	0	0
Erythrocytosis	.	.	2	1
.... minimal	.	.	2	1
.... mild	.	.	0	0
LYMPH NODE, ILIAC				
Examined	5	5	5	5
No Visible Lesions	5	1	4	3
Erythrocytosis	0	0	1	0
.... minimal	0	0	1	0
.... mild	0	0	0	0

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, ILIAC (Continued...)				
Hemorrhage; perinodal	0	0	0	0
.... mild	0	0	0	0
Increased cellularity; lymphoid	0	3	0	2
.... minimal	0	3	0	1
.... mild	0	0	0	1
.... moderate	0	0	0	0
.... marked	0	0	0	0
Inflammation, mixed cell; perinodal	0	1	0	2
.... minimal	0	1	0	2
.... mild	0	0	0	0
Inflammation, neutrophilic	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
.... moderate	0	0	0	0
LYMPH NODE, INGUINAL				
Examined	5	5	5	5
No Visible Lesions	5	4	5	4
Not Examined: Not Present In Wet Tissues.	.	.	0	0
Increased cellularity; lymphoid	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, INGUINAL (Continued...)				
Erythrocytosis	0	1	0	0
.... minimal	0	1	0	0
Inflammation, neutrophilic	0	0	0	0
.... minimal	0	0	0	0
.... moderate	0	0	0	0
Inflammation, mixed cell; perinodal	0	0	0	1
.... minimal	0	0	0	1
.... moderate	0	0	0	0
LYMPH NODE, MANDIBULAR				
Examined	5	5	5	5
No Visible Lesions	3	3	3	3
Plasmacytosis	1	0	1	0
.... minimal	0	0	0	0
.... mild	1	0	1	0
.... moderate	0	0	0	0
Increased cellularity; lymphoid	1	1	2	2
.... minimal	0	0	0	2
.... mild	1	1	2	0
.... moderate	0	0	0	0
Erythrocytosis	1	2	0	0
.... minimal	1	2	0	0

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5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
LYMPH NODE, MESENTERIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
LYMPH NODE, POPLITEAL				
Examined	5	5	5	5
No Visible Lesions	5	3	5	1
Erythrocytosis	0	0	0	0
.... mild	0	0	0	0
Inflammation, mixed cell; perinodal	0	2	0	4
.... minimal	0	2	0	4
.... mild	0	0	0	0
Increased cellularity; lymphoid	0	1	0	0
.... minimal	0	1	0	0
Inflammation, neutrophilic	0	0	0	0
.... minimal	0	0	0	0
MUSCLE, SKELETAL				
Examined	5	5	5	5
No Visible Lesions	4	4	2	3
Degeneration/necrosis; myofiber	1	0	1	1
.... minimal	1	0	1	1
Infiltration, mononuclear cell	0	1	3	2
.... minimal	0	1	3	2

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
NERVE, OPTIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
NERVE, SCIATIC				
Examined	5	5	5	5
No Visible Lesions	5	0	5	0
Inflammation, mixed cell; perineurial	0	5	0	5
.... minimal	0	5	0	5
.... mild	0	0	0	0
.... moderate	0	0	0	0
OVARY				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
Dilatation; bursal	.	.	0	0
.... minimal	.	.	0	0
OVIDUCT				
Examined	.	.	0	1
Dilatation	.	.	.	1
.... moderate	.	.	.	1
PANCREAS				
Examined	5	5	5	5
No Visible Lesions	5	4	5	5

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
PANCREAS (Continued...)				
Atrophy; acinar	0	0	0	0
.... minimal	0	0	0	0
Dilatation; ductular	0	0	0	0
.... marked	0	0	0	0
Inflammation; islet of langerhans	0	1	0	0
.... minimal	0	1	0	0
SITE, INJECTION				
Examined	5	5	5	5
No Visible Lesions	2	0	2	0
Degeneration/necrosis; myofiber	1	1	1	1
.... minimal	1	1	1	1
.... mild	0	0	0	0
Inflammation, mixed cell; dermal	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Inflammation, mixed cell; subcutis/perimuscular	0	5	0	5
.... minimal	0	5	0	5
.... mild	0	0	0	0
.... moderate	0	0	0	0
Inflammation, mixed cell; muscular	0	0	0	1
.... minimal	0	0	0	1

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Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
SITE, INJECTION (Continued...)				
.... mild	0	0	0	0
Infiltration, mononuclear cell; muscular	1	4	3	4
.... minimal	1	4	3	3
.... mild	0	0	0	1
Granuloma; muscular	0	0	0	0
.... minimal	0	0	0	0
Hyperplasia; epidermal	0	1	0	0
.... minimal	0	1	0	0
Inflammation; dermal	1	1	0	0
.... minimal	1	1	0	0
SKIN				
Examined	5	5	5	5
No Visible Lesions	5	5	5	4
Inflammation; dermal	0	0	0	1
.... minimal	0	0	0	1
SMALL INTESTINE, DUODENUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SMALL INTESTINE, ILEUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
SMALL INTESTINE, JEJUNUM				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, CERVICAL				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, LUMBAR				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPINAL CORD, THORACIC				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
SPLEEN				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Extramedullary hematopoiesis; increased	0	0	0	0
.... minimal	0	0	0	0
Infiltration, neutrophilic; red pulp	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
Decreased cellularity; periarteriolar lymphoid sheath	0	0	0	0
.... minimal	0	0	0	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
SPLEEN (Continued...)				
.... mild	0	0	0	0
Increased cellularity; red pulp	0	0	0	0
.... minimal	0	0	0	0
.... mild	0	0	0	0
STOMACH				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
TESTIS				
Examined	5	5	.	.
No Visible Lesions	4	5	.	.
Atrophy; tubular	1	0	.	.
.... minimal	1	0	.	.
Dilatation; rete testis	1	0	.	.
.... minimal	1	0	.	.
THYMUS				
Examined	5	5	5	5
No Visible Lesions	5	5	4	3
Hemorrhage	0	0	1	2
.... minimal	0	0	1	2
.... mild	0	0	0	0
Tingible body macrophages; increased	0	0	0	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
THYMUS (Continued...)				
.... minimal	0	0	0	0
TONGUE				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Infiltration, mononuclear cell	0	0	0	0
.... minimal	0	0	0	0
TRACHEA				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
URINARY BLADDER				
Examined	5	5	5	5
No Visible Lesions	5	5	5	5
Not Examined: Not Present In Wet Tissues.	.	.	0	0
UTERUS				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
VAGINA				
Examined	.	.	5	5
No Visible Lesions	.	.	5	5
Not Examined: Not Present In Wet Tissues.	.	.	0	0

Appendix 18

Summary of Microscopic Pathology

5002400

Removal Reason(s): RECOVERY EUTHANASIA	Male		Female	
	0 ug/dose Group 1	96 ug/dose Group 4	0 ug/dose Group 1	96 ug/dose Group 4
Number of Animals:	5	5	5	5
NO CORRELATE				
Examined	3	3	2	3
No correlating lesion	3	3	2	3

Appendix 18

Appendix 1
Individual Absolute Organ Weights

Appendix 18

Individual Absolute Organ Weights Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed	OPMP	Only one of the paired organs present – Macroscopic pathology
AVS	Suspected aberrant value	OPOP	Only one of the paired organs present
COME	See Comment Value Excluded	OUM	Organ unidentifiable macroscopically
COMI	See Comment Value Included	MPE	Macroscopic pathology – Excluded from mean
LIBW	Lung infused before weighing	MPI	Macroscopic pathology – Included in mean
NC	Not calculable	TERR	Technical error
OA	Omitted activity	UPTD	Unable to perform due to technical difficulty
ONP	Organ not present	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study:

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Epididymis (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Prostate (g)	Gland Thyroid (g)
	-	-	-	-	-	-	-
1001	357	1.858	0.905	0.0505	0.0117	0.892	0.0133
1002	416	2.014	1.008	0.0459	0.0123	0.999	0.0194
1003	370	2.009	1.144	0.0459	0.0116	1.175	0.0150
1004	360	2.007	1.020	0.0583	0.0095	1.354	0.0168
1005	370	2.007	1.032	0.0492	0.0126	1.206	0.0186
1006	360	1.946	0.975	0.0532	0.0104	1.087	0.0163
1007	393	1.947	1.115	0.0563	0.0114	1.164	0.0157
1008	427	2.013	0.945	0.0645	0.0126	1.223	0.0161
1009	415	2.100	1.136	0.0617	0.0140	1.141	0.0153
1010	460	1.991	1.146	0.0728	0.0131	1.193	0.0205
Mean	392.8	1.9892	1.0426	0.05583	0.01192	1.1434	0.01670
SD	35.3	0.0627	0.0881	0.00869	0.00131	0.1272	0.00219
N	10	10	10	10	10	10	10

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (Absolute)						
	Heart (g)	Kidney (g)	Liver (g)	Lung (g)	Spleen (g)	Testis (g)	Thymus (g)
	-	-	-	-	-	-	-
1001	1.371	2.417	12.141	1.304	0.696	3.400	0.363
1002	1.315	2.407	11.389	1.256	0.726	3.691	0.431
1003	1.269	2.519	10.142	1.395	0.730	3.577	0.266
1004	1.187	2.454	11.856	1.305	0.696	3.179	0.294
1005	1.415	2.672	11.378	1.497	0.843	3.816	0.453
1006	1.226	2.391	11.341	1.463	0.769	3.934	0.511
1007	1.231	2.313	11.414	1.347	0.652	3.588	0.439
1008	1.408	2.825	12.544	1.540	0.836	3.595	0.399
1009	1.451	2.971	12.972	1.424	0.777	3.627	0.533
1010	1.322	2.948	14.643	1.545	0.955	4.024	0.686
Mean	1.3195	2.5917	11.9820	1.4076	0.7680	3.6431	0.4375
SD	0.0904	0.2446	1.2135	0.1032	0.0896	0.2464	0.1218
N	10	10	10	10	10	10	10

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

10 ug/dose Group 2		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Epididymis (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Prostate (g)	Gland Thyroid (g)
	-	-	-	-	-	-	-
2001	411	2.011	1.112	0.0532	0.0120	1.255	0.0147
2002	409	1.900	1.099	0.0523	0.0106	1.097	0.0192
2003	375	1.936	0.987	0.0529	0.0105	1.146	0.0179
2004	352	2.003	1.137	0.0552	0.0090	1.308	0.0159
2005	358	2.082	0.924	0.0474	0.0102	1.321	0.0113
2006	404	1.932	0.888	0.0581	0.0113	1.086	0.0186
2007	364	1.958	1.030	0.0603	0.0117	0.976	0.0120
2008	480	2.119	1.168	0.0731	0.0146	1.168	0.0184
2009	418	2.147	1.090	0.0630	0.0146	1.021	0.0198
2010	383	2.038	1.019	0.0560	0.0092	0.751	0.0192
Mean	395.4	2.0126	1.0454	0.05715	0.01137	1.1129	0.01670
SD	38.0	0.0836	0.0922	0.00712	0.00196	0.1715	0.00309
N	10	10	10	10	10	10	10
%Diff	0.7	1.1764	0.2686	2.36432	-4.61409	-2.6675	0.00000

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight (Absolute)						
	Heart (g)	Kidney (g)	Liver (g)	Lung (g)	Spleen (g)	Testis (g)	Thymus (g)
	-	-	-	-	-	-	-
2001	1.479	2.969	12.742	1.516	0.801	4.390	0.589
2002	1.203	2.667	13.640	1.459	0.722	4.190	0.496
2003	1.299	2.495	11.329	1.403	0.738	3.777	0.404
2004	1.210	2.368	10.027	1.331	0.621	3.563	0.257
2005	1.161	2.244	9.860	1.390	0.646	3.588	0.272
2006	1.256	2.557	11.422	1.522	0.811	3.558	0.450
2007	1.314	2.404	11.496	1.449	0.800	3.679	0.364
2008	1.442	3.009	14.703	1.617	1.023	4.069	0.518
2009	1.589	2.927	13.897	1.627	0.857	3.747	0.474
2010	1.213	2.675	11.264	1.413	0.603	3.980	0.409
Mean	1.3166	2.6315	12.0380	1.4727	0.7622	3.8541	0.4233
SD	0.1412	0.2672	1.6392	0.0972	0.1262	0.2893	0.1052
N	10	10	10	10	10	10	10
%Diff	-0.2198	1.5357	0.4674	4.6249	-0.7552	5.7918	-3.2457

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

30 ug/dose Group 3		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Epididymis (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Prostate (g)	Gland Thyroid (g)
	-	-	-	-	-	-	-
3001	338	1.986	0.933	0.0553	0.0110	0.956	0.0160
3002	376	2.041	1.000	0.0640	0.0103	1.045	0.0162
3003	391	2.074	0.989	0.0535	0.0125	1.250	0.0179
3004	332	1.938	0.995	0.0505	0.0099	0.956	0.0140
3005	378	1.980	0.891	0.0458	0.0122	0.937	0.0128
3006	428	2.136	0.943	0.0581	0.0111	0.943	0.0174
3007	412	2.075	0.911	0.0568	0.0102	1.115	0.0153
3008	396	1.940	1.102	0.0505	0.0115	1.149	0.0112
3009	386	2.068	0.978	0.0547	0.0125	0.995	0.0147
3010	435	2.061	0.961	0.0696	0.0131	0.937	0.0174
Mean	387.2	2.0299	0.9703	0.05588	0.01143	1.0283	0.01529
SD	33.9	0.0656	0.0589	0.00689	0.00111	0.1090	0.00216
N	10	10	10	10	10	10	10
%Diff	-1.4	2.0460	-6.9346	0.08956	-4.11074	-10.0665	-8.44311

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight (Absolute)						
	Heart (g)	Kidney (g)	Liver (g)	Lung (g)	Spleen (g)	Testis (g)	Thymus (g)
	-	-	-	-	-	-	-
3001	1.274	2.260	10.262	1.341	0.694	3.547	0.335
3002	1.286	2.404	12.158	1.416	0.716	4.178	0.346
3003	1.341	2.721	11.943	1.419	0.770	3.850	0.387
3004	1.068	2.136	10.596	1.206	0.732	3.249	0.297
3005	1.520	2.686	11.155	1.469	0.770	3.181	0.447
3006	1.408	2.779	13.770	1.717	1.083	3.986	0.546
3007	1.393	2.893	13.742	1.573	0.855	3.601	0.431
3008	1.520	2.560	13.633	1.412	0.896	3.708	0.379
3009	1.357	2.553	10.679	1.587	0.850	3.453	0.741
3010	1.460	2.919	13.908	1.465	0.798	3.730	0.477
Mean	1.3627	2.5911	12.1846	1.4605	0.8164	3.6483	0.4386
SD	0.1346	0.2612	1.4762	0.1413	0.1139	0.3116	0.1292
N	10	10	10	10	10	10	10
%Diff	3.2740	-0.0232	1.6909	3.7582	6.3021	0.1427	0.2514

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Epididymis (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Prostate (g)	Gland Thyroid (g)
	-	-	-	-	-	-	-
4001	378	1.810	0.896	0.0482	0.0145	1.104	0.0183
4002	381	2.081	1.015	0.0561	0.0115	1.123	0.0174
4003	378	1.922	0.986	0.0734	0.0144	1.001	0.0144
4004	452	2.129	1.022	0.0844	0.0152	1.237	0.0147
4005	396	1.944	0.985	0.0569	0.0120	0.811	0.0143
4006	396	2.151	1.073	0.0635	0.0126	0.998	0.0136
4007	391	1.976	1.009	0.0671	0.0118	1.033	0.0214
4008	338 [a]	1.902	1.042	0.0485	0.0094	0.941	0.0144
4009	428	2.217	1.079	0.0577	0.0163	1.012	0.0188
4010	367 [a]	1.945	0.915	0.0535	0.0096	0.894	0.0155
Mean	390.5	2.0077	1.0022	0.06093	0.01273	1.0154	0.01628
SD	31.6	0.1295	0.0601	0.01142	0.00232	0.1208	0.00256
N	10	10	10	10	10	10	10
%Diff	-0.6	0.9300	-3.8749	9.13487	6.79530	-11.1947	-2.51497

[a] [RC:value confirmed]

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (Absolute)						
	Heart (g)	Kidney (g)	Liver (g)	Lung (g)	Spleen (g)	Testis (g)	Thymus (g)
	-	-	-	-	-	-	-
4001	1.474	2.794	12.532	1.598	0.819	3.566	0.630
4002	1.304	2.697	12.272	1.571	0.868	3.781	0.449
4003	1.334	2.787	12.607	1.583	0.829	3.651	0.546
4004	1.518	3.018	15.387	1.614	0.900	3.931	0.573
4005	1.437	2.601	12.204	1.633	0.876	3.998	0.543
4006	1.367	2.871	11.845	1.514	1.046	3.967	0.514
4007	1.327	2.765	13.698	1.572	0.740	4.089	0.517
4008	1.215	2.359	12.331	1.360	0.819	3.451	0.237
4009	1.625	2.870	14.694	1.652	1.076	3.760	0.475
4010	1.323	2.337	14.343	1.415	0.787	3.578	0.476
Mean	1.3924	2.7099	13.1913	1.5512	0.8760	3.7772	0.4960
SD	0.1206	0.2203	1.2388	0.0951	0.1078	0.2141	0.1051
N	10	10	10	10	10	10	10
%Diff	5.5248	4.5607	10.0926	10.2018	14.0625	3.6809	13.3714

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Thyroid (g)	Heart (g)	Kidney (g)
	-	-	-	-	-	-	-
1501	257	2.327	0.0622	0.0153	0.0109	1.046	1.714
1502	239	1.692	0.0680	0.0132	0.0137	1.085	1.701
1503	237	1.849	0.0608	0.0170	0.0145	0.980	1.767
1504	239	1.957	0.0610	0.0126	0.0120	0.956	1.657
1505	260	1.866	0.0656	0.0170	0.0131	1.025	1.795
1506	258	1.898	0.0668	0.0163	0.0153	1.013	1.836
1507	232	1.838	0.0641	0.0161	0.0093 I	0.943	1.767
1508	250	1.932	0.0575	0.0167	0.0199	1.093	1.613
1509	249	1.977	0.0543	0.0155	0.0133	0.887	1.714
1510	252	1.895	0.0725	0.0186	0.0161	0.997	1.887
Mean	247.3	1.9231	0.06328	0.01583	0.01381	1.0025	1.7451
SD	9.9	0.1626	0.00529	0.00180	0.00294	0.0642	0.0823
N	10	10	10	10	10	10	10

I = Include

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (Absolute)					
	Liver (g)	Lung (g)	Ovary (g)	Spleen (g)	Thymus (g)	Uterus (g)
	-	-	-	-	-	-
1501	8.098	1.110	0.098	0.628	0.360	0.448
1502	8.130	1.126	0.102	0.633	0.359	1.184 [a]
1503	7.490	1.056	0.089	0.507	0.400	0.442
1504	7.379	1.096	0.090	0.580	0.363	0.588
1505	7.527	1.169	0.099	0.542	0.376	0.429
1506	7.181	1.145	0.102	0.588	0.364	0.644
1507	7.700	1.031	0.097	0.470	0.331	0.570
1508	7.586	1.181	0.134	0.588	0.473	1.200 [a]
1509	6.714	1.137	0.098	0.477	0.354	0.999 [a]
1510	7.957	1.150	0.246 I	0.591	0.395	0.517
Mean	7.5762	1.1201	0.1155	0.5604	0.3775	0.7021
SD	0.4330	0.0479	0.0475	0.0587	0.0390	0.3061
N	10	10	10	10	10	10

I = Include
[a] [RC:estrus]

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

10 ug/dose Group 2		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Thyroid (g)	Heart (g)	Kidney (g)
	-	-	-	-	-	-	-
2501	258	1.883	0.0636	0.0157	0.0157	1.003	1.979
2502	241	1.893	0.0560	0.0138	0.0101	0.975	1.578
2503	223	1.856	0.0486	0.0130	0.0127	0.832	1.536
2604	268	1.935	0.0688	0.0164	0.0117	1.115	1.815
2505	254	1.697	0.0410	0.0152	0.0130	1.011	1.564
2506	235	1.852	0.0524	0.0180	0.0144	0.947	1.554
2507	245 [a]	1.964	0.0550	0.0168	0.0122	1.058	1.697
2508	224	1.824	0.0608	0.0143	0.0137	0.881	1.505
2509	228	1.795	0.0526	0.0142	0.0148	0.979	1.642
2510	230	1.909	0.0698	0.0187	0.0120	0.867	1.649
Mean	240.6	1.8608	0.05686	0.01561	0.01303	0.9668	1.6519
SD	15.4	0.0765	0.00902	0.00186	0.00166	0.0880	0.1466
N	10	10	10	10	10	10	10
%Diff	-2.7	-3.2396	-10.14539	-1.38977	-5.64808	-3.5611	-5.3407

[a] [RC:value confirmed]

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight (Absolute)					
	Liver (g)	Lung (g)	Ovary (g)	Spleen (g)	Thymus (g)	Uterus (g)
	-	-	-	-	-	-
2501	7.798	1.201	0.079	0.572	0.325	1.033 [a]
2502	6.870	1.223	0.090	0.584	0.465	0.472
2503	6.332	0.980	0.081	0.531	0.329	0.525
2604	7.992	1.322	0.114	0.592	0.446	0.554
2505	7.840	1.190	0.069	0.518	0.300	0.460
2506	7.977	1.081	0.099	0.480	0.358	0.540
2507	7.881	1.183	0.113	0.629	0.332	0.389
2508	6.947	1.076	0.091	0.572	0.463	0.540
2509	8.220	1.172	0.100	0.522	0.356	0.559
2510	7.673	1.083	0.104	0.568	0.197	0.491
Mean	7.5530	1.1511	0.0940	0.5568	0.3571	0.5563
SD	0.6152	0.0968	0.0148	0.0435	0.0831	0.1756
N	10	10	10	10	10	10
%Diff	-0.3062	2.7676	-18.6147	-0.6424	-5.4040	-20.7663

[a] [RC:estrus]

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

30 ug/dose Group 3		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Thyroid (g)	Heart (g)	Kidney (g)
	-	-	-	-	-	-	-
3501	248	1.817	0.0544	0.0135	0.0119	0.924	1.639
3502	225	1.837	0.0625	0.0129	0.0107	0.933	1.545
3503	213	1.782	0.0615	0.0159	0.0156	0.905	1.446
3504	236	1.902	0.0620	0.0131	0.0116	0.952	1.626
3505	248	1.939	0.0508	0.0133	0.0120	0.935	1.667
3506	230	1.750	0.0602	0.0144	0.0104	0.917	1.608
3507	231	1.726	0.0570	0.0140	0.0174	0.864	1.657
3508	241	1.889	0.0616	0.0129	0.0131	0.981	1.674
3509	231	1.879	0.0711	0.0145	0.0147	0.999	1.721
3510	233 [a]	1.906	0.0752	0.0164	0.0162	1.048	1.756
Mean	233.6	1.8427	0.06163	0.01409	0.01336	0.9458	1.6339
SD	10.5	0.0721	0.00721	0.00123	0.00245	0.0522	0.0880
N	10	10	10	10	10	10	10
%Diff	-5.5	-4.1807	-2.60746	-10.99179	-3.25851	-5.6559	-6.3721

[a] [RC:value confirmed]

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight (Absolute)					
	Liver (g)	Lung (g)	Ovary (g)	Spleen (g)	Thymus (g)	Uterus (g)
	-	-	-	-	-	-
3501	6.819	1.079	0.092	0.632	0.312	0.793 [a]
3502	6.753	1.209	0.108	0.615	0.356	0.784
3503	6.257	0.944	0.087	0.459	0.340	0.477
3504	6.880	1.258	0.124	0.595	0.477	0.575
3505	7.681	1.234	0.092	0.615	0.309	0.596
3506	7.859	1.065	0.119	0.552	0.315	0.649
3507	7.072	1.157	0.088	0.478	0.290	0.419
3508	8.072	1.210	0.131	0.696	0.376	0.853
3509	8.737	1.140	0.125	0.783	0.500	0.625
3510	7.836	1.244	0.111	0.602	0.398	0.611
Mean	7.3966	1.1540	0.1077	0.6027	0.3673	0.6382
SD	0.7571	0.0996	0.0169	0.0950	0.0720	0.1383
N	10	10	10	10	10	10
%Diff	-2.3706	3.0265	-6.7532	7.5482	-2.7020	-9.1013

[a] [RC:estrus]

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Thyroid (g)	Heart (g)	Kidney (g)
	-	-	-	-	-	-	-
4501	293	1.721	0.0736	0.0144	0.0130	1.056	1.898
4502	218	1.848	0.0738	0.0142	0.0102	1.005	1.644
4503	234	1.919	0.0701	0.0167	0.0177	0.918	1.661
4504	246	1.871	0.0613	0.0151	0.0137	1.038	1.591
4505	220	1.862	0.0654	0.0160	0.0126	0.975	1.817
4506	208	1.812	0.0658	0.0133	0.0121	0.828	1.430
4507	273	1.945	0.0639	0.0164	0.0177	1.083	1.975
4508	243	1.975	0.0772	0.0121	0.0082	1.041	1.689
4509	230	1.953	0.0729	0.0157	0.0135	0.929	1.750
4510	211	1.727	0.0809	0.0105	0.0170	1.149	1.534
Mean	237.6	1.8633	0.07049	0.01444	0.01357	1.0022	1.6989
SD	27.4	0.0895	0.00629	0.00199	0.00315	0.0927	0.1660
N	10	10	10	10	10	10	10
%Diff	-3.9	-3.1096	11.39381	-8.78080	-1.73787	-0.0299	-2.6474

Appendix 18

Individual Absolute Organ Weights: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (Absolute)					
	Liver (g)	Lung (g)	Ovary (g)	Spleen (g)	Thymus (g)	Uterus (g)
	-	-	-	-	-	-
4501	9.486	1.281	0.112	0.739	0.446	0.536
4502	6.938	1.130	0.108	0.584	0.297	0.414
4503	8.055	1.166	0.091	0.534	0.428	0.494
4504	7.464	1.056	0.096	0.611	0.254	0.904 [a]
4505	7.721	1.006	0.101	0.590	0.334	0.461
4506	6.848	1.003	0.103	0.621	0.272	0.817 [a]
4507	8.988	1.275	0.091	0.651	0.505	0.625
4508	8.280	1.188	0.099	0.561	0.251	0.601
4509	7.625	1.024	0.069	0.631	0.260	1.086 [a]
4510	7.235	1.351	0.115	0.670	0.230	0.712
Mean	7.8640	1.1480	0.0985	0.6192	0.3277	0.6650
SD	0.8581	0.1257	0.0132	0.0586	0.0972	0.2150
N	10	10	10	10	10	10
%Diff	3.7987	2.4908	-14.7186	10.4925	-13.1921	-5.2841

[a] [RC:estrus]

Appendix 18

Individual Absolute Organ Weights: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Epididymis (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Prostate (g)	Gland Thyroid (g)
	-	-	-	-	-	-	-
1011	429	2.111	1.229	0.0570	0.0159	0.871	0.0149
1012	464	2.121	1.295	0.0635	0.0146	1.228	0.0180
1013	331	2.049	1.150	0.0510	0.0104	0.912	0.0082
1014	431	2.099	1.196	0.0572	0.0134	1.208	0.0160
1015	500	2.103	1.157	0.0617	0.0150	1.117	0.0153
Mean	431.0	2.0966	1.2054	0.05808	0.01386	1.0672	0.01448
SD	63.0	0.0279	0.0593	0.00486	0.00213	0.1664	0.00371
N	5	5	5	5	5	5	5

Appendix 18

Individual Absolute Organ Weights: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (Absolute)						
	Heart (g)	Kidney (g)	Liver (g)	Lung (g)	Spleen (g)	Testis (g)	Thymus (g)
	-	-	-	-	-	-	-
1011	1.652	2.823	15.266	1.376	0.599	4.050	0.490
1012	1.430	2.690	12.326	1.422	0.745	3.556	0.449
1013	1.071	1.963	8.444	1.118	0.619	3.741	0.301
1014	1.794	2.721	13.412	1.442	0.991	3.838	0.473
1015	1.732	3.075	14.690	1.683	0.755	3.570	0.397
Mean	1.5358	2.6544	12.8276	1.4082	0.7418	3.7510	0.4220
SD	0.2941	0.4151	2.7029	0.2013	0.1563	0.2049	0.0762
N	5	5	5	5	5	5	5

Appendix 18

Individual Absolute Organ Weights: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Epididymis (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Prostate (g)	Gland Thyroid (g)
	-	-	-	-	-	-	-
4011	410	2.104	1.200	0.0464	0.0128	0.936	0.0122
4012	404	2.083	1.225	0.0602	0.0110	0.925	0.0189
4013	387	1.847	1.211	0.0497	0.0123	0.916	0.0111
4014	448 [a]	2.082	1.228	0.0526	0.0149	0.933	0.0175
4015	425	2.188	1.197	0.0539	0.0121	1.078	0.0173
Mean	414.8	2.0608	1.2122	0.05256	0.01262	0.9576	0.01540
SD	23.0	0.1272	0.0141	0.00515	0.00143	0.0678	0.00350
N	5	5	5	5	5	5	5
%Diff	-3.8	-1.7075	0.5641	-9.50413	-8.94661	-10.2699	6.35359

[a] [RC:Value Confirmed]

Appendix 18

Individual Absolute Organ Weights: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (Absolute)						
	Heart (g)	Kidney (g)	Liver (g)	Lung (g)	Spleen (g)	Testis (g)	Thymus (g)
	-	-	-	-	-	-	-
4011	1.490	2.894	11.236	1.369	0.834	3.946	0.384
4012	1.263	2.531	10.577	1.429	0.632	3.850	0.392
4013	1.343	2.567	11.942	1.265	0.735	3.547	0.286
4014	1.683	3.062	13.558	1.705	0.930	3.799	0.489
4015	1.325	2.742	12.539	1.601	0.716	3.528	0.310
Mean	1.4208	2.7592	11.9704	1.4738	0.7694	3.7340	0.3722
SD	0.1686	0.2231	1.1539	0.1776	0.1150	0.1871	0.0798
N	5	5	5	5	5	5	5
%Diff	-7.4880	3.9482	-6.6825	4.6584	3.7207	-0.4532	-11.8009

Appendix 18

Individual Absolute Organ Weights: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Thyroid (g)	Heart (g)	Kidney (g)
	-	-	-	-	-	-	-
1511	274	2.024	0.0745	0.0179	0.0157	1.157	1.776
1512	263	1.853	0.0579	0.0153	0.0141	1.053	1.901 [b]
1513	245 [a]	1.998	0.0479	0.0176	0.0100	0.968	1.631
1514	246 [a]	1.880	0.0613	0.0165	0.0126	1.058	1.571
1515	248	1.738	0.0544	0.0128	0.0130	1.011	1.636
Mean	255.2	1.8986	0.05920	0.01602	0.01308	1.0494	1.7030
SD	12.8	0.1160	0.00989	0.00207	0.00210	0.0703	0.1338
N	5	5	5	5	5	5	5

[a] [RC:Value Confirmed]
[b] [RC:Put in formalin few seconds before weighing]

Appendix 18

Individual Absolute Organ Weights: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (Absolute)					
	Liver (g)	Lung (g)	Ovary (g)	Spleen (g)	Thymus (g)	Uterus (g)
	-	-	-	-	-	-
1511	7.190	1.224	0.094	0.526	0.389	1.161 [a]
1512	7.900	1.110	0.099	0.485	0.439	0.429
1513	8.093	1.075	0.111	0.487	0.322	0.498
1514	7.215	1.096	0.117	0.453	0.300	0.389
1515	8.463	1.156	0.089	0.632	0.354	0.470
Mean	7.7722	1.1322	0.1020	0.5166	0.3608	0.5894
SD	0.5581	0.0593	0.0117	0.0695	0.0551	0.3222
N	5	5	5	5	5	5

[a] [RC:estrus]

Appendix 18

Individual Absolute Organ Weights: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4		Organ Weight (Absolute)					
	Terminal Body Wt (g)	Brain (g)	Gland Adrenal (g)	Gland Pituitary (g)	Gland Thyroid (g)	Heart (g)	Kidney (g)
	-	-	-	-	-	-	-
4511	247	1.754	0.0616	0.0157	0.0128	0.928	1.637
4512	251	1.860	0.0669	0.0177	0.0155	1.080	1.775
4513	247	1.938 [b]	0.0631	0.0177	0.0114	0.895	1.673
4514	246 [a]	1.842	0.0583	0.0151	0.0108	1.351	1.734
4515	251 [a]	1.765	0.0653	0.0188	0.0131	1.105	1.430
Mean	248.4	1.8318	0.06304	0.01700	0.01272	1.0718	1.6498
SD	2.4	0.0753	0.00334	0.00154	0.00182	0.1810	0.1340
N	5	5	5	5	5	5	5
%Diff	-2.7	-3.5184	6.48649	6.11735	-2.75229	2.1346	-3.1239

[a] [RC:Value Confirmed]
[b] [RC:Put in formalin a few seconds before weighing]

Appendix 18

Individual Absolute Organ Weights: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (Absolute)					
	Liver (g)	Lung (g)	Ovary (g)	Spleen (g)	Thymus (g)	Uterus (g)
	-	-	-	-	-	-
4511	7.794	1.145	0.129	0.459	0.286	0.370
4512	7.812	1.143	0.087	0.492	0.355	0.409
4513	7.291	1.034	0.084	0.517	0.291	1.003 [a]
4514	7.279	1.227	0.115	0.541	0.370	0.597
4515	6.699	1.077	0.103	0.468	0.461	0.482
Mean	7.3750	1.1252	0.1036	0.4954	0.3526	0.5722
SD	0.4582	0.0737	0.0189	0.0340	0.0712	0.2559
N	5	5	5	5	5	5
%Diff	-5.1105	-0.6183	1.5686	-4.1038	-2.2727	-2.9182

[a] [RC:estrus]

Appendix 18

Appendix 2
Individual Organ Weights Relative to Body Weight

Appendix 18

Individual Organ Weights Relative to Body Weight Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed	OPMP	Only one of the paired organs present – Macroscopic pathology
AVS	Suspected aberrant value	OPOP	Only one of the paired organs present
COME	See Comment Value Excluded	OUM	Organ unidentifiable macroscopically
COMI	See Comment Value Included	MPE	Macroscopic pathology – Excluded from mean
LIBW	Lung infused before weighing	MPI	Macroscopic pathology – Included in mean
NC	Not calculable	TERR	Technical error
OA	Omitted activity	UPTD	Unable to perform due to technical difficulty
ONP	Organ not present	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study:

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (BW)						
	Brain (%)	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)
	-	-	-	-	-	-	-
1001	0.5204	0.2535	0.0141	0.0033	0.2499	0.0037	0.3840
1002	0.4841	0.2423	0.0110	0.0030	0.2401	0.0047	0.3161
1003	0.5430	0.3092	0.0124	0.0031	0.3176	0.0041	0.3430
1004	0.5575	0.2833	0.0162	0.0026	0.3761	0.0047	0.3297
1005	0.5424	0.2789	0.0133	0.0034	0.3259	0.0050	0.3824
1006	0.5406	0.2708	0.0148	0.0029	0.3019	0.0045	0.3406
1007	0.4954	0.2837	0.0143	0.0029	0.2962	0.0040	0.3132
1008	0.4714	0.2213	0.0151	0.0030	0.2864	0.0038	0.3297
1009	0.5060	0.2737	0.0149	0.0034	0.2749	0.0037	0.3496
1010	0.4328	0.2491	0.0158	0.0028	0.2593	0.0045	0.2874
Mean	0.50937	0.26660	0.01420	0.00304	0.29285	0.00426	0.33758
SD	0.03912	0.02522	0.00157	0.00025	0.04061	0.00047	0.02991
N	10	10	10	10	10	10	10

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (BW)					
	Kidney (%)	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-	-
1001	0.6770	3.4008	0.3653	0.1950	0.9524	0.1017
1002	0.5786	2.7377	0.3019	0.1745	0.8873	0.1036
1003	0.6808	2.7411	0.3770	0.1973	0.9668	0.0719
1004	0.6817	3.2933	0.3625	0.1933	0.8831	0.0817
1005	0.7222	3.0751	0.4046	0.2278	1.0314	0.1224
1006	0.6642	3.1503	0.4064	0.2136	1.0928	0.1419
1007	0.5885	2.9043	0.3427	0.1659	0.9130	0.1117
1008	0.6616	2.9377	0.3607	0.1958	0.8419	0.0934
1009	0.7159	3.1258	0.3431	0.1872	0.8740	0.1284
1010	0.6409	3.1833	0.3359	0.2076	0.8748	0.1491
Mean	0.66114	3.05495	0.36001	0.19581	0.93172	0.11059
SD	0.04748	0.22186	0.03163	0.01799	0.07948	0.02513
N	10	10	10	10	10	10

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight (BW)						
	Brain (%)	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)
	-	-	-	-	-	-	-
2001	0.4893	0.2706	0.0129	0.0029	0.3054	0.0036	0.3599
2002	0.4645	0.2687	0.0128	0.0026	0.2682	0.0047	0.2941
2003	0.5163	0.2632	0.0141	0.0028	0.3056	0.0048	0.3464
2004	0.5690	0.3230	0.0157	0.0026	0.3716	0.0045	0.3438
2005	0.5816	0.2581	0.0132	0.0028	0.3690	0.0032	0.3243
2006	0.4782	0.2198	0.0144	0.0028	0.2688	0.0046	0.3109
2007	0.5379	0.2830	0.0166	0.0032	0.2681	0.0033	0.3610
2008	0.4415	0.2433	0.0152	0.0030	0.2433	0.0038	0.3004
2009	0.5136	0.2608	0.0151	0.0035	0.2443	0.0047	0.3801
2010	0.5321	0.2661	0.0146	0.0024	0.1961	0.0050	0.3167
Mean	0.51240	0.26565	0.01446	0.00287	0.28404	0.00422	0.33376
SD	0.04481	0.02648	0.00123	0.00032	0.05529	0.00068	0.02871
N	10	10	10	10	10	10	10
%Diff	0.59493	-0.35539	1.86691	-5.62956	-3.00802	-0.87246	-1.13271

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight (BW)					
	Kidney (%)	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-	-
2001	0.7224	3.1002	0.3689	0.1949	1.0681	0.1433
2002	0.6521	3.3350	0.3567	0.1765	1.0244	0.1213
2003	0.6653	3.0211	0.3741	0.1968	1.0072	0.1077
2004	0.6727	2.8486	0.3781	0.1764	1.0122	0.0730
2005	0.6268	2.7542	0.3883	0.1804	1.0022	0.0760
2006	0.6329	2.8272	0.3767	0.2007	0.8807	0.1114
2007	0.6604	3.1582	0.3981	0.2198	1.0107	0.1000
2008	0.6269	3.0631	0.3369	0.2131	0.8477	0.1079
2009	0.7002	3.3246	0.3892	0.2050	0.8964	0.1134
2010	0.6984	2.9410	0.3689	0.1574	1.0392	0.1068
Mean	0.66582	3.03733	0.37360	0.19212	0.97889	0.10608
SD	0.03306	0.19996	0.01753	0.01916	0.07513	0.02039
N	10	10	10	10	10	10
%Diff	0.70921	-0.57681	3.77349	-1.88364	5.06245	-4.08183

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight (BW)						
	Brain (%)	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)
	-	-	-	-	-	-	-
3001	0.5876	0.2760	0.0164	0.0033	0.2828	0.0047	0.3769
3002	0.5428	0.2660	0.0170	0.0027	0.2779	0.0043	0.3420
3003	0.5304	0.2529	0.0137	0.0032	0.3197	0.0046	0.3430
3004	0.5837	0.2997	0.0152	0.0030	0.2880	0.0042	0.3217
3005	0.5238	0.2357	0.0121	0.0032	0.2479	0.0034	0.4021
3006	0.4991	0.2203	0.0136	0.0026	0.2203	0.0041	0.3290
3007	0.5036	0.2211	0.0138	0.0025	0.2706	0.0037	0.3381
3008	0.4899	0.2783	0.0128	0.0029	0.2902	0.0028	0.3838
3009	0.5358	0.2534	0.0142	0.0032	0.2578	0.0038	0.3516
3010	0.4738	0.2209	0.0160	0.0030	0.2154	0.0040	0.3356
Mean	0.52705	0.25244	0.01447	0.00296	0.26706	0.00396	0.35238
SD	0.03767	0.02774	0.00161	0.00028	0.03236	0.00057	0.02632
N	10	10	10	10	10	10	10
%Diff	3.47052	-5.31193	1.90038	-2.47579	-8.80608	-6.89216	4.38386

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight (BW)					
	Kidney (%)	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-	-
3001	0.6686	3.0361	0.3967	0.2053	1.0494	0.0991
3002	0.6394	3.2335	0.3766	0.1904	1.1112	0.0920
3003	0.6959	3.0545	0.3629	0.1969	0.9847	0.0990
3004	0.6434	3.1916	0.3633	0.2205	0.9786	0.0895
3005	0.7106	2.9511	0.3886	0.2037	0.8415	0.1183
3006	0.6493	3.2173	0.4012	0.2530	0.9313	0.1276
3007	0.7022	3.3354	0.3818	0.2075	0.8740	0.1046
3008	0.6465	3.4427	0.3566	0.2263	0.9364	0.0957
3009	0.6614	2.7666	0.4111	0.2202	0.8946	0.1920
3010	0.6710	3.1972	0.3368	0.1834	0.8575	0.1097
Mean	0.66882	3.14259	0.37756	0.21073	0.94591	0.11273
SD	0.02592	0.19540	0.02289	0.02014	0.08655	0.03026
N	10	10	10	10	10	10
%Diff	1.16296	2.86895	4.87431	7.62303	1.52273	1.93519

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (BW)						
	Brain (%)	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)
	-	-	-	-	-	-	-
4001	0.4788	0.2370	0.0128	0.0038	0.2921	0.0048	0.3899
4002	0.5462	0.2664	0.0147	0.0030	0.2948	0.0046	0.3423
4003	0.5085	0.2608	0.0194	0.0038	0.2648	0.0038	0.3529
4004	0.4710	0.2261	0.0187	0.0034	0.2737	0.0033	0.3358
4005	0.4909	0.2487	0.0144	0.0030	0.2048	0.0036	0.3629
4006	0.5432	0.2710	0.0160	0.0032	0.2520	0.0034	0.3452
4007	0.5054	0.2581	0.0172	0.0030	0.2642	0.0055	0.3394
4008	0.5627	0.3083	0.0143	0.0028	0.2784	0.0043	0.3595
4009	0.5180	0.2521	0.0135	0.0038	0.2364	0.0044	0.3797
4010	0.5300	0.2493	0.0146	0.0026	0.2436	0.0042	0.3605
Mean	0.51547	0.25779	0.01555	0.00325	0.26048	0.00419	0.35681
SD	0.03025	0.02218	0.00221	0.00044	0.02735	0.00068	0.01759
N	10	10	10	10	10	10	10
%Diff	1.19594	-3.30546	9.55117	6.86989	-11.05356	-1.66373	5.69421

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (BW)					
	Kidney (%)	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-	-
4001	0.7392	3.3153	0.4228	0.2167	0.9434	0.1667
4002	0.7079	3.2210	0.4123	0.2278	0.9924	0.1178
4003	0.7373	3.3352	0.4188	0.2193	0.9659	0.1444
4004	0.6677	3.4042	0.3571	0.1991	0.8697	0.1268
4005	0.6568	3.0818	0.4124	0.2212	1.0096	0.1371
4006	0.7250	2.9912	0.3823	0.2641	1.0018	0.1298
4007	0.7072	3.5033	0.4020	0.1893	1.0458	0.1322
4008	0.6979	3.6482	0.4024	0.2423	1.0210	0.0701
4009	0.6706	3.4332	0.3860	0.2514	0.8785	0.1110
4010	0.6368	3.9082	0.3856	0.2144	0.9749	0.1297
Mean	0.69463	3.38416	0.39816	0.22457	0.97029	0.12657
SD	0.03520	0.26686	0.02031	0.02288	0.05831	0.02494
N	10	10	10	10	10	10
%Diff	5.06588	10.77638	10.59675	14.68763	4.13949	14.44386

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (BW)						
	Brain (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)
	-	-	-	-	-	-	-
1501	0.9054	0.0242	0.0060	0.0042	0.4070	0.6669	3.1510
1502	0.7079	0.0285	0.0055	0.0057	0.4540	0.7117	3.4017
1503	0.7802	0.0257	0.0072	0.0061	0.4135	0.7456	3.1603
1504	0.8188	0.0255	0.0053	0.0050	0.4000	0.6933	3.0874
1505	0.7177	0.0252	0.0065	0.0050	0.3942	0.6904	2.8950
1506	0.7357	0.0259	0.0063	0.0059	0.3926	0.7116	2.7833
1507	0.7922	0.0276	0.0069	0.0040	0.4065	0.7616	3.3190
1508	0.7728	0.0230	0.0067	0.0080	0.4372	0.6452	3.0344
1509	0.7940	0.0218	0.0062	0.0053	0.3562	0.6884	2.6964
1510	0.7520	0.0288	0.0074	0.0064	0.3956	0.7488	3.1575
Mean	0.77767	0.02562	0.00640	0.00558	0.40569	0.70635	3.06861
SD	0.05717	0.00225	0.00069	0.00114	0.02639	0.03726	0.22319
N	10	10	10	10	10	10	10

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (BW)				
	Lung (%)	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-	-
1501	0.4319	0.0381	0.2444	0.1401	0.1743
1502	0.4711	0.0427	0.2649	0.1502	0.4954
1503	0.4456	0.0376	0.2139	0.1688	0.1865
1504	0.4586	0.0377	0.2427	0.1519	0.2460
1505	0.4496	0.0381	0.2085	0.1446	0.1650
1506	0.4438	0.0395	0.2279	0.1411	0.2496
1507	0.4444	0.0418	0.2026	0.1427	0.2457
1508	0.4724	0.0536	0.2352	0.1892	0.4800
1509	0.4566	0.0394	0.1916	0.1422	0.4012
1510	0.4563	0.0976	0.2345	0.1567	0.2052
Mean	0.45304	0.04660	0.22661	0.15274	0.28489
SD	0.01261	0.01856	0.02228	0.01558	0.12598
N	10	10	10	10	10

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight (BW)						
	Brain (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)
	-	-	-	-	-	-	-
2501	0.7298	0.0247	0.0061	0.0061	0.3888	0.7671	3.0225
2502	0.7855	0.0232	0.0057	0.0042	0.4046	0.6548	2.8506
2503	0.8323	0.0218	0.0058	0.0057	0.3731	0.6888	2.8395
2604	0.7220	0.0257	0.0061	0.0044	0.4160	0.6772	2.9821
2505	0.6681	0.0161	0.0060	0.0051	0.3980	0.6157	3.0866
2506	0.7881	0.0223	0.0077	0.0061	0.4030	0.6613	3.3945
2507	0.8016	0.0224	0.0069	0.0050	0.4318	0.6927	3.2167
2508	0.8143	0.0271	0.0064	0.0061	0.3933	0.6719	3.1013
2509	0.7873	0.0231	0.0062	0.0065	0.4294	0.7202	3.6053
2510	0.8300	0.0303	0.0081	0.0052	0.3770	0.7170	3.3361
Mean	0.77590	0.02368	0.00650	0.00544	0.40150	0.68665	3.14352
SD	0.05297	0.00374	0.00081	0.00079	0.01992	0.04156	0.24554
N	10	10	10	10	10	10	10
%Diff	-0.22797	-7.55676	1.56357	-2.49760	-1.03323	-2.78885	2.44119

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight (BW)				
	Lung (%)	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-	-
2501	0.4655	0.0306	0.2217	0.1260	0.4004
2502	0.5075	0.0373	0.2423	0.1929	0.1959
2503	0.4395	0.0363	0.2381	0.1475	0.2354
2604	0.4933	0.0425	0.2209	0.1664	0.2067
2505	0.4685	0.0272	0.2039	0.1181	0.1811
2506	0.4600	0.0421	0.2043	0.1523	0.2298
2507	0.4829	0.0461	0.2567	0.1355	0.1588
2508	0.4804	0.0406	0.2554	0.2067	0.2411
2509	0.5140	0.0439	0.2289	0.1561	0.2452
2510	0.4709	0.0452	0.2470	0.0857	0.2135
Mean	0.47823	0.03919	0.23192	0.14873	0.23078
SD	0.02245	0.00630	0.01921	0.03544	0.06570
N	10	10	10	10	10
%Diff	5.56183	-15.89554	2.34641	-2.62647	-18.99446

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight (BW)						
	Brain (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)
	-	-	-	-	-	-	-
3501	0.7327	0.0219	0.0054	0.0048	0.3726	0.6609	2.7496
3502	0.8164	0.0278	0.0057	0.0048	0.4147	0.6867	3.0013
3503	0.8366	0.0289	0.0075	0.0073	0.4249	0.6789	2.9376
3504	0.8059	0.0263	0.0056	0.0049	0.4034	0.6890	2.9153
3505	0.7819	0.0205	0.0054	0.0048	0.3770	0.6722	3.0972
3506	0.7609	0.0262	0.0063	0.0045	0.3987	0.6991	3.4170
3507	0.7472	0.0247	0.0061	0.0075	0.3740	0.7173	3.0615
3508	0.7838	0.0256	0.0054	0.0054	0.4071	0.6946	3.3494
3509	0.8134	0.0308	0.0063	0.0064	0.4325	0.7450	3.7823
3510	0.8180	0.0323	0.0070	0.0070	0.4498	0.7536	3.3631
Mean	0.78968	0.02648	0.00605	0.00574	0.40546	0.69973	3.16741
SD	0.03421	0.00366	0.00073	0.00118	0.02601	0.03034	0.30667
N	10	10	10	10	10	10	10
%Diff	1.54414	3.37485	-5.40256	2.97252	-0.05690	-0.93750	3.21974

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight (BW)				
	Lung (%)	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-	-
3501	0.4351	0.0371	0.2548	0.1258	0.3198
3502	0.5373	0.0480	0.2733	0.1582	0.3484
3503	0.4432	0.0408	0.2155	0.1596	0.2239
3504	0.5331	0.0525	0.2521	0.2021	0.2436
3505	0.4976	0.0371	0.2480	0.1246	0.2403
3506	0.4630	0.0517	0.2400	0.1370	0.2822
3507	0.5009	0.0381	0.2069	0.1255	0.1814
3508	0.5021	0.0544	0.2888	0.1560	0.3539
3509	0.4935	0.0541	0.3390	0.2165	0.2706
3510	0.5339	0.0476	0.2584	0.1708	0.2622
Mean	0.49396	0.04615	0.25768	0.15761	0.27264
SD	0.03671	0.00719	0.03745	0.03194	0.05514
N	10	10	10	10	10
%Diff	9.03380	-0.96437	13.71379	3.18930	-4.29978

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (BW)						
	Brain (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)
	-	-	-	-	-	-	-
4501	0.5874	0.0251	0.0049	0.0044	0.3604	0.6478	3.2375
4502	0.8477	0.0339	0.0065	0.0047	0.4610	0.7541	3.1826
4503	0.8201	0.0300	0.0071	0.0076	0.3923	0.7098	3.4423
4504	0.7606	0.0249	0.0061	0.0056	0.4220	0.6467	3.0341
4505	0.8464	0.0297	0.0073	0.0057	0.4432	0.8259	3.5095
4506	0.8712	0.0316	0.0064	0.0058	0.3981	0.6875	3.2923
4507	0.7125	0.0234	0.0060	0.0065	0.3967	0.7234	3.2923
4508	0.8128	0.0318	0.0050	0.0034	0.4284	0.6951	3.4074
4509	0.8491	0.0317	0.0068	0.0059	0.4039	0.7609	3.3152
4510	0.8185	0.0383	0.0050	0.0081	0.5445	0.7270	3.4289
Mean	0.79261	0.03004	0.00612	0.00576	0.42505	0.71783	3.31423
SD	0.08608	0.00455	0.00089	0.00140	0.05072	0.05419	0.14103
N	10	10	10	10	10	10	10
%Diff	1.92019	17.27971	-4.44288	3.22318	4.77276	1.62461	8.00430

Appendix 18

Individual Organ Weights Relative to Body Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (BW)				
	Lung (%)	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-	-
4501	0.4372	0.0382	0.2522	0.1522	0.1829
4502	0.5183	0.0495	0.2679	0.1362	0.1899
4503	0.4983	0.0389	0.2282	0.1829	0.2111
4504	0.4293	0.0390	0.2484	0.1033	0.3675
4505	0.4573	0.0459	0.2682	0.1518	0.2095
4506	0.4822	0.0495	0.2986	0.1308	0.3928
4507	0.4670	0.0333	0.2385	0.1850	0.2289
4508	0.4889	0.0407	0.2309	0.1033	0.2473
4509	0.4452	0.0300	0.2743	0.1130	0.4722
4510	0.6403	0.0545	0.3175	0.1090	0.3374
Mean	0.48640	0.04197	0.26246	0.13675	0.28396
SD	0.06098	0.00773	0.02904	0.03079	0.10076
N	10	10	10	10	10
%Diff	7.36468	-9.94249	15.82386	-10.46916	-0.32502

Appendix 18

Individual Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (BW)						
	Brain (%)	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)
	-	-	-	-	-	-	-
1011	0.4921	0.2865	0.0133	0.0037	0.2030	0.0035	0.3851
1012	0.4571	0.2791	0.0137	0.0031	0.2647	0.0039	0.3082
1013	0.6190	0.3474	0.0154	0.0031	0.2755	0.0025	0.3236
1014	0.4870	0.2775	0.0133	0.0031	0.2803	0.0037	0.4162
1015	0.4206	0.2314	0.0123	0.0030	0.2234	0.0031	0.3464
Mean	0.49517	0.28438	0.01360	0.00322	0.24938	0.00332	0.35590
SD	0.07488	0.04142	0.00113	0.00028	0.03426	0.00056	0.04445
N	5	5	5	5	5	5	5

Appendix 18

Individual Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (BW)					
	Kidney (%)	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-	-
1011	0.6580	3.5585	0.3207	0.1396	0.9441	0.1142
1012	0.5797	2.6565	0.3065	0.1606	0.7664	0.0968
1013	0.5931	2.5511	0.3378	0.1870	1.1302	0.0909
1014	0.6313	3.1118	0.3346	0.2299	0.8905	0.1097
1015	0.6150	2.9380	0.3366	0.1510	0.7140	0.0794
Mean	0.61543	2.96317	0.32723	0.17363	0.88903	0.09821
SD	0.03100	0.40033	0.01347	0.03601	0.16346	0.01413
N	5	5	5	5	5	5

Appendix 18

Individual Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (BW)						
	Brain (%)	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)
	-	-	-	-	-	-	-
4011	0.5132	0.2927	0.0113	0.0031	0.2283	0.0030	0.3634
4012	0.5156	0.3032	0.0149	0.0027	0.2290	0.0047	0.3126
4013	0.4773	0.3129	0.0128	0.0032	0.2367	0.0029	0.3470
4014	0.4647	0.2741	0.0117	0.0033	0.2083	0.0039	0.3757
4015	0.5148	0.2816	0.0127	0.0028	0.2536	0.0041	0.3118
Mean	0.49712	0.29291	0.01270	0.00304	0.23117	0.00370	0.34210
SD	0.02427	0.01571	0.00139	0.00025	0.01638	0.00077	0.02913
N	5	5	5	5	5	5	5
%Diff	0.39399	3.00117	-6.62953	-5.63788	-7.30143	11.42467	-3.87621

Appendix 18

Individual Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (BW)					
	Kidney (%)	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-	-
4011	0.7059	2.7405	0.3339	0.2034	0.9624	0.0937
4012	0.6265	2.6181	0.3537	0.1564	0.9530	0.0970
4013	0.6633	3.0858	0.3269	0.1899	0.9165	0.0739
4014	0.6835	3.0263	0.3806	0.2076	0.8480	0.1092
4015	0.6452	2.9504	0.3767	0.1685	0.8301	0.0729
Mean	0.66486	2.88421	0.35435	0.18517	0.90201	0.08934
SD	0.03118	0.19792	0.02430	0.02215	0.06030	0.01563
N	5	5	5	5	5	5
%Diff	8.03169	-2.66489	8.28950	6.64716	1.46051	-9.03840

Appendix 18

Individual Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (BW)						
	Brain (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)
	-	-	-	-	-	-	-
1511	0.7387	0.0272	0.0065	0.0057	0.4223	0.6482	2.6241
1512	0.7046	0.0220	0.0058	0.0054	0.4004	0.7228	3.0038
1513	0.8155	0.0196	0.0072	0.0041	0.3951	0.6657	3.3033
1514	0.7642	0.0249	0.0067	0.0051	0.4301	0.6386	2.9329
1515	0.7008	0.0219	0.0052	0.0052	0.4077	0.6597	3.4125
Mean	0.74476	0.02312	0.00628	0.00511	0.41110	0.66700	3.05532
SD	0.04735	0.00296	0.00080	0.00062	0.01473	0.03290	0.31331
N	5	5	5	5	5	5	5

Appendix 18

Individual Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight (BW)				
	Lung (%)	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-	-
1511	0.4467	0.0343	0.1920	0.1420	0.4237
1512	0.4221	0.0376	0.1844	0.1669	0.1631
1513	0.4388	0.0453	0.1988	0.1314	0.2033
1514	0.4455	0.0476	0.1841	0.1220	0.1581
1515	0.4661	0.0359	0.2548	0.1427	0.1895
Mean	0.44384	0.04014	0.20283	0.14100	0.22755
SD	0.01588	0.00592	0.02970	0.01681	0.11123
N	5	5	5	5	5

Appendix 18

Individual Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (BW)						
	Brain (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)
	-	-	-	-	-	-	-
4511	0.7101	0.0249	0.0064	0.0052	0.3757	0.6628	3.1555
4512	0.7410	0.0267	0.0071	0.0062	0.4303	0.7072	3.1124
4513	0.7846	0.0255	0.0072	0.0046	0.3623	0.6773	2.9518
4514	0.7488	0.0237	0.0061	0.0044	0.5492	0.7049	2.9589
4515	0.7032	0.0260	0.0075	0.0052	0.4402	0.5697	2.6689
Mean	0.73755	0.02537	0.00684	0.00512	0.43155	0.66437	2.96950
SD	0.03274	0.00113	0.00057	0.00069	0.07386	0.05613	0.19089
N	5	5	5	5	5	5	5
%Diff	-0.96817	9.72591	8.91548	0.17846	4.97565	-0.39421	-2.80872

Appendix 18

Individual Organ Weights Relative to Body Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight (BW)				
	Lung (%)	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-	-
4511	0.4636	0.0522	0.1858	0.1158	0.1498
4512	0.4554	0.0347	0.1960	0.1414	0.1629
4513	0.4186	0.0340	0.2093	0.1178	0.4061
4514	0.4988	0.0467	0.2199	0.1504	0.2427
4515	0.4291	0.0410	0.1865	0.1837	0.1920
Mean	0.45309	0.04174	0.19951	0.14182	0.23071
SD	0.03149	0.00783	0.01485	0.02774	0.10432
N	5	5	5	5	5
%Diff	2.08306	3.97435	-1.63798	0.58108	1.38707

Appendix 18

Appendix 3
Individual Organ Weights Relative to Brain Weight

Appendix 18

Individual Organ Weights Relative to Brain Weight Explanation Page

Abbreviation	Description	Abbreviation	Description
--	Not scheduled to be performed	OPMP	Only one of the paired organs present – Macroscopic pathology
AVS	Suspected aberrant value	OPOP	Only one of the paired organs present
COME	See Comment Value Excluded	OUM	Organ unidentifiable macroscopically
COMI	See Comment Value Included	MPE	Macroscopic pathology – Excluded from mean
LIBW	Lung infused before weighing	MPI	Macroscopic pathology – Included in mean
NC	Not calculable	TERR	Technical error
OA	Omitted activity	UPTD	Unable to perform due to technical difficulty
ONP	Organ not present	X	Excluded from mean

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study:

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight/Brain Ratio						
	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)
	-	-	-	-	-	-	-
1001	48.7083	2.7180	0.6297	48.0086	0.7158	73.7890	130.0861
1002	50.0497	2.2790	0.6107	49.6028	0.9633	65.2929	119.5134
1003	56.9438	2.2847	0.5774	58.4868	0.7466	63.1658	125.3858
1004	50.8221	2.9048	0.4733	67.4639	0.8371	59.1430	122.2720
1005	51.4200	2.4514	0.6278	60.0897	0.9268	70.5032	133.1340
1006	50.1028	2.7338	0.5344	55.8582	0.8376	63.0010	122.8674
1007	57.2676	2.8916	0.5855	59.7843	0.8064	63.2255	118.7982
1008	46.9449	3.2042	0.6259	60.7551	0.7998	69.9454	140.3378
1009	54.0952	2.9381	0.6667	54.3333	0.7286	69.0952	141.4762
1010	57.5590	3.6565	0.6580	59.9196	1.0296	66.3988	148.0663
Mean	52.39133	2.80622	0.59895	57.43023	0.83915	66.35599	130.19372
SD	3.82196	0.42222	0.05897	5.71309	0.10434	4.43758	10.22934
N	10	10	10	10	10	10	10

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight/Brain Ratio				
	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-
1001	653.4446	70.1830	37.4596	182.9925	19.5371
1002	565.4916	62.3635	36.0477	183.2671	21.4002
1003	504.8283	69.4375	36.3365	178.0488	13.2404
1004	590.7324	65.0224	34.6786	158.3956	14.6487
1005	566.9158	74.5889	42.0030	190.1345	22.5710
1006	582.7852	75.1799	39.5170	202.1583	26.2590
1007	586.2352	69.1834	33.4874	184.2835	22.5475
1008	623.1495	76.5027	41.5301	178.5892	19.8212
1009	617.7143	67.8095	37.0000	172.7143	25.3810
1010	735.4596	77.5992	47.9658	202.1095	34.4550
Mean	602.67564	70.78700	38.60257	183.26933	21.98611
SD	61.37180	5.06224	4.29133	13.07775	6.03017
N	10	10	10	10	10

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight/Brain Ratio						
	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)
	-	-	-	-	-	-	-
2001	55.2959	2.6455	0.5967	62.4068	0.7310	73.5455	147.6380
2002	57.8421	2.7526	0.5579	57.7368	1.0105	63.3158	140.3684
2003	50.9814	2.7324	0.5424	59.1942	0.9246	67.0971	128.8740
2004	56.7649	2.7559	0.4493	65.3020	0.7938	60.4094	118.2227
2005	44.3804	2.2767	0.4899	63.4486	0.5427	55.7637	107.7810
2006	45.9627	3.0072	0.5849	56.2112	0.9627	65.0104	132.3499
2007	52.6047	3.0797	0.5975	49.8468	0.6129	67.1093	122.7783
2008	55.1203	3.4497	0.6890	55.1203	0.8683	68.0510	142.0009
2009	50.7685	2.9343	0.6800	47.5547	0.9222	74.0102	136.3298
2010	50.0000	2.7478	0.4514	36.8499	0.9421	59.5191	131.2561
Mean	51.97209	2.83818	0.56391	55.36714	0.83109	65.38315	130.75991
SD	4.45785	0.30841	0.08402	8.62169	0.15722	5.87043	11.97139
N	10	10	10	10	10	10	10
%Diff	-0.80021	1.13913	-5.85023	-3.59235	-0.96090	-1.46609	0.43488

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight/Brain Ratio				
	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-
2001	633.6151	75.3854	39.8309	218.2994	29.2889
2002	717.8947	76.7895	38.0000	220.5263	26.1053
2003	585.1756	72.4690	38.1198	195.0930	20.8678
2004	500.5991	66.4503	31.0035	177.8832	12.8308
2005	473.5831	66.7627	31.0279	172.3343	13.0644
2006	591.2008	78.7785	41.9772	184.1615	23.2919
2007	587.1297	74.0041	40.8580	187.8958	18.5904
2008	693.8650	76.3096	48.2775	192.0245	24.4455
2009	647.2753	75.7802	39.9162	174.5226	22.0773
2010	552.6987	69.3327	29.5878	195.2895	20.0687
Mean	598.30372	73.20619	37.85988	191.80300	21.06309
SD	77.89450	4.32357	5.81933	16.65058	5.26431
N	10	10	10	10	10
%Diff	-0.72542	3.41756	-1.92392	4.65636	-4.19822

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight/Brain Ratio						
	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)
	-	-	-	-	-	-	-
3001	46.9789	2.7845	0.5539	48.1370	0.8056	64.1490	113.7966
3002	48.9956	3.1357	0.5047	51.2004	0.7937	63.0083	117.7854
3003	47.6856	2.5796	0.6027	60.2700	0.8631	64.6577	131.1958
3004	51.3416	2.6058	0.5108	49.3292	0.7224	55.1084	110.2167
3005	45.0000	2.3131	0.6162	47.3232	0.6465	76.7677	135.6566
3006	44.1479	2.7200	0.5197	44.1479	0.8146	65.9176	130.1030
3007	43.9036	2.7373	0.4916	53.7349	0.7373	67.1325	139.4217
3008	56.8041	2.6031	0.5928	59.2268	0.5773	78.3505	131.9588
3009	47.2921	2.6451	0.6044	48.1141	0.7108	65.6190	123.4526
3010	46.6279	3.3770	0.6356	45.4634	0.8443	70.8394	141.6303
Mean	47.87773	2.75012	0.56323	50.69470	0.75157	67.15501	127.52173
SD	3.85378	0.30138	0.05320	5.48373	0.09057	6.77248	10.78003
N	10	10	10	10	10	10	10
%Diff	-8.61518	-1.99890	-5.96348	-11.72820	-10.43774	1.20415	-2.05232

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight/Brain Ratio				
	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-
3001	516.7170	67.5227	34.9446	178.6002	16.8681
3002	595.6884	69.3778	35.0808	204.7036	16.9525
3003	575.8438	68.4185	37.1263	185.6316	18.6596
3004	546.7492	62.2291	37.7709	167.6471	15.3251
3005	563.3838	74.1919	38.8889	160.6566	22.5758
3006	644.6629	80.3839	50.7022	186.6105	25.5618
3007	662.2651	75.8072	41.2048	173.5422	20.7711
3008	702.7320	72.7835	46.1856	191.1340	19.5361
3009	516.3926	76.7408	41.1025	166.9729	35.8317
3010	674.8180	71.0820	38.7191	180.9801	23.1441
Mean	599.92529	71.85374	40.17258	179.64787	21.52258
SD	67.27060	5.25492	4.95565	13.12123	5.94860
N	10	10	10	10	10
%Diff	-0.45636	1.50697	4.06712	-1.97603	-2.10832

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight/Brain Ratio						
	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)
	-	-	-	-	-	-	-
4001	49.5028	2.6630	0.8011	60.9945	1.0110	81.4365	154.3646
4002	48.7746	2.6958	0.5526	53.9644	0.8361	62.6622	129.6012
4003	51.3007	3.8189	0.7492	52.0812	0.7492	69.4069	145.0052
4004	48.0038	3.9643	0.7140	58.1024	0.6905	71.3011	141.7567
4005	50.6687	2.9270	0.6173	41.7181	0.7356	73.9198	133.7963
4006	49.8838	2.9521	0.5858	46.3970	0.6323	63.5518	133.4728
4007	51.0628	3.3957	0.5972	52.2773	1.0830	67.1559	139.9291
4008	54.7844	2.5499	0.4942	49.4742	0.7571	63.8801	124.0273
4009	48.6694	2.6026	0.7352	45.6473	0.8480	73.2972	129.4542
4010	47.0437	2.7506	0.4936	45.9640	0.7969	68.0206	120.1542
Mean	49.96946	3.03201	0.63401	50.66205	0.81397	69.46320	135.15617
SD	2.17070	0.51460	0.10938	6.00427	0.13944	5.78383	10.27013
N	10	10	10	10	10	10	10
%Diff	-4.62265	8.04611	5.85440	-11.78505	-3.00070	4.68264	3.81159

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight/Brain Ratio				
	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-
4001	692.3757	88.2873	45.2486	197.0166	34.8066
4002	589.7165	75.4926	41.7107	181.6915	21.5762
4003	655.9313	82.3621	43.1322	189.9584	28.4079
4004	722.7337	75.8102	42.2734	184.6407	26.9140
4005	627.7778	84.0021	45.0617	205.6584	27.9321
4006	550.6741	70.3859	48.6285	184.4258	23.8959
4007	693.2186	79.5547	37.4494	206.9332	26.1640
4008	648.3176	71.5037	43.0599	181.4406	12.4606
4009	662.7876	74.5151	48.5341	169.5986	21.4253
4010	737.4293	72.7506	40.4627	183.9589	24.4730
Mean	658.09621	77.46642	43.55612	188.53226	24.80556
SD	57.86693	5.88228	3.46376	11.61615	5.81431
N	10	10	10	10	10
%Diff	9.19575	9.43594	12.83219	2.87170	12.82375

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight/Brain Ratio						
	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)	Lung (%)
	-	-	-	-	-	-	-
1501	2.6730	0.6575	0.4684	44.9506	73.6571	348.0017	47.7009
1502	4.0189	0.7801	0.8097	64.1253	100.5319	480.4965	66.5485
1503	3.2883	0.9194	0.7842	53.0016	95.5652	405.0838	57.1120
1504	3.1170	0.6438	0.6132	48.8503	84.6704	377.0567	56.0041
1505	3.5155	0.9110	0.7020	54.9303	96.1951	403.3762	62.6474
1506	3.5195	0.8588	0.8061	53.3720	96.7334	378.3456	60.3267
1507	3.4875	0.8760	0.5060	51.3058	96.1371	418.9336	56.0936
1508	2.9762	0.8644	1.0300	56.5735	83.4886	392.6501	61.1284
1509	2.7466	0.7840	0.6727	44.8660	86.6970	339.6055	57.5114
1510	3.8259	0.9815	0.8496	52.6121	99.5778	419.8945	60.6860
Mean	3.31683	0.82766	0.72420	52.45874	91.32536	396.34442	58.57588
SD	0.44199	0.11086	0.16845	5.66347	8.73210	40.19150	5.03862
N	10	10	10	10	10	10	10

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight/Brain Ratio			
	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-
1501	4.2114	26.9875	15.4706	19.2523
1502	6.0284	37.4113	21.2175	69.9764
1503	4.8134	27.4202	21.6333	23.9048
1504	4.5989	29.6372	18.5488	30.0460
1505	5.3055	29.0461	20.1501	22.9904
1506	5.3741	30.9800	19.1781	33.9305
1507	5.2775	25.5713	18.0087	31.0120
1508	6.9358	30.4348	24.4824	62.1118
1509	4.9570	24.1275	17.9059	50.5311
1510	12.9815	31.1873	20.8443	27.2823
Mean	6.04835	29.28032	19.74397	37.10374
SD	2.55276	3.69955	2.49376	17.54940
N	10	10	10	10

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight/Brain Ratio						
	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)	Lung (%)
	-	-	-	-	-	-	-
2501	3.3776	0.8338	0.8338	53.2661	105.0982	414.1264	63.7812
2502	2.9583	0.7290	0.5335	51.5055	83.3597	362.9160	64.6064
2503	2.6185	0.7004	0.6843	44.8276	82.7586	341.1638	52.8017
2604	3.5556	0.8475	0.6047	57.6227	93.7984	413.0233	68.3204
2505	2.4160	0.8957	0.7661	59.5757	92.1626	461.9918	70.1237
2506	2.8294	0.9719	0.7775	51.1339	83.9093	430.7235	58.3693
2507	2.8004	0.8554	0.6212	53.8697	86.4053	401.2729	60.2342
2508	3.3333	0.7840	0.7511	48.3004	82.5110	380.8662	58.9912
2509	2.9304	0.7911	0.8245	54.5404	91.4763	457.9387	65.2925
2510	3.6564	0.9796	0.6286	45.4164	86.3803	401.9382	56.7313
Mean	3.04758	0.83884	0.70252	52.00585	88.78599	406.59608	61.92521
SD	0.41266	0.09288	0.10257	4.83076	7.07296	38.42205	5.42027
N	10	10	10	10	10	10	10
%Diff	-8.11769	1.35072	-2.99319	-0.86333	-2.78058	2.58655	5.71793

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

10 ug/dose Group 2	Organ Weight/Brain Ratio			
	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-
2501	4.1954	30.3771	17.2597	54.8593
2502	4.7544	30.8505	24.5642	24.9340
2503	4.3642	28.6099	17.7263	28.2866
2604	5.8915	30.5943	23.0491	28.6305
2505	4.0660	30.5245	17.6783	27.1067
2506	5.3456	25.9179	19.3305	29.1577
2507	5.7536	32.0265	16.9043	19.8065
2508	4.9890	31.3596	25.3838	29.6053
2509	5.5710	29.0808	19.8329	31.1421
2510	5.4479	29.7538	10.3195	25.7203
Mean	5.03786	29.90949	19.20484	29.92488
SD	0.66489	1.72782	4.40494	9.31645
N	10	10	10	10
%Diff	-16.70687	2.14876	-2.73057	-19.34808

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight/Brain Ratio						
	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)	Lung (%)
	-	-	-	-	-	-	-
3501	2.9939	0.7430	0.6549	50.8531	90.2036	375.2889	59.3836
3502	3.4023	0.7022	0.5825	50.7893	84.1045	367.6102	65.8138
3503	3.4512	0.8923	0.8754	50.7856	81.1448	351.1223	52.9742
3504	3.2597	0.6887	0.6099	50.0526	85.4890	361.7245	66.1409
3505	2.6199	0.6859	0.6189	48.2207	85.9722	396.1320	63.6411
3506	3.4400	0.8229	0.5943	52.4000	91.8857	449.0857	60.8571
3507	3.3024	0.8111	1.0081	50.0579	96.0023	409.7335	67.0336
3508	3.2610	0.6829	0.6935	51.9322	88.6183	427.3160	64.0551
3509	3.7839	0.7717	0.7823	53.1666	91.5913	464.9814	60.6706
3510	3.9454	0.8604	0.8499	54.9843	92.1301	411.1228	65.2676
Mean	3.34598	0.76611	0.72697	51.32423	88.71418	401.41174	62.58375
SD	0.37147	0.07749	0.14509	1.88466	4.49463	38.15963	4.25048
N	10	10	10	10	10	10	10
%Diff	0.87888	-7.43631	0.38318	-2.16267	-2.85921	1.27851	6.84219

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

30 ug/dose Group 3	Organ Weight/Brain Ratio			
	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-
3501	5.0633	34.7826	17.1712	43.6434
3502	5.8792	33.4785	19.3794	42.6783
3503	4.8822	25.7576	19.0797	26.7677
3504	6.5195	31.2829	25.0789	30.2313
3505	4.7447	31.7174	15.9360	30.7375
3506	6.8000	31.5429	18.0000	37.0857
3507	5.0985	27.6941	16.8019	24.2758
3508	6.9349	36.8449	19.9047	45.1562
3509	6.6525	41.6711	26.6099	33.2624
3510	5.8237	31.5845	20.8814	32.0567
Mean	5.83983	32.63563	19.88431	34.58949
SD	0.85076	4.48920	3.49787	7.26367
N	10	10	10	10
%Diff	-3.44744	11.45926	0.71081	-6.77629

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight/Brain Ratio						
	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)	Lung (%)
	-	-	-	-	-	-	-
4501	4.2766	0.8367	0.7554	61.3597	110.2847	551.1912	74.4335
4502	3.9935	0.7684	0.5519	54.3831	88.9610	375.4329	61.1472
4503	3.6529	0.8702	0.9224	47.8374	86.5555	419.7499	60.7608
4504	3.2763	0.8071	0.7322	55.4784	85.0347	398.9311	56.4404
4505	3.5124	0.8593	0.6767	52.3631	97.5832	414.6617	54.0279
4506	3.6313	0.7340	0.6678	45.6954	78.9183	377.9249	55.3532
4507	3.2853	0.8432	0.9100	55.6812	101.5424	462.1080	65.5527
4508	3.9089	0.6127	0.4152	52.7089	85.5190	419.2405	60.1519
4509	3.7327	0.8039	0.6912	47.5678	89.6057	390.4250	52.4322
4510	4.6844	0.6080	0.9844	66.5316	88.8246	418.9346	78.2281
Mean	3.79544	0.77434	0.73072	53.96065	91.28293	422.85996	61.85279
SD	0.43905	0.09572	0.17441	6.40323	9.23617	51.64817	8.60370
N	10	10	10	10	10	10	10
%Diff	14.42970	-6.44212	0.90034	2.86302	-0.04647	6.69003	5.59430

Appendix 18

Individual Organ Weights Relative to Brain Weight: Main Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight/Brain Ratio			
	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-
4501	6.5078	42.9402	25.9152	31.1447
4502	5.8442	31.6017	16.0714	22.4026
4503	4.7421	27.8270	22.3033	25.7426
4504	5.1309	32.6563	13.5756	48.3164
4505	5.4243	31.6864	17.9377	24.7583
4506	5.6843	34.2715	15.0110	45.0883
4507	4.6787	33.4704	25.9640	32.1337
4508	5.0127	28.4051	12.7089	30.4304
4509	3.5330	32.3093	13.3129	55.6068
4510	6.6589	38.7956	13.3179	41.2276
Mean	5.32169	33.39635	17.61179	35.68513
SD	0.92441	4.53152	5.24093	11.21048
N	10	10	10	10
%Diff	-12.01414	14.05730	-10.79915	-3.82338

Appendix 18

Individual Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight/Brain Ratio						
	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)
	-	-	-	-	-	-	-
1011	58.2189	2.7001	0.7532	41.2601	0.7058	78.2568	133.7281
1012	61.0561	2.9939	0.6884	57.8972	0.8487	67.4210	126.8270
1013	56.1249	2.4890	0.5076	44.5095	0.4002	52.2694	95.8028
1014	56.9795	2.7251	0.6384	57.5512	0.7623	85.4693	129.6332
1015	55.0166	2.9339	0.7133	53.1146	0.7275	82.3585	146.2197
Mean	57.47921	2.76841	0.66016	50.86652	0.68890	73.15500	126.44215
SD	2.31782	0.20175	0.09491	7.61356	0.17032	13.52277	18.66370
N	5	5	5	5	5	5	5

Appendix 18

Individual Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight/Brain Ratio				
	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-
1011	723.1644	65.1824	28.3752	191.8522	23.2117
1012	581.1410	67.0438	35.1249	167.6568	21.1693
1013	412.1035	54.5632	30.2099	182.5769	14.6901
1014	638.9709	68.6994	47.2130	182.8490	22.5345
1015	698.5259	80.0285	35.9011	169.7575	18.8778
Mean	610.78113	67.10347	35.36481	178.93846	20.09669
SD	123.97092	9.09061	7.35106	10.08541	3.44652
N	5	5	5	5	5

Appendix 18

Individual Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight/Brain Ratio						
	Epididymis (%)	Gland Adrenal (%)	Gland Pituitary (%)	Gland Prostate (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)
	-	-	-	-	-	-	-
4011	57.0342	2.2053	0.6084	44.4867	0.5798	70.8175	137.5475
4012	58.8094	2.8901	0.5281	44.4071	0.9073	60.6337	121.5074
4013	65.5658	2.6909	0.6659	49.5939	0.6010	72.7125	138.9821
4014	58.9817	2.5264	0.7157	44.8127	0.8405	80.8357	147.0701
4015	54.7075	2.4634	0.5530	49.2687	0.7907	60.5576	125.3199
Mean	59.01973	2.55522	0.61421	46.51383	0.74388	69.11140	134.08543
SD	4.04457	0.25603	0.07772	2.67012	0.14627	8.63681	10.48339
N	5	5	5	5	5	5	5
%Diff	2.68013	-7.70084	-6.95938	-8.55709	7.98101	-5.52743	6.04489

Appendix 18

Individual Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Male Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight/Brain Ratio				
	Liver (%)	Lung (%)	Spleen (%)	Testis (%)	Thymus (%)
	-	-	-	-	-
4011	534.0304	65.0665	39.6388	187.5475	18.2510
4012	507.7772	68.6030	30.3409	184.8296	18.8190
4013	646.5620	68.4894	39.7943	192.0411	15.4846
4014	651.2008	81.8924	44.6686	182.4688	23.4870
4015	573.0804	73.1718	32.7239	161.2431	14.1682
Mean	582.53017	71.44464	37.43329	181.62603	18.04195
SD	64.89462	6.51206	5.81525	11.93706	3.60009
N	5	5	5	5	5
%Diff	-4.62538	6.46938	5.84898	1.50195	-10.22425

Appendix 18

Individual Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight/Brain Ratio						
	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)	Lung (%)
	-	-	-	-	-	-	-
1511	3.6808	0.8844	0.7757	57.1640	87.7470	355.2372	60.4743
1512	3.1247	0.8257	0.7609	56.8268	102.5904	426.3357	59.9029
1513	2.3974	0.8809	0.5005	48.4484	81.6316	405.0551	53.8038
1514	3.2606	0.8777	0.6702	56.2766	83.5638	383.7766	58.2979
1515	3.1300	0.7365	0.7480	58.1703	94.1312	486.9390	66.5132
Mean	3.11871	0.84102	0.69106	55.37723	89.93282	411.46870	59.79842
SD	0.46276	0.06320	0.11405	3.93421	8.54535	49.71612	4.57557
N	5	5	5	5	5	5	5

Appendix 18

Individual Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

0 ug/dose Group 1	Organ Weight/Brain Ratio			
	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-
1511	4.6443	25.9881	19.2194	57.3617
1512	5.3427	26.1738	23.6913	23.1516
1513	5.5556	24.3744	16.1161	24.9249
1514	6.2234	24.0957	15.9574	20.6915
1515	5.1208	36.3636	20.3682	27.0426
Mean	5.37735	27.39913	19.07050	30.63446
SD	0.58137	5.09697	3.22016	15.12199
N	5	5	5	5

Appendix 18

Individual Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight/Brain Ratio						
	Gland Adrenal (%)	Gland Pituitary (%)	Gland Thyroid (%)	Heart (%)	Kidney (%)	Liver (%)	Lung (%)
	-	-	-	-	-	-	-
4511	3.5120	0.8951	0.7298	52.9076	93.3295	444.3558	65.2794
4512	3.5968	0.9516	0.8333	58.0645	95.4301	420.0000	61.4516
4513	3.2559	0.9133	0.5882	46.1816	86.3261	376.2126	53.3540
4514	3.1650	0.8198	0.5863	73.3442	94.1368	395.1683	66.6124
4515	3.6997	1.0652	0.7422	62.6062	81.0198	379.5467	61.0198
Mean	3.44589	0.92899	0.69597	58.62084	90.04848	403.05668	61.54343
SD	0.22722	0.08997	0.10698	10.25115	6.16065	28.84545	5.17207
N	5	5	5	5	5	5	5
%Diff	10.49069	10.45981	0.71017	5.85730	0.12861	-2.04439	2.91816

Appendix 18

Individual Organ Weights Relative to Brain Weight: Recovery Study

5002400

Sex: Female Day(s) Relative to Start Date

96 ug/dose Group 4	Organ Weight/Brain Ratio			
	Ovary (%)	Spleen (%)	Thymus (%)	Uterus (%)
	-	-	-	-
4511	7.3546	26.1688	16.3056	21.0946
4512	4.6774	26.4516	19.0860	21.9892
4513	4.3344	26.6770	15.0155	51.7544
4514	6.2432	29.3702	20.0869	32.4104
4515	5.8357	26.5156	26.1190	27.3088
Mean	5.68906	27.03664	19.32259	30.91150
SD	1.22079	1.31739	4.31522	12.50629
N	5	5	5	5
%Diff	5.79678	-1.32302	1.32188	0.90433

Appendix 18

Appendix 4
Individual Macroscopic and Microscopic Pathology

Appendix 18

Individual Macroscopic and Microscopic Pathology Explanation Page

Abbreviation	Description
(G)	Gross Pathology
(H)	Histopathology
(TGL)	Trackable Gross Lesion
< or >	Value outside the validation rule range in Provantis
Cass	Cassette
GALT	Gut associated lymphoid tissue
ID	Identification
LN	Lymph Node
LT	Left
RT	Right
SS	Special Stain

Note: This is a comprehensive list of abbreviations. All of the abbreviations listed may not be applicable to this report.

Dosing Information

Dosing information is abbreviated on various data outputs; the following represents the dosing information for this study:

Group No.	Test Material	Dose Level (µg/dose)
1	Reference Item	0
2	mRNA-1893	10
3	mRNA-1893	30
4	mRNA-1893	96

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1001 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 357g

Organ Weights:

BRAIN	1.858g	EPIDIDYMIS	0.905g	GLAND, ADRENAL	0.0505g
GLAND, PITUITARY	0.0117g	GLAND, PROSTATE	0.892g	GLAND, THYROID	0.0133g
HEART	1.371g	KIDNEY	2.417g	LIVER	12.141g
LUNG	1.304g	SPLEEN	0.696g	TESTIS	3.400g
THYMUS	0.363g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, ILIAC;	
Focus, dark (TGL): >10, right	LYMPH NODE, ILIAC; Erythrocytosis; mild (H)
LYMPH NODE, MANDIBULAR;	
Enlargement (TGL): Bilateral	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; bilateral ; mild (H)
Focus, dark (TGL): 1, right	NO CORRELATE; No correlating lesion (H)
LYMPH NODE, POPLITEAL;	
Focus, dark (TGL): >10, right	LYMPH NODE, POPLITEAL; Erythrocytosis; mild (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

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Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1001 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

BRAIN;
Hemorrhage; ventricular; mild

GLAND, PROSTATE;
Inflammation; focal; minimal: with epithelial hyperplasia

KIDNEY;
Basophilia; tubular; unilateral; multifocal; minimal

LIVER;
Extramedullary hematopoiesis; minimal

LYMPH NODE, ILIAC;
Erythrocytosis; mild ..... LYMPH NODE, ILIAC; Focus, dark (G)

LYMPH NODE, MANDIBULAR;
Increased cellularity; lymphoid; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

LYMPH NODE, POPLITEAL;
Erythrocytosis; mild ..... LYMPH NODE, POPLITEAL; Focus, dark (G)

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber

NO CORRELATE;
No correlating lesion ..... LYMPH NODE, MANDIBULAR; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	EPIDIDYMIS	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE		GLAND, THYROID
HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LUNG	LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC	

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1001 Group: 1 Sex: Male (continued)

The following tissues were within normal limits: (continued)

MUSCLE, SKELETAL	NERVE, OPTIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1002 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 416g

Organ Weights:

BRAIN	2.014g	EPIDIDYMIS	1.008g	GLAND, ADRENAL	0.0459g
GLAND, PITUITARY	0.0123g	GLAND, PROSTATE	0.999g	GLAND, THYROID	0.0194g
HEART	1.315g	KIDNEY	2.407g	LIVER	11.389g
LUNG	1.256g	SPLEEN	0.726g	TESTIS	3.691g
THYMUS	0.431g				

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

GLAND, PROSTATE;
Infiltration, mononuclear cell; minimal

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal

LIVER;
Vacuolation; hepatocellular; focal; minimal

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1002 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

LUNG;
Hemorrhage; multifocal; minimal: chronic,with erythrophagocyto-
sis and pigment

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON	
LARGE INTESTINE, RECTUM		LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR	
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	PANCREAS	SITE, INJECTION	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1003 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 370g

Organ Weights:

BRAIN	2.009g	EPIDIDYMIS	1.144g	GLAND, ADRENAL	0.0459g
GLAND, PITUITARY	0.0116g	GLAND, PROSTATE	1.175g	GLAND, THYROID	0.0150g
HEART	1.269g	KIDNEY	2.519g	LIVER	10.142g
LUNG	1.395g	SPLEEN	0.730g	TESTIS	3.577g
THYMUS	0.266g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
PANCREAS; Mass; [a] (TGL): 10 mm in diameter, pale, dark, firm, cystic, cut surface: fluid pale clear	PANCREAS; Dilatation; ductular; marked (H)
SPLEEN; Irregular surface (TGL)	NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1003 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

LIVER;
Vacuolation; hepatocellular; focal; minimal

LUNG;
Hemorrhage; focal; minimal: acute
Macrophage aggregation; alveolar; focal; minimal

PANCREAS;
Dilatation; ductular; marked: with inflammation and hemorrhage PANCREAS; Mass; [a] (G)

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Inflammation, mixed cell; multifocal; minimal; subcutis/perimuscular

NO CORRELATE;
No correlating lesion ..... SPLEEN; Irregular surface (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		GLAND, THYROID	HEART	LARGE INTESTINE, CECUM	
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL	
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1004 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 360g

Organ Weights:

BRAIN	2.007g	EPIDIDYMIS	1.020g	GLAND, ADRENAL	0.0583g
GLAND, PITUITARY	0.0095g	GLAND, PROSTATE	1.354g	GLAND, THYROID	0.0168g
HEART	1.187g	KIDNEY	2.454g	LIVER	11.856g
LUNG	1.305g	SPLEEN	0.696g	TESTIS	3.179g
THYMUS	0.294g				

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

KIDNEY;
Cast; hyaline; unilateral; minimal
Basophilia; tubular; unilateral; multifocal; minimal
Cyst; unilateral; minimal

LIVER;
Infiltration, mononuclear cell; multifocal; minimal

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1004 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);
Infiltration, mononuclear cell; focal; minimal; muscular

TESTIS;
Dilatation; bilateral; minimal; rete testis

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		GLAND, THYROID	HEART	LARGE INTESTINE, CECUM	
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LUNG	LYMPH NODE, ILIAC
LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	PANCREAS	SKIN	
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1005 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 370g

Organ Weights:

BRAIN	2.007g	EPIDIDYMIS	1.032g	GLAND, ADRENAL	0.0492g
GLAND, PITUITARY	0.0126g	GLAND, PROSTATE	1.206g	GLAND, THYROID	0.0186g
HEART	1.415g	KIDNEY	2.672g	LIVER	11.378g
LUNG	1.497g	SPLEEN	0.843g	TESTIS	3.816g
THYMUS	0.453g				

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

HEART;
Infiltration, mononuclear cell; focal; minimal: with myofiber
degeneration

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

MUSCLE, SKELETAL;
Degeneration/necrosis; multifocal; minimal; myofiber

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1005 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION;
Granuloma; focal; minimal; muscular: with foreign body

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		GLAND, THYROID	KIDNEY	LARGE INTESTINE, CECUM	
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, ILIAC
LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL
NERVE, OPTIC	NERVE, SCIATIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1006 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 360g

Organ Weights:

BRAIN	1.946g	EPIDIDYMIS	0.975g	GLAND, ADRENAL	0.0532g
GLAND, PITUITARY	0.0104g	GLAND, PROSTATE	1.087g	GLAND, THYROID	0.0163g
HEART	1.226g	KIDNEY	2.391g	LIVER	11.341g
LUNG	1.463g	SPLEEN	0.769g	TESTIS	3.934g
THYMUS	0.511g				

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

HEART;
Infiltration, mononuclear cell; multifocal; minimal: with
myofiber degeneration

LIVER;
Necrosis; hepatocellular; focal; minimal: with inflammation and
hemorrhage

LUNG;
Fibrosis; pleural; focal; minimal

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1006 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

LUNG (continued);
Macrophage aggregation; alveolar; focal; minimal

LYMPH NODE, MANDIBULAR;
Plasmacytosis; mild
Increased cellularity; lymphoid; minimal

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		GLAND, THYROID	KIDNEY	LARGE INTESTINE, CECUM	
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	PANCREAS	SITE, INJECTION	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1007 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 393g

Organ Weights:

BRAIN	1.947g	EPIDIDYMIS	1.115g	GLAND, ADRENAL	0.0563g
GLAND, PITUITARY	0.0114g	GLAND, PROSTATE	1.164g	GLAND, THYROID	0.0157g
HEART	1.231g	KIDNEY	2.313g	LIVER	11.414g
LUNG	1.347g	SPLEEN	0.652g	TESTIS	3.588g
THYMUS	0.439g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

LUNG;
Focus, dark (TGL): 2, left lobe ..... LUNG; Hemorrhage; multifocal; minimal (H)

LYMPH NODE, ILIAC;
Focus, dark (TGL): 2, left ..... LYMPH NODE, ILIAC; Hemorrhage; unilateral; mild; perinodal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PROSTATE;
Inflammation; focal; minimal: with epithelial hyperplasia

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1007 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

KIDNEY;
Basophilia; tubular; bilateral; multifocal; minimal

LIVER;
Extramedullary hematopoiesis; minimal

LUNG;
Hemorrhage; multifocal; minimal: chronic, with inflammatory cells, erythrophagocytosis and hemoglobin crystals ..... LUNG; Focus, dark (G)

LYMPH NODE, ILIAC;
Hemorrhage; unilateral; mild; perinodal ..... LYMPH NODE, ILIAC; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON	
LARGE INTESTINE, RECTUM		LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	PANCREAS	SITE, INJECTION	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1008 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 427g

Organ Weights:

BRAIN	2.013g	EPIDIDYMIS	0.945g	GLAND, ADRENAL	0.0645g
GLAND, PITUITARY	0.0126g	GLAND, PROSTATE	1.223g	GLAND, THYROID	0.0161g
HEART	1.408g	KIDNEY	2.825g	LIVER	12.544g
LUNG	1.540g	SPLEEN	0.836g	TESTIS	3.595g
THYMUS	0.399g				

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

LUNG;
Hemorrhage; focal; minimal: chronic, with inflammatory cells,
erythrophagocytosis and hemoglobin crystals
Macrophage aggregation; alveolar; focal; minimal

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1008 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);
Infiltration, mononuclear cell; multifocal; minimal; muscular

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		GLAND, THYROID	HEART	KIDNEY	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1009 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 415g

Organ Weights:

BRAIN	2.100g	EPIDIDYMIS	1.136g	GLAND, ADRENAL	0.0617g
GLAND, PITUITARY	0.0140g	GLAND, PROSTATE	1.141g	GLAND, THYROID	0.0153g
HEART	1.451g	KIDNEY	2.971g	LIVER	12.972g
LUNG	1.424g	SPLEEN	0.777g	TESTIS	3.627g
THYMUS	0.533g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

LUNG;
Focus, dark (TGL): 1, right middle ..... NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

KIDNEY;
Dilatation; unilateral; minimal; pelvis
Basophilia; tubular; unilateral; focal; minimal

LIVER;
Infiltration, mononuclear cell; multifocal; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1009 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

NO CORRELATE;
No correlating lesion ..... LUNG; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		GLAND, THYROID	HEART	LARGE INTESTINE, CECUM	
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL	
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	PANCREAS	SITE, INJECTION	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1010 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 460g

Organ Weights:

BRAIN	1.991g	EPIDIDYMIS	1.146g	GLAND, ADRENAL	0.0728g
GLAND, PITUITARY	0.0131g	GLAND, PROSTATE	1.193g	GLAND, THYROID	0.0205g
HEART	1.322g	KIDNEY	2.948g	LIVER	14.643g
LUNG	1.545g	SPLEEN	0.955g	TESTIS	4.024g
THYMUS	0.686g				

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

EYE;
Rosette; unilateral; mild; retina

KIDNEY;
Cast; hyaline; unilateral; minimal
Basophilia; tubular; unilateral; multifocal; minimal

LUNG;
osseous metaplasia

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1010 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

LYMPH NODE, MANDIBULAR;
Plasmacytosis; minimal
Increased cellularity; lymphoid; mild

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PITUITARY
GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE		GLAND, THYROID
HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LIVER	LUNG	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	PANCREAS	SITE, INJECTION	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

The following tissues have not been examined:

GLAND, PARATHYROID; NOT PRESENT IN SECTION.

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1011 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 429g

Organ Weights:

BRAIN	2.111g	EPIDIDYMIS	1.229g	GLAND, ADRENAL	0.0570g
GLAND, PITUITARY	0.0159g	GLAND, PROSTATE	0.871g	GLAND, THYROID	0.0149g
HEART	1.652g	KIDNEY	2.823g	LIVER	15.266g
LUNG	1.376g	SPLEEN	0.599g	TESTIS	4.050g
THYMUS	0.490g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, MANDIBULAR;	
Enlargement (TGL): Bilateral.	LYMPH NODE, MANDIBULAR; Plasmacytosis; bilateral; mild (H)
	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; bilateral ; mild (H)
Focus, dark (TGL): 1 to 2, bilateral.	NO CORRELATE; No correlating lesion (H)
THYMUS;	
Focus, dark (TGL): 2.	NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

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Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1011 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal
Cyst; unilateral; minimal

LIVER;
Extramedullary hematopoiesis; minimal

LUNG;
Hemorrhage; focal; minimal: acute

LYMPH NODE, MANDIBULAR;
Plasmacytosis; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)
Increased cellularity; lymphoid; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

MUSCLE, SKELETAL;
Degeneration/necrosis; focal; minimal; myofiber

SITE, INJECTION;
Infiltration, mononuclear cell; focal; minimal; muscular

NO CORRELATE;
No correlating lesion ..... LYMPH NODE, MANDIBULAR; Focus, dark (G)
THYMUS; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		GLAND, THYROID	HEART	LARGE INTESTINE, CECUM	
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		NERVE, OPTIC	NERVE, SCIATIC
PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM	
SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC
SPLEEN	STOMACH	TESTIS	THYMUS	TONGUE	TRACHEA
URINARY BLADDER					

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1011 Group: 1 Sex: Male (continued)

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1012 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 464g

Organ Weights:

BRAIN	2.121g	EPIDIDYMIS	1.295g	GLAND, ADRENAL	0.0635g
GLAND, PITUITARY	0.0146g	GLAND, PROSTATE	1.228g	GLAND, THYROID	0.0180g
HEART	1.430g	KIDNEY	2.690g	LIVER	12.326g
LUNG	1.422g	SPLEEN	0.745g	TESTIS	3.556g
THYMUS	0.449g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Eye left damaged.

LUNG;
Focus, dark (TGL): 1, left lobe, right accessory, right middle. NO CORRELATE; No correlating lesion (H)

LYMPH NODE, MANDIBULAR;
Focus, dark (TGL): 1, left. ..... LYMPH NODE, MANDIBULAR; Erythrocytosis; unilateral; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1012 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

BONE, FEMUR;
Inflammation; periosteal; focal; minimal: with hyperplasia

EYE;
one retina available for examination

GLAND, PROSTATE;
Infiltration, mononuclear cell; minimal

HEART;
Inflammation, perivascular; focal; minimal: aorta

KIDNEY;
Basophilia; tubular; unilateral; multifocal; minimal

LUNG;
osseous metaplasia

LYMPH NODE, MANDIBULAR;
Erythrocytosis; unilateral; minimal ..... LYMPH NODE, MANDIBULAR; Focus, dark (G)

SITE, INJECTION;
Inflammation; dermal; multifocal; minimal: chronic, subepiderm-
al and perifollicular

NO CORRELATE;
No correlating lesion ..... LUNG; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, STERNUM	BRAIN	EPIDIDYMIS	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE		GLAND, THYROID
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LUNG	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC	
LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	PANCREAS
SKIN	SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1012 Group: 1 Sex: Male (continued)

The following tissues were within normal limits: (continued)

SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC	
SPLEEN	STOMACH	TESTIS	THYMUS	TONGUE	TRACHEA	
URINARY BLADDER						

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1013 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 331g

Organ Weights:

BRAIN	2.049g	EPIDIDYMIS	1.150g	GLAND, ADRENAL	0.0510g
GLAND, PITUITARY	0.0104g	GLAND, PROSTATE	0.912g	GLAND, THYROID	0.0082g
HEART	1.071g	KIDNEY	1.963g	LIVER	8.444g
LUNG	1.118g	SPLEEN	0.619g	TESTIS	3.741g
THYMUS	0.301g				

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Salivary gland mandibular right accidentally cut; Prostate
accidentally cut; Brain accidentally cut.

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PROSTATE;
Infiltration, mononuclear cell; minimal

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1013 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

TESTIS;
Dilatation; unilateral; minimal; rete testis
Atrophy; tubular; unilateral; minimal

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON	
LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL	
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	PANCREAS	SITE, INJECTION	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1014 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 431g

Organ Weights:

BRAIN	2.099g	EPIDIDYMIS	1.196g	GLAND, ADRENAL	0.0572g
GLAND, PITUITARY	0.0134g	GLAND, PROSTATE	1.208g	GLAND, THYROID	0.0160g
HEART	1.794g	KIDNEY	2.721g	LIVER	13.412g
LUNG	1.442g	SPLEEN	0.991g	TESTIS	3.838g
THYMUS	0.473g				

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Adrenal gland right accidentally cut.

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

HEART;
Infiltration, mononuclear cell; focal; minimal

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1014 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		GLAND, THYROID	LARGE INTESTINE, CECUM		
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, ILIAC
LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	PANCREAS	SITE, INJECTION	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1015 Group: 1 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 500g

Organ Weights:

BRAIN	2.103g	EPIDIDYMIS	1.157g	GLAND, ADRENAL	0.0617g
GLAND, PITUITARY	0.0150g	GLAND, PROSTATE	1.117g	GLAND, THYROID	0.0153g
HEART	1.732g	KIDNEY	3.075g	LIVER	14.690g
LUNG	1.683g	SPLEEN	0.755g	TESTIS	3.570g
THYMUS	0.397g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

LUNG;
Focus, dark (TGL): 1, edge, left lobe ..... NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PROSTATE;
Infiltration, mononuclear cell; minimal

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal
Cyst; unilateral; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1015 Group: 1 Sex: Male (continued)

Histo Pathology Observations:

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal: with alveolar wall thickening

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber

NO CORRELATE;
No correlating lesion ..... LUNG; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON	
LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL	
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	PANCREAS	SKIN	
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1501 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 257g

Organ Weights:

BRAIN	2.327g	GLAND, ADRENAL	0.0622g	GLAND, PITUITARY	0.0153g
GLAND, THYROID	0.0109g	HEART	1.046g	KIDNEY	1.714g
LIVER	8.098g	LUNG	1.110g	OVARY	0.098g
SPLEEN	0.628g	THYMUS	0.360g	UTERUS	0.448g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, MANDIBULAR;	
Enlargement (TGL): Bilateral	LYMPH NODE, MANDIBULAR; Plasmacytosis; moderate (H)
	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; moderate (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PITUITARY;
Cyst; minimal: pars distalis

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; mild

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1501 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, MANDIBULAR;
Plasmacytosis; moderate ..... LYMPH NODE, MANDIBULAR; Enlargement (G)
Increased cellularity; lymphoid; moderate ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; focal; minimal; subcutis/perimuscular
Infiltration, mononuclear cell; multifocal; minimal; muscular

TONGUE;
Infiltration, mononuclear cell; focal; minimal

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	KIDNEY
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LUNG	LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	OVARY	PANCREAS	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	THYMUS	TRACHEA	URINARY BLADDER	UTERUS	VAGINA

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1502 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 239g

Organ Weights:

BRAIN	1.692g	GLAND, ADRENAL	0.0680g	GLAND, PITUITARY	0.0132g
GLAND, THYROID	0.0137g	HEART	1.085g	KIDNEY	1.701g
LIVER	8.130g	LUNG	1.126g	OVARY	0.102g
SPLEEN	0.633g	THYMUS	0.359g	UTERUS	1.184g

Gross Pathology Observations:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Urinary bladder submitted detached cass A.

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

HEART;
Infiltration, mononuclear cell; focal; minimal

KIDNEY;
Cyst; unilateral; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1502 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION;
Infiltration, mononuclear cell; focal; minimal; muscular

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LUNG	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	THYMUS
TONGUE	TRACHEA	URINARY BLADDER	UTERUS	VAGINA	

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1503 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 237g

Organ Weights:

BRAIN	1.849g	GLAND, ADRENAL	0.0608g	GLAND, PITUITARY	0.0170g
GLAND, THYROID	0.0145g	HEART	0.980g	KIDNEY	1.767g
LIVER	7.490g	LUNG	1.056g	OVARY	0.089g
SPLEEN	0.507g	THYMUS	0.400g	UTERUS	0.442g

Gross Pathology Observations:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

KIDNEY;
- Basophilia; tubular; bilateral; multifocal; minimal
- Cyst; unilateral; minimal
- Inflammation; unilateral; focal; minimal: chronic, interstitial

LYMPH NODE, ILIAC;
- Increased cellularity; lymphoid; minimal

SITE, INJECTION;
- Degeneration/necrosis; focal; minimal; myofiber

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1503 Group: 1 Sex: Female (continued)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LUNG	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	THYMUS
TONGUE	TRACHEA	URINARY BLADDER	UTERUS	VAGINA	

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1504 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 239g

Organ Weights:

BRAIN	1.957g	GLAND, ADRENAL	0.0610g	GLAND, PITUITARY	0.0126g
GLAND, THYROID	0.0120g	HEART	0.956g	KIDNEY	1.657g
LIVER	7.379g	LUNG	1.096g	OVARY	0.090g
SPLEEN	0.580g	THYMUS	0.363g	UTERUS	0.588g

Gross Pathology Observations:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

LIVER;
Vacuolation; hepatocellular; focal; minimal

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Inflammation, mixed cell; focal; minimal; subcutis/perimuscular

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1504 Group: 1 Sex: Female (continued)

The following tissues were within normal limits: (continued)

ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
KIDNEY	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR	
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	THYMUS
TONGUE	TRACHEA	URINARY BLADDER	UTERUS	VAGINA	

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1505 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 260g

Organ Weights:

BRAIN	1.866g	GLAND, ADRENAL	0.0656g	GLAND, PITUITARY	0.0170g
GLAND, THYROID	0.0131g	HEART	1.025g	KIDNEY	1.795g
LIVER	7.527g	LUNG	1.169g	OVARY	0.099g
SPLEEN	0.542g	THYMUS	0.376g	UTERUS	0.429g

Gross Pathology Observations:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; minimal

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1505 Group: 1 Sex: Female (continued)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LUNG	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	THYMUS
TONGUE	TRACHEA	URINARY BLADDER	UTERUS	VAGINA	

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1506 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 258g

Organ Weights:

BRAIN	1.898g	GLAND, ADRENAL	0.0668g	GLAND, PITUITARY	0.0163g
GLAND, THYROID	0.0153g	HEART	1.013g	KIDNEY	1.836g
LIVER	7.181g	LUNG	1.145g	OVARY	0.102g
SPLEEN	0.588g	THYMUS	0.364g	UTERUS	0.644g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LIVER;	
Focus, pale (TGL): 1, fissure, right medial.	LIVER; Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal (H)
THYMUS;	
Focus, dark (TGL): >10	THYMUS; Hemorrhage; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

GLAND, THYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1506 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

KIDNEY;
Basophilia; tubular; bilateral; multifocal; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: micro and macrovesicular ..... LIVER; Focus, pale (G)

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, MANDIBULAR;
Increased cellularity; lymphoid; mild

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

PANCREAS;
Atrophy; acinar; multifocal; minimal: lobular, with inflammation

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber

THYMUS;
Hemorrhage; minimal ..... THYMUS; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL	
MUSCLE, SKELETAL	NERVE, OPTIC	OVARY	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA		

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1506 Group: 1 Sex: Female (continued)

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1507 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 232g

Organ Weights:

BRAIN	1.838g	GLAND, ADRENAL	0.0641g	GLAND, PITUITARY	0.0161g
GLAND, THYROID	0.0093gPI	HEART	0.943g	KIDNEY	1.767g
LIVER	7.700g	LUNG	1.031g	OVARY	0.097g
SPLEEN	0.470g	THYMUS	0.331g	UTERUS	0.570g

Gross Pathology Observations: Correlated with:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GLAND, THYROID;
Left not found
ONE OF A PAIR AVAILABLE FOR EVALUATION.
Enlargement (TGL): Right ..... NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

GLAND, THYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding, PI = Macroscopic Pathology - Included in mean

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1507 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

MUSCLE, SKELETAL;
Degeneration/necrosis; focal; minimal; myofiber

SITE, INJECTION;
Inflammation, mixed cell; multifocal; minimal; subcutis/perimuscular

NO CORRELATE;
No correlating lesion ..... GLAND, THYROID; Enlargement (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
KIDNEY	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL	
NERVE, OPTIC	NERVE, SCIATIC	OVARY	PANCREAS	SKIN	
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1508 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 250g

Organ Weights:

BRAIN	1.932g	GLAND, ADRENAL	0.0575g	GLAND, PITUITARY	0.0167g
GLAND, THYROID	0.0199g	HEART	1.093g	KIDNEY	1.613g
LIVER	7.586g	LUNG	1.181g	OVARY	0.134g
SPLEEN	0.588g	THYMUS	0.473g	UTERUS	1.200g

Gross Pathology Observations:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; focal; minimal; subcutis/perimuscular

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
KIDNEY	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LIVER	LUNG	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL	
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	OVARY	PANCREAS	SKIN

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1508 Group: 1 Sex: Female (continued)

The following tissues were within normal limits: (continued)

SMALL INTESTINE, DUODENUM	SMALL INTESTINE, ILEUM	SMALL INTESTINE, JEJUNUM			
SPINAL CORD, CERVICAL	SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC			SPLEEN
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1509 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 249g

Organ Weights:

BRAIN	1.977g	GLAND, ADRENAL	0.0543g	GLAND, PITUITARY	0.0155g
GLAND, THYROID	0.0133g	HEART	0.887g	KIDNEY	1.714g
LIVER	6.714g	LUNG	1.137g	OVARY	0.098g
SPLEEN	0.477g	THYMUS	0.354g	UTERUS	0.999g

Gross Pathology Observations: Correlated with:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

THYMUS;
Focus, dark (TGL): >10 ..... THYMUS; Hemorrhage; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; multifocal; minimal: with
myofiber degeneration

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1509 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Inflammation, mixed cell; focal; minimal; subcutis/perimuscular
Infiltration, mononuclear cell; multifocal; minimal; muscular

THYMUS;
Hemorrhage; minimal: one lobe ..... THYMUS; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		NERVE, OPTIC	NERVE, SCIATIC
OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA		

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1510 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 252g

Organ Weights:

BRAIN	1.895g	GLAND, ADRENAL	0.0725g	GLAND, PITUITARY	0.0186g
GLAND, THYROID	0.0161g	HEART	0.997g	KIDNEY	1.887g
LIVER	7.957g	LUNG	1.150g	OVARY	0.246g>PI
SPLEEN	0.591g	THYMUS	0.395g	UTERUS	0.517g

Gross Pathology Observations: Correlated with:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

OVARY;
Cyst, pale (TGL): 1, left ..... OVARY; Dilatation; bursal; unilateral; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

HEART;
Infiltration, mononuclear cell; focal; minimal

KIDNEY;
Inflammation; unilateral; multifocal; minimal: chronic, inters-
titial

LUNG;
osseous metaplasia

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding, PI = Macroscopic Pathology - Included in mean

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1510 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

LUNG (continued);
Macrophage aggregation; alveolar; multifocal; minimal

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; focal; minimal

OVARY;
Dilatation; bursal; unilateral; minimal ..... OVARY; Cyst, pale (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		NERVE, OPTIC	NERVE, SCIATIC
PANCREAS	SITE, INJECTION	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	THYMUS
TONGUE	TRACHEA	URINARY BLADDER	UTERUS	VAGINA	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1511 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 274g

Organ Weights:

BRAIN	2.024g	GLAND, ADRENAL	0.0745g	GLAND, PITUITARY	0.0179g
GLAND, THYROID	0.0157g	HEART	1.157g	KIDNEY	1.776g
LIVER	7.190g	LUNG	1.224g	OVARY	0.094g
SPLEEN	0.526g	THYMUS	0.389g	UTERUS	1.161g

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Pituitary gland accidentally cut.

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1511 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; focal; minimal

SITE, INJECTION;
Infiltration, mononuclear cell; focal; minimal; muscular

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		NERVE, OPTIC	NERVE, SCIATIC
OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	THYMUS
TONGUE	TRACHEA	URINARY BLADDER	UTERUS	VAGINA	

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1512 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 263g

Organ Weights:

BRAIN	1.853g	GLAND, ADRENAL	0.0579g	GLAND, PITUITARY	0.0153g
GLAND, THYROID	0.0141g	HEART	1.053g	KIDNEY	1.901g
LIVER	7.900g	LUNG	1.110g	OVARY	0.099g
SPLEEN	0.485g	THYMUS	0.439g	UTERUS	0.429g

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS;	
LN lesion submitted with pancreas; Uterus accidentally cut.	
LYMPH NODE;	
Enlargement (TGL): Pancreatic	NO CORRELATE; No correlating lesion (H)
Discoloration, mottled (TGL): Pancreatic	LYMPH NODE; Erythrocytosis; minimal (H)
LYMPH NODE, MANDIBULAR;	
Enlargement (TGL): Bilateral	LYMPH NODE, MANDIBULAR; Plasmacytosis; bilateral; mild (H)
	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; bilateral; mild (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1512 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

GLAND, HARDERIAN;
Infiltration, mononuclear cell; focal; minimal: with acinar atrophy

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

LUNG;
Hemorrhage; focal; minimal: acute

LYMPH NODE;
Erythrocytosis; minimal: pancreatic ..... LYMPH NODE; Discoloration, mottled (G)

LYMPH NODE, MANDIBULAR;
Plasmacytosis; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)
Increased cellularity; lymphoid; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

THYMUS;
Hemorrhage; minimal

NO CORRELATE;
No correlating lesion ..... LYMPH NODE; Enlargement (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	KIDNEY
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	OVARY	PANCREAS	SITE, INJECTION
SKIN	SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		
SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC
SPLEEN	STOMACH	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1512 Group: 1 Sex: Female (continued)

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1513 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 245g<

Organ Weights:

BRAIN	1.998g	GLAND, ADRENAL	0.0479g	GLAND, PITUITARY	0.0176g
GLAND, THYROID	0.0100g	HEART	0.968g	KIDNEY	1.631g
LIVER	8.093g	LUNG	1.075g	OVARY	0.111g
SPLEEN	0.487g	THYMUS	0.322g	UTERUS	0.498g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; Lymph node lesion submitted with pancreas; Brain accidentally cut.	
LYMPH NODE; Focus, dark (TGL): >10, pancreatic.	LYMPH NODE; Erythrocytosis; minimal (H)
LYMPH NODE, MANDIBULAR; Enlargement (TGL): Bilateral.	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; bilateral ; mild (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1513 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

EYE;
Rosette; unilateral; mild; retina

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE;
Erythrocytosis; minimal: pancreatic ..... LYMPH NODE; Focus, dark (G)

LYMPH NODE, MANDIBULAR;
Increased cellularity; lymphoid; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

SITE, INJECTION;
Infiltration, mononuclear cell; focal; minimal; muscular

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	KIDNEY
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL
MUSCLE, SKELETAL	NERVE, OPTIC	NERVE, SCIATIC	OVARY	PANCREAS	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1514 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 246g<

Organ Weights:

BRAIN	1.880g	GLAND, ADRENAL	0.0613g	GLAND, PITUITARY	0.0165g
GLAND, THYROID	0.0126g	HEART	1.058g	KIDNEY	1.571g
LIVER	7.215g	LUNG	1.096g	OVARY	0.117g
SPLEEN	0.453g	THYMUS	0.300g	UTEROS	0.389g

Gross Pathology Observations: Correlated with:

Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Liver lesion right lateral submitted cass B; Brain accidentally cut.

GLAND, ADRENAL;
Focus, dark (TGL): 6, left. ..... NO CORRELATE; No correlating lesion (H)

LIVER;
Focus, pale (TGL): 1, near hilus, right lateral. ..... LIVER; Tension lipidosis; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LIVER;
Tension lipidosis; minimal ..... LIVER; Focus, pale (G)

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1514 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

MUSCLE, SKELETAL;
Degeneration/necrosis; focal; minimal; myofiber
Infiltration, mononuclear cell; focal; minimal

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Infiltration, mononuclear cell; multifocal; minimal; muscular

NO CORRELATE;
No correlating lesion ..... GLAND, ADRENAL; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
KIDNEY	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR	
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		NERVE, OPTIC	NERVE, SCIATIC
OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	THYMUS
TONGUE	TRACHEA	URINARY BLADDER	UTERUS	VAGINA	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1515 Group: 1 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 0 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 248g

Organ Weights:

BRAIN	1.738g	GLAND, ADRENAL	0.0544g	GLAND, PITUITARY	0.0128g
GLAND, THYROID	0.0130g	HEART	1.011g	KIDNEY	1.636g
LIVER	8.463g	LUNG	1.156g	OVARY	0.089g
SPLEEN	0.632g	THYMUS	0.354g	UTERUS	0.470g

Gross Pathology Observations:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Uterus accidentally cut; Brain accidentally cut.

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

EYE;
Rosette; unilateral; mild; retina

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal
Cyst; unilateral; mild

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 1515 Group: 1 Sex: Female (continued)

Histo Pathology Observations:

KIDNEY (continued);
Inflammation; unilateral; focal; minimal: chronic, interstitial

LIVER;
Vacuolation; hepatocellular; focal; minimal

LUNG;
Hemorrhage; focal; minimal: acute
Macrophage aggregation; alveolar; multifocal; minimal: with alveolar wall thickening

LYMPH NODE, ILIAC;
Erythrocytosis; minimal

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; multifocal; minimal

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL
NERVE, OPTIC	NERVE, SCIATIC	OVARY	PANCREAS	SITE, INJECTION	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2001 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 411g

Organ Weights:

BRAIN	2.011g	EPIDIDYMIS	1.112g	GLAND, ADRENAL	0.0532g
GLAND, PITUITARY	0.0120g	GLAND, PROSTATE	1.255g	GLAND, THYROID	0.0147g
HEART	1.479g	KIDNEY	2.969g	LIVER	12.742g
LUNG	1.516g	SPLEEN	0.801g	TESTIS	4.390g
THYMUS	0.589g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

KIDNEY;
Dilatation; pelvis (TGL): Right ..... KIDNEY; Dilatation; mild; pelvis (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

KIDNEY;
Dilatation; mild; pelvis ..... KIDNEY; Dilatation; pelvis (G)
Basophilia; tubular; focal; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to
midzonal: microvesicular

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2001 Group: 2 Sex: Male (continued)

Histo Pathology Observations:

LYMPH NODE, ILIAC;
Erythrocytosis; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Inflammation, mixed cell; minimal; subcutis/perimuscular
Inflammation, mixed cell; minimal; muscular
Infiltration, mononuclear cell; focal; minimal; muscular

The following tissues were within normal limits:

BONE MARROW	GLAND, SEMINAL VESICLE		LYMPH NODE, INGUINAL	SPLEEN

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2002 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 409g

Organ Weights:

BRAIN	1.900g	EPIDIDYMIS	1.099g	GLAND, ADRENAL	0.0523g
GLAND, PITUITARY	0.0106g	GLAND, PROSTATE	1.097g	GLAND, THYROID	0.0192g
HEART	1.203g	KIDNEY	2.667g	LIVER	13.640g
LUNG	1.459g	SPLEEN	0.722g	TESTIS	4.190g
THYMUS	0.496g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION; Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LYMPH NODE, ILIAC;
Erythrocytosis; mild

LYMPH NODE, INGUINAL;
Erythrocytosis; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2002 Group: 2 Sex: Male (continued)

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema ..... SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Swelling (G)

The following tissues were within normal limits:

BONE MARROW	GLAND, SEMINAL VESICLE	LIVER	SPLEEN	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2003 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 375g

Organ Weights:

BRAIN	1.936g	EPIDIDYMIS	0.987g	GLAND, ADRENAL	0.0529g
GLAND, PITUITARY	0.0105g	GLAND, PROSTATE	1.146g	GLAND, THYROID	0.0179g
HEART	1.299g	KIDNEY	2.495g	LIVER	11.329g
LUNG	1.403g	SPLEEN	0.738g	TESTIS	3.777g
THYMUS	0.404g				

Gross Pathology Observations:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

LIVER;
Necrosis; hepatocellular; focal; minimal: with hemorrhage

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2003 Group: 2 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema, extending into perifemoral tissue
Inflammation, mixed cell; mild; muscular: with edema
Infiltration, mononuclear cell; focal; minimal; muscular

The following tissues were within normal limits:

BONE MARROW	GLAND, SEMINAL VESICLE	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	SPLEEN

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2004 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 352g

Organ Weights:

BRAIN	2.003g	EPIDIDYMIS	1.137g	GLAND, ADRENAL	0.0552g
GLAND, PITUITARY	0.0090g	GLAND, PROSTATE	1.308g	GLAND, THYROID	0.0159g
HEART	1.210g	KIDNEY	2.368g	LIVER	10.027g
LUNG	1.331g	SPLEEN	0.621g	TESTIS	3.563g
THYMUS	0.257g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LIVER;	
Focus, pale (TGL): 1, fissure, right medial	LIVER; Tension lipidosis; minimal (H)
LYMPH NODE, POPLITEAL;	
Enlargement (TGL): Right	LYMPH NODE, POPLITEAL; Inflammation, mixed cell; mild; perinodal (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2004 Group: 2 Sex: Male (continued)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LIVER;
Tension lipidosis; minimal ..... LIVER; Focus, pale (G)

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal ..... LYMPH NODE, POPLITEAL; Enlargement (G)

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)

The following tissues were within normal limits:

BONE MARROW GLAND, SEMINAL VESICLE LYMPH NODE, ILIAC LYMPH NODE, INGUINAL SPLEEN

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2005 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 358g

Organ Weights:

BRAIN	2.082g	EPIDIDYMIS	0.924g	GLAND, ADRENAL	0.0474g
GLAND, PITUITARY	0.0102g	GLAND, PROSTATE	1.321g	GLAND, THYROID	0.0113g
HEART	1.161g	KIDNEY	2.244g	LIVER	9.860g
LUNG	1.390g	SPLEEN	0.646g	TESTIS	3.588g
THYMUS	0.272g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

THYMUS;
Focus, dark (TGL): 3 ..... NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2005 Group: 2 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; minimal; subcutis/perimuscular: with edema
Inflammation, mixed cell; minimal; muscular: with edema
Infiltration, mononuclear cell; focal; minimal; muscular

NO CORRELATE;
No correlating lesion ..... THYMUS; Focus, dark (G)

The following tissues were within normal limits:

BONE MARROW	GLAND, SEMINAL VESICLE	LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	SPLEEN
THYMUS					

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2006 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 404g

Organ Weights:

BRAIN	1.932g	EPIDIDYMIS	0.888g	GLAND, ADRENAL	0.0581g
GLAND, PITUITARY	0.0113g	GLAND, PROSTATE	1.086g	GLAND, THYROID	0.0186g
HEART	1.256g	KIDNEY	2.557g	LIVER	11.422g
LUNG	1.522g	SPLEEN	0.811g	TESTIS	3.558g
THYMUS	0.450g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION; Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LYMPH NODE, ILIAC;
Erythrocytosis; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2006 Group: 2 Sex: Male (continued)

Histo Pathology Observations:

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Swelling (G)

The following tissues were within normal limits:

BONE MARROW GLAND, SEMINAL VESICLE LIVER LYMPH NODE, INGUINAL SPLEEN

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2007 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 364g

Organ Weights:

BRAIN	1.958g	EPIDIDYMIS	1.030g	GLAND, ADRENAL	0.0603g
GLAND, PITUITARY	0.0117g	GLAND, PROSTATE	0.976g	GLAND, THYROID	0.0120g
HEART	1.314g	KIDNEY	2.404g	LIVER	11.496g
LUNG	1.449g	SPLEEN	2.800g	TESTIS	3.679g
THYMUS	0.364g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; Sciatic nerve right submitted in two pieces	
LYMPH NODE, MANDIBULAR; Enlargement (TGL): Bilateral	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; unilateral; mild (H)
Any remaining study plan required tissues, which have been examined, have no visible lesions	

Histopathology Observations:	
LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; unilateral; mild	LYMPH NODE, MANDIBULAR; Enlargement (G)

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2007 Group: 2 Sex: Male (continued)

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema
Inflammation, mixed cell; mild; muscular: with edema

The following tissues were within normal limits:

BONE MARROW GLAND, SEMINAL VESICLE LIVER LYMPH NODE, ILIAC LYMPH NODE, INGUINAL
SPLEEN

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2008 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 480g

Organ Weights:

BRAIN	2.119g	EPIDIDYMIS	1.168g	GLAND, ADRENAL	0.0731g
GLAND, PITUITARY	0.0146g	GLAND, PROSTATE	1.168g	GLAND, THYROID	0.0184g
HEART	1.442g	KIDNEY	3.009g	LIVER	14.703g
LUNG	1.617g	SPLEEN	1.023g	TESTIS	4.069g
THYMUS	0.518g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LUNG; Focus, dark (TGL): 3 to 5, right caudal, left lobe	LUNG; Hemorrhage; focal; mild (H)
SITE, INJECTION; Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

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Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2008 Group: 2 Sex: Male (continued)

Histo Pathology Observations:

LUNG;
Hemorrhage; focal; mild: chronic, with inflammatory cells, erythrophagocytosis, hemoglobin crystals and perivascular mixed cell infiltration ..... LUNG; Focus, dark (G)
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema ..... SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Swelling (G)

The following tissues were within normal limits:

BONE MARROW GLAND, SEMINAL VESICLE LIVER LYMPH NODE, INGUINAL SPLEEN

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2009 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 418g

Organ Weights:

BRAIN	2.147g	EPIDIDYMIS	1.090g	GLAND, ADRENAL	0.0630g
GLAND, PITUITARY	0.0146g	GLAND, PROSTATE	1.021g	GLAND, THYROID	0.0198g
HEART	1.589g	KIDNEY	2.927g	LIVER	13.897g
LUNG	1.627g	SPLEEN	0.857g	TESTIS	3.747g
THYMUS	0.474g				

Gross Pathology Observations:
Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:
NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; moderate; subcutis/perimuscular: with
edema and hemorrhage
Inflammation, mixed cell; mild; muscular: with edema
Inflammation, mixed cell; dermal; minimal

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2009 Group: 2 Sex: Male (continued)

The following tissues were within normal limits:

BONE MARROW GLAND, SEMINAL VESICLE LIVER LYMPH NODE, ILIAC LYMPH NODE, INGUINAL
LYMPH NODE, POPLITEAL SPLEEN

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2010 Group: 2 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 383g

Organ Weights:

BRAIN	2.038g	EPIDIDYMIS	1.019g	GLAND, ADRENAL	0.0560g
GLAND, PITUITARY	0.0092g	GLAND, PROSTATE	0.751g	GLAND, THYROID	0.0192g
HEART	1.213g	KIDNEY	2.675g	LIVER	11.264g
LUNG	1.413g	SPLEEN	0.603g	TESTIS	3.980g
THYMUS	0.409g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

LUNG;
Focus, dark (TGL): 1 to 3. ..... NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2010 Group: 2 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION;
   Degeneration/necrosis; multifocal; minimal; myofiber
   Inflammation, mixed cell; moderate; subcutis/perimuscular: with
      edema
   Inflammation, mixed cell; mild; muscular: with edema

NO CORRELATE;
   No correlating lesion ..... LUNG; Focus, dark (G)

The following tissues were within normal limits:

BONE MARROW	GLAND, SEMINAL VESICLE	LIVER	LUNG	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL
SPLEEN					

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2501 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 258g

Organ Weights:

BRAIN	1.883g	GLAND, ADRENAL	0.0636g	GLAND, PITUITARY	0.0157g
GLAND, THYROID	0.0157g	HEART	1.003g	KIDNEY	1.979g
LIVER	7.798g	LUNG	1.201g	OVARY	0.079g
SPLEEN	0.572g	THYMUS	0.325g	UTERUS	1.033g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION; Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2501 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Swelling (G)

The following tissues were within normal limits:

BONE MARROW	LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	SPLEEN

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2502 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 241g

Organ Weights:

BRAIN	1.893g	GLAND, ADRENAL	0.0560g	GLAND, PITUITARY	0.0138g
GLAND, THYROID	0.0101g	HEART	0.975g	KIDNEY	1.578g
LIVER	6.870g	LUNG	1.223g	OVARY	0.090g
SPLEEN	0.584g	THYMUS	0.465g	UTEROS	0.472g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION; Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2502 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; multifocal; mild; myofiber: with hemorrhage
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Swelling (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW LIVER LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2503 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 223g

Organ Weights:

BRAIN	1.856g	GLAND, ADRENAL	0.0486g	GLAND, PITUITARY	0.0130g
GLAND, THYROID	0.0127g	HEART	0.832g	KIDNEY	1.536g
LIVER	6.332g	LUNG	0.980g	OVARY	0.081g
SPLEEN	0.531g	THYMUS	0.329g	UTERUS	0.525g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GLAND, ADRENAL;	
Focus, dark (TGL): 2, left	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LIVER;
Hypertrophy; minimal; kupffer cell

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2503 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

NO CORRELATE;
No correlating lesion ..... GLAND, ADRENAL; Focus, dark (G)

The following tissues were within normal limits:

BONE MARROW GLAND, ADRENAL LYMPH NODE, ILIAC LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2604 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 268g

Organ Weights:

BRAIN	1.935g	GLAND, ADRENAL	0.0688g	GLAND, PITUITARY	0.0164g
GLAND, THYROID	0.0117g	HEART	1.115g	KIDNEY	1.815g
LIVER	7.992g	LUNG	1.322g	OVARY	0.114g
SPLEEN	0.592g	THYMUS	0.446g	UTERUS	0.554g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION; Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LIVER;
Extramedullary hematopoiesis; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2604 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Swelling (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2505 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 254g

Organ Weights:

BRAIN	1.697g	GLAND, ADRENAL	0.0410g	GLAND, PITUITARY	0.0152g
GLAND, THYROID	0.0130g	HEART	1.011g	KIDNEY	1.564g
LIVER	7.840g	LUNG	1.190g	OVARY	0.069g
SPLEEN	0.518g	THYMUS	0.300g	UTERUS	0.460g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; ID chip damaged.	
LYMPH NODE, MANDIBULAR; Enlargement (TGL): Bilateral	LYMPH NODE, MANDIBULAR; Plasmacytosis; bilateral; mild (H) LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; bilateral ; mild (H)
THYMUS; Focus, dark (TGL): 2, left	NO CORRELATE; No correlating lesion (H)
Any remaining study plan required tissues, which have been examined, have no visible lesions	

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2505 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal

LYMPH NODE, MANDIBULAR;
Plasmacytosis; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)
Increased cellularity; lymphoid; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema
Inflammation, mixed cell; minimal; muscular: with edema
Inflammation, mixed cell; dermal; minimal
Hyperplasia; epidermal; minimal

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

NO CORRELATE;
No correlating lesion ..... THYMUS; Focus, dark (G)

The following tissues were within normal limits:

BONE MARROW LIVER LYMPH NODE, INGUINAL THYMUS

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2506 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 235g

Organ Weights:

BRAIN	1.852g	GLAND, ADRENAL	0.0524g	GLAND, PITUITARY	0.0180g
GLAND, THYROID	0.0144g	HEART	0.947g	KIDNEY	1.554g
LIVER	7.977g	LUNG	1.081g	OVARY	0.099g
SPLEEN	0.480g	THYMUS	0.358g	UTEROS	0.540g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION; Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2506 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema, extending into perifemoral tissue ..... SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Swelling (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW LIVER LYMPH NODE, ILIAC LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2507 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 245g<

Organ Weights:

BRAIN	1.964g	GLAND, ADRENAL	0.0550g	GLAND, PITUITARY	0.0168g
GLAND, THYROID	0.0122g	HEART	1.058g	KIDNEY	1.697g
LIVER	7.881g	LUNG	1.183g	OVARY	0.113g
SPLEEN	0.629g	THYMUS	0.332g	UTERUS	0.389g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, ILIAC;	
Enlargement (TGL): Right	LYMPH NODE, ILIAC; Increased cellularity; lymphoid; minimal (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
THYMUS;	
Focus, dark (TGL): >10	NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2507 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

LIVER;
Hypertrophy; minimal; kupffer cell

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal ..... LYMPH NODE, ILIAC; Enlargement (G)

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema and microabscess ..... SITE, INJECTION; Abnormal consistency; firm (G)
Inflammation, mixed cell; minimal; muscular ..... SITE, INJECTION; Abnormal consistency; firm (G)
Inflammation, mixed cell; dermal; minimal
Hyperplasia; epidermal; minimal

NO CORRELATE;
No correlating lesion ..... THYMUS; Focus, dark (G)

The following tissues were within normal limits:

BONE MARROW LYMPH NODE, INGUINAL SPLEEN THYMUS

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2508 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 224g

Organ Weights:

BRAIN	1.824g	GLAND, ADRENAL	0.0608g	GLAND, PITUITARY	0.0143g
GLAND, THYROID	0.0137g	HEART	0.881g	KIDNEY	1.505g
LIVER	6.947g	LUNG	1.076g	OVARY	0.091g
SPLEEN	0.572g	THYMUS	0.463g	UTERUS	0.540g

Gross Pathology Observations:

Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

SITE, INJECTION;
Thick (TGL): Right ..... SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2508 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW	LIVER	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2509 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 228g<

Organ Weights:

BRAIN	1.795g	GLAND, ADRENAL	0.0526g	GLAND, PITUITARY	0.0142g
GLAND, THYROID	0.0148g	HEART	0.979g	KIDNEY	1.642g
LIVER	8.220g	LUNG	1.172g	OVARY	0.100g
SPLEEN	0.522g	THYMUS	0.356g	UTERUS	0.559g

Gross Pathology Observations:
Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:
LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2509 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema
Inflammation, mixed cell; minimal; muscular: with edema

The following tissues were within normal limits:

BONE MARROW	LIVER	LYMPH NODE, INGUINAL	SPLEEN

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2510 Group: 2 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 10 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 230g<

Organ Weights:

BRAIN	1.909g	GLAND, ADRENAL	0.0698g	GLAND, PITUITARY	0.0187g
GLAND, THYROID	0.0120g	HEART	0.867g	KIDNEY	1.649g
LIVER	7.673g	LUNG	1.083g	OVARY	0.104g
SPLEEN	0.568g	THYMUS	0.197g	UTERUS	0.491g

Gross Pathology Observations:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to
midzonal: microvesicular

LYMPH NODE, ILIAC;
Erythrocytosis; minimal
Increased cellularity; lymphoid; minimal

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 2510 Group: 2 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Inflammation, mixed cell; minimal; subcutis/perimuscular: with edema, extending into perifemoral tissue
Inflammation, mixed cell; minimal; muscular: with edema

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

LYMPH NODE, INGUINAL

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3001 Group: 3 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 338g

Organ Weights:

BRAIN	1.986g	EPIDIDYMIS	0.933g	GLAND, ADRENAL	0.0553g
GLAND, PITUITARY	0.0110g	GLAND, PROSTATE	0.956g	GLAND, THYROID	0.0160g
HEART	1.274g	KIDNEY	2.260g	LIVER	10.262g
LUNG	1.341g	SPLEEN	0.694g	TESTIS	3.547g
THYMUS	0.335g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Brain accidentally cut.

LUNG;
Focus, dark (TGL): 2 to >10 ..... LUNG; Hemorrhage; multifocal; minimal (H)

THYMUS;
Focus, dark (TGL): 4 ..... THYMUS; Hemorrhage; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3001 Group: 3 Sex: Male (continued)

Histo Pathology Observations:

LIVER;
Hypertrophy; minimal; kupffer cell

LUNG;
osseous metaplasia
Hemorrhage; multifocal; minimal: acute ..... LUNG; Focus, dark (G)

LYMPH NODE, ILIAC;
Erythrocytosis; minimal
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema
Inflammation, mixed cell; mild; muscular: with edema

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

THYMUS;
Hemorrhage; minimal ..... THYMUS; Focus, dark (G)

The following tissues were within normal limits:

BONE MARROW	GLAND, SEMINAL VESICLE	LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3002 Group: 3 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 376g

Organ Weights:

BRAIN	2.041g	EPIDIDYMIS	1.000g	GLAND, ADRENAL	0.0640g
GLAND, PITUITARY	0.0103g	GLAND, PROSTATE	1.045g	GLAND, THYROID	0.0162g
HEART	1.286g	KIDNEY	2.404g	LIVER	12.158g
LUNG	1.416g	SPLEEN	0.716g	TESTIS	4.178g
THYMUS	0.346g				

Gross Pathology Observations:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Correlated with:

KIDNEY;
Dilatation; pelvis (TGL): Right ..... KIDNEY; Dilatation; moderate; pelvis (H)

SITE, INJECTION;
Swelling (TGL): Right ..... SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3002 Group: 3 Sex: Male (continued)

Histo Pathology Observations:

KIDNEY;
Dilatation; moderate; pelvis ..... KIDNEY; Dilatation; pelvis (G)
Basophilia; tubular; focal; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Swelling (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW | GLAND, SEMINAL VESICLE | LIVER | LYMPH NODE, ILIAC | LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3003 Group: 3 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 391g

Organ Weights:

BRAIN	2.074g	EPIDIDYMIS	0.989g	GLAND, ADRENAL	0.0535g
GLAND, PITUITARY	0.0125g	GLAND, PROSTATE	1.250g	GLAND, THYROID	0.0179g
HEART	1.341g	KIDNEY	2.721g	LIVER	11.943g
LUNG	1.419g	SPLEEN	0.770g	TESTIS	3.850g
THYMUS	0.387g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LUNG;	
Focus, dark (TGL): 1, edge, left lobe, right caudal	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3003 Group: 3 Sex: Male (continued)

Histo Pathology Observations:

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)

SPLEEN;
Infiltration, neutrophilic; mild; red pulp

NO CORRELATE;
No correlating lesion ..... LUNG; Focus, dark (G)

The following tissues were within normal limits:

BONE MARROW	GLAND, SEMINAL VESICLE	LUNG	LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3004 | Group: 3 | Sex: Male | Species: Rat | Strain: Sprague Dawley

Test Material: mRNA-1893 | Dose: 30 ug/dose | Route: Intramuscular, Injection | Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 | Study Day No. (Week): 30 (5) | Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 | ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 332g

Organ Weights:

BRAIN	1.938g	EPIDIDYMIS	0.995g	GLAND, ADRENAL	0.0505g
GLAND, PITUITARY	0.0099g	GLAND, PROSTATE	0.956g	GLAND, THYROID	0.0140g
HEART	1.068g	KIDNEY	2.136g	LIVER	10.596g
LUNG	1.206g	SPLEEN	0.732g	TESTIS	3.249g
THYMUS	0.297g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS;	
Brain accidentally cut.	
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3004 Group: 3 Sex: Male (continued)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LIVER;
Necrosis; hepatocellular; focal; minimal
Extramedullary hematopoiesis; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; mild; red pulp

The following tissues were within normal limits:

BONE MARROW GLAND, SEMINAL VESICLE LYMPH NODE, ILIAC LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3005 Group: 3 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 378g

Organ Weights:

BRAIN	1.980g	EPIDIDYMIS	0.891g	GLAND, ADRENAL	0.0458g
GLAND, PITUITARY	0.0122g	GLAND, PROSTATE	0.937g	GLAND, THYROID	0.0128g
HEART	1.520g	KIDNEY	2.686g	LIVER	11.155g
LUNG	1.469g	SPLEEN	0.770g	TESTIS	3.181g
THYMUS	0.447g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
KIDNEY; Dilatation; pelvis (TGL): Right	KIDNEY; Dilatation; mild; pelvis (H)
SITE, INJECTION; Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3005 Group: 3 Sex: Male (continued)

Histo Pathology Observations:

KIDNEY;
Dilatation; mild; pelvis ..... KIDNEY; Dilatation; pelvis (G)

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema and microabscess ..... SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW	GLAND, SEMINAL VESICLE	LIVER	LYMPH NODE, INGUINAL	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3006 Group: 3 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 428g

Organ Weights:

BRAIN	2.136g	EPIDIDYMIS	0.943g	GLAND, ADRENAL	0.0581g
GLAND, PITUITARY	0.0111g	GLAND, PROSTATE	0.943g	GLAND, THYROID	0.0174g
HEART	1.408g	KIDNEY	2.779g	LIVER	13.770g
LUNG	1.717g	SPLEEN	1.083g	TESTIS	3.986g
THYMUS	0.546g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
KIDNEY;	
Dilatation; pelvis (TGL): right	KIDNEY; Dilatation; mild; pelvis (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

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Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3006 Group: 3 Sex: Male (continued)

Histo Pathology Observations:

KIDNEY;
Dilatation; mild; pelvis ..... KIDNEY; Dilatation; pelvis (G)
Cast; hyaline; minimal
Basophilia; tubular; focal; minimal: with dilatation

LIVER;
Necrosis; hepatocellular; focal; minimal
Extramedullary hematopoiesis; minimal
Infiltration, mononuclear cell; multifocal; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema and microabscess ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp
Extramedullary hematopoiesis; increased; minimal

The following tissues were within normal limits:

BONE MARROW GLAND, SEMINAL VESICLE LYMPH NODE, ILIAC LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3007 Group: 3 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 412g

Organ Weights:

BRAIN	2.075g	EPIDIDYMIS	0.911g	GLAND, ADRENAL	0.0568g
GLAND, PITUITARY	0.0102g	GLAND, PROSTATE	1.115g	GLAND, THYROID	0.0153g
HEART	1.393g	KIDNEY	2.893g	LIVER	13.742g
LUNG	1.573g	SPLEEN	0.855g	TESTIS	3.601g
THYMUS	0.431g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LUNG;	
Focus, dark (TGL): 1, right middle	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3007 Group: 3 Sex: Male (continued)

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

LYMPH NODE, ILIAC;
Erythrocytosis; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

NO CORRELATE;
No correlating lesion ..... LUNG; Focus, dark (G)

The following tissues were within normal limits:

GLAND, SEMINAL VESICLE LIVER LUNG LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3008 Group: 3 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 396g

Organ Weights:

BRAIN	1.940g	EPIDIDYMIS	1.102g	GLAND, ADRENAL	0.0505g
GLAND, PITUITARY	0.0115g	GLAND, PROSTATE	1.149g	GLAND, THYROID	0.0112g
HEART	1.520g	KIDNEY	2.560g	LIVER	13.633g
LUNG	1.412g	SPLEEN	0.896g	TESTIS	3.708g
THYMUS	0.379g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3008 Group: 3 Sex: Male (continued)

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

LYMPH NODE, ILIAC;
Erythrocytosis; minimal
Increased cellularity; lymphoid; mild

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

GLAND, SEMINAL VESICLE LIVER LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3009 Group: 3 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 386g

Organ Weights:

BRAIN	2.068g	EPIDIDYMIS	0.978g	GLAND, ADRENAL	0.0547g
GLAND, PITUITARY	0.0125g	GLAND, PROSTATE	0.995g	GLAND, THYROID	0.0147g
HEART	1.357g	KIDNEY	2.553g	LIVER	10.679g
LUNG	1.587g	SPLEEN	0.850g	TESTIS	3.453g
THYMUS	0.741g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS;	
Sciatic nerve right submitted in two pieces.	
KIDNEY;	
Dilatation; pelvis (TGL): right	KIDNEY; Dilatation; minimal; pelvis (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3009 Group: 3 Sex: Male (continued)

Histo Pathology Observations:

KIDNEY;
Dilatation; minimal; pelvis ..... KIDNEY; Dilatation; pelvis (G)
Basophilia; tubular; focal; minimal

LIVER;
Hypertrophy; minimal; kupffer cell
Extramedullary hematopoiesis; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; moderate

LYMPH NODE, INGUINAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema, extending into perifemoral tissue ..... SITE, INJECTION; Abnormal consistency; firm (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW GLAND, SEMINAL VESICLE

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3010 Group: 3 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 435g

Organ Weights:

BRAIN	2.061g	EPIDIDYMIS	0.961g	GLAND, ADRENAL	0.0696g
GLAND, PITUITARY	0.0131g	GLAND, PROSTATE	0.937g	GLAND, THYROID	0.0174g
HEART	1.460g	KIDNEY	2.919g	LIVER	13.908g
LUNG	1.465g	SPLEEN	0.798g	TESTIS	3.730g
THYMUS	0.477g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
KIDNEY;	
Dilatation; pelvis (TGL): right	KIDNEY; Dilatation; mild; pelvis (H)
SITE, INJECTION;	
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3010 Group: 3 Sex: Male (continued)

Histo Pathology Observations:

KIDNEY;
Dilatation; mild; pelvis ..... KIDNEY; Dilatation; pelvis (G)

LIVER;
Extramedullary hematopoiesis; minimal

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW GLAND, SEMINAL VESICLE LYMPH NODE, ILIAC

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3501 Group: 3 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 248g<

Organ Weights:

BRAIN	1.817g	GLAND, ADRENAL	0.0544g	GLAND, PITUITARY	0.0135g
GLAND, THYROID	0.0119g	HEART	0.924g	KIDNEY	1.639g
LIVER	6.819g	LUNG	1.079g	OVARY	0.092g
SPLEEN	0.632g	THYMUS	0.312g	UTERUS	0.793g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LIVER; Focus, pale (TGL): 1, fissure, right medial	LIVER; Tension lipidosis; minimal (H)
LYMPH NODE, MANDIBULAR; Enlargement (TGL): Right	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION; Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3501 Group: 3 Sex: Female (continued)

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; mild; periportal to midzonal: micro and macrovesicular
Tension lipidosis; minimal ..... LIVER; Focus, pale (G)

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; mild

LYMPH NODE, INGUINAL;
Erythrocytosis; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild: extending into nerve

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema, extending into perifemoral tissue ..... SITE, INJECTION; Thick (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; mild; red pulp

NO CORRELATE;
No correlating lesion ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3501 Group: 3 Sex: Female (continued)

The following tissues were within normal limits:

LYMPH NODE, MANDIBULAR

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3502 Group: 3 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 225g

Organ Weights:

BRAIN	1.837g	GLAND, ADRENAL	0.0625g	GLAND, PITUITARY	0.0129g		
GLAND, THYROID	0.0107g	HEART	0.933g	KIDNEY	1.545g		
LIVER	6.753g	LUNG	1.209g	OVARY	0.108g		
SPLEEN	0.615g	THYMUS	0.356g	UTERUS	0.784g		

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, MANDIBULAR;	
Focus, dark (TGL): >10, right	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LIVER;
Hypertrophy; minimal; kupffer cell

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3502 Group: 3 Sex: Female (continued)

Histo Pathology Observations:

LIVER (continued);
Necrosis; hepatocellular; focal; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; mild

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

NO CORRELATE;
No correlating lesion ..... LYMPH NODE, MANDIBULAR; Focus, dark (G)

The following tissues were within normal limits:

BONE MARROW LYMPH NODE, INGUINAL LYMPH NODE, MANDIBULAR

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3503 Group: 3 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 213g<

Organ Weights:

BRAIN	1.782g	GLAND, ADRENAL	0.0615g	GLAND, PITUITARY	0.0159g
GLAND, THYROID	0.0156g	HEART	0.905g	KIDNEY	1.446g
LIVER	6.257g	LUNG	0.944g	OVARY	0.087g
SPLEEN	0.459g	THYMUS	0.340g	UTEROS	0.477g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; Brain accidentally cut.	
SITE, INJECTION; Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
THYMUS; Focus, dark (TGL): 3	THYMUS; Hemorrhage; minimal (H)
Any remaining study plan required tissues, which have been examined, have no visible lesions	

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3503 Group: 3 Sex: Female (continued)

Histo Pathology Observations:

LIVER;
Vacuolation; hepatocellular; multifocal; mild; periportal to midzonal: microvesicular

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; mild
Inflammation, neutrophilic; multifocal; minimal: with necrosis

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema and hemorrhage, extending into perifemoral tissue .... SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

THYMUS;
Hemorrhage; minimal ..... THYMUS; Focus, dark (G)

The following tissues were within normal limits:

BONE MARROW LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3504 Group: 3 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 236g<

Organ Weights:

BRAIN	1.902g	GLAND, ADRENAL	0.0620g	GLAND, PITUITARY	0.0131g
GLAND, THYROID	0.0116g	HEART	0.952g	KIDNEY	1.626g
LIVER	6.880g	LUNG	1.258g	OVARY	0.124g
SPLEEN	0.595g	THYMUS	0.477g	UTERUS	0.575g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LIVER;	
Focus, pale (TGL): 1. fissure, right medial	LIVER; Tension lipidosis; minimal (H)
SITE, INJECTION;	
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3504 Group: 3 Sex: Female (continued)

Histo Pathology Observations:

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular
Tension lipidosis; minimal ..... LIVER; Focus, pale (G)

LYMPH NODE, ILIAC;
Erythrocytosis; minimal
Increased cellularity; lymphoid; mild

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema and hemorrhage ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3505 | Group: 3 | Sex: Female | Species: Rat | Strain: Sprague Dawley

Test Material: mRNA-1893 | Dose: 30 ug/dose | Route: Intramuscular, Injection | Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 | Study Day No. (Week): 30 (5) | Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 | ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 248g

Organ Weights:

BRAIN	1.939g	GLAND, ADRENAL	0.0508g	GLAND, PITUITARY	0.0133g
GLAND, THYROID	0.0120g	HEART	0.935g	KIDNEY	1.667g
LIVER	7.681g	LUNG	1.234g	OVARY	0.092g
SPLEEN	0.615g	THYMUS	0.309g	UTERUS	0.596g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; Lymph node mandibular left submitted cass B.	
LYMPH NODE, MANDIBULAR; Enlargement (TGL): Bilateral	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; unilateral; minimal (H)
SITE, INJECTION; Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3505 Group: 3 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

LYMPH NODE, MANDIBULAR;
Increased cellularity; lymphoid; unilateral; minimal ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema, extending into perifemoral tissue ..... SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW LIVER LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3506 Group: 3 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 230g

Organ Weights:

BRAIN	1.750g	GLAND, ADRENAL	0.0602g	GLAND, PITUITARY	0.0144g
GLAND, THYROID	0.0104g	HEART	0.917g	KIDNEY	1.608g
LIVER	7.859g	LUNG	1.065g	OVARY	0.119g
SPLEEN	0.552g	THYMUS	0.315g	UTERUS	0.649g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION;	
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; minimal; subcutis/peri-muscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; minimal; subcutis/peri-muscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3506 Group: 3 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; mild
Inflammation, neutrophilic; multifocal; mild: with necrosis

LYMPH NODE, INGUINAL;
Erythrocytosis; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal
Inflammation, neutrophilic; focal; minimal: with necrosis

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; minimal; subcutis/perimuscular: with edema, extending into perifemoral tissue ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; mild; red pulp

The following tissues were within normal limits:

BONE MARROW LIVER

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3507 Group: 3 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 231g<

Organ Weights:

BRAIN	1.726g	GLAND, ADRENAL	0.0570g	GLAND, PITUITARY	0.0140g
GLAND, THYROID	0.0174g	HEART	0.864g	KIDNEY	1.657g
LIVER	7.072g	LUNG	1.157g	OVARY	0.088g
SPLEEN	0.478g	THYMUS	0.290g	UTERUS	0.419g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS;	
Brain accidentally cut.	
KIDNEY;	
Dilatation; pelvis (TGL): left	KIDNEY; Dilatation; mild; pelvis (H)
LYMPH NODE, ILIAC;	
Enlargement (TGL): Right	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3507 Group: 3 Sex: Female (continued)

Gross Pathology Observations:	Correlated with:
SITE, INJECTION (continued);	
Swelling (TGL) (continued)	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:	
KIDNEY;	
Dilatation; mild; pelvis	KIDNEY; Dilatation; pelvis (G)
LIVER;	
Hypertrophy; mild; kupffer cell	
LYMPH NODE, ILIAC;	
Inflammation, mixed cell; minimal; perinodal	
Inflammation, neutrophilic; focal; minimal: with necrosis	
LYMPH NODE, POPLITEAL;	
Inflammation, mixed cell; mild; perinodal	
NERVE, SCIATIC;	
Inflammation, mixed cell; perineurial; moderate	
SITE, INJECTION;	
Degeneration/necrosis; multifocal; minimal; myofiber	
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema, extending into perifemoral tissue	SITE, INJECTION; Abnormal consistency; firm (G)
	SITE, INJECTION; Swelling (G)
	SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema	SITE, INJECTION; Abnormal consistency; firm (G)
	SITE, INJECTION; Swelling (G)
	SITE, INJECTION; Thick (G)
Hyperplasia; epidermal; minimal	

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3507 Group: 3 Sex: Female (continued)

Histo Pathology Observations:

SPLEEN;
Increased cellularity; minimal; red pulp
Infiltration, neutrophilic; minimal; red pulp

NO CORRELATE;
No correlating lesion ..... LYMPH NODE, ILIAC; Enlargement (G)

The following tissues were within normal limits:

BONE MARROW	LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3508 Group: 3 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 241g

Organ Weights:

BRAIN	1.889g	GLAND, ADRENAL	0.0616g	GLAND, PITUITARY	0.0129g
GLAND, THYROID	0.0131g	HEART	0.981g	KIDNEY	1.674g
LIVER	8.072g	LUNG	1.210g	OVARY	0.131g
SPLEEN	0.696g	THYMUS	0.376g	UTERUS	0.853g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; LN lesion submitted with pancreas.	
LYMPH NODE; Discoloration, mottled (TGL): Pancreatic	LYMPH NODE; Erythrocytosis; mild (H)
LYMPH NODE, POPLITEAL; Enlargement (TGL): Right	LYMPH NODE, POPLITEAL; Increased cellularity; lymphoid; minimal (H)
SITE, INJECTION; Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3508 Group: 3 Sex: Female (continued)

Gross Pathology Observations:	Correlated with:
SITE, INJECTION (continued);	
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

LIVER;	
Hypertrophy; minimal; kupffer cell	
LYMPH NODE;	
Erythrocytosis; mild: pancreatic	LYMPH NODE; Discoloration, mottled (G)
LYMPH NODE, ILIAC;	
Erythrocytosis; minimal	
Increased cellularity; lymphoid; mild	
LYMPH NODE, POPLITEAL;	
Inflammation, mixed cell; minimal; perinodal	
Increased cellularity; lymphoid; minimal	LYMPH NODE, POPLITEAL; Enlargement (G)
NERVE, SCIATIC;	
Inflammation, mixed cell; perineurial; mild	
SITE, INJECTION;	
Degeneration/necrosis; multifocal; minimal; myofiber	
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema, extending into perifemoral tissue	SITE, INJECTION; Swelling (G)
	SITE, INJECTION; Thick (G)
Inflammation, mixed cell; minimal; muscular: with edema	SITE, INJECTION; Swelling (G)
	SITE, INJECTION; Thick (G)
Hyperplasia; epidermal; minimal	
SPLEEN;	
Infiltration, neutrophilic; minimal; red pulp	

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3508 Group: 3 Sex: Female (continued)

The following tissues were within normal limits:

BONE MARROW	LYMPH NODE, INGUINAL

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3509 Group: 3 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 231g<

Organ Weights:

BRAIN	1.879g	GLAND, ADRENAL	0.0711g	GLAND, PITUITARY	0.0145g
GLAND, THYROID	0.0147g	HEART	0.999g	KIDNEY	1.721g
LIVER	8.737g	LUNG	1.140g	OVARY	0.125g
SPLEEN	0.783g	THYMUS	0.500g	UTERUS	0.625g

Gross Pathology Observations:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Correlated with:

SITE, INJECTION;
Thick (TGL): Right. ..... SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:
LIVER;
Hypertrophy; mild; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3509 Group: 3 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; mild
Inflammation, neutrophilic; multifocal; minimal: with necrosis

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema, extending into perifemoral tissue ..... SITE, INJECTION; Thick (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3510 Group: 3 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 30 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 233g<

Organ Weights:

BRAIN	1.906g	GLAND, ADRENAL	0.0752g	GLAND, PITUITARY	0.0164g
GLAND, THYROID	0.0162g	HEART	1.048g	KIDNEY	1.756g
LIVER	7.836g	LUNG	1.244g	OVARY	0.111g
SPLEEN	0.602g	THYMUS	0.398g	UTERUS	0.611g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION;	
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Focus, dark (TGL): 3, right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)

Any remaining study plan required tissues, which have been examined, have no visible

lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 3510 Group: 3 Sex: Female (continued)

Histo Pathology Observations:

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; mild
Inflammation, neutrophilic; focal; minimal: with necrosis

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema and hemorrhage ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
SITE, INJECTION; Focus, dark (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

BONE MARROW LYMPH NODE, INGUINAL

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4001 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 378g

Organ Weights:

BRAIN	1.810g	EPIDIDYMIS	0.896g	GLAND, ADRENAL	0.0482g
GLAND, PITUITARY	0.0145g	GLAND, PROSTATE	1.104g	GLAND, THYROID	0.0183g
HEART	1.474g	KIDNEY	2.794g	LIVER	12.532g
LUNG	1.598g	SPLEEN	0.819g	TESTIS	3.566g
THYMUS	0.630g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LUNG;	
Focus, dark (TGL): 1, right cranial, right middle, right caudal, right accessory	NO CORRELATE; No correlating lesion (H)
LYMPH NODE, ILIAC;	
Enlargement (TGL): Right	LYMPH NODE, ILIAC; Increased cellularity; lymphoid; marked (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4001 Group: 4 Sex: Male (continued)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

LIVER;
Hypertrophy; minimal; kupffer cell

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
Erythrocytosis; minimal
Increased cellularity; lymphoid; marked ..... LYMPH NODE, ILIAC; Enlargement (G)

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; mild

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

PANCREAS;
Atrophy; acinar; focal; minimal: lobular

SITE, INJECTION;
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)

SPLEEN;
Infiltration, neutrophilic; mild; red pulp
Extramedullary hematopoiesis; increased; minimal

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4001 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

NO CORRELATE;
No correlating lesion ..... LUNG; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	HEART	KIDNEY	LARGE INTESTINE, CECUM		
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LYMPH NODE, MANDIBULAR	
LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL	NERVE, OPTIC	SKIN	
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH
TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4002 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 381g

Organ Weights:

BRAIN	2.081g	EPIDIDYMIS	1.015g	GLAND, ADRENAL	0.0561g
GLAND, PITUITARY	0.0115g	GLAND, PROSTATE	1.123g	GLAND, THYROID	0.0174g
HEART	1.304g	KIDNEY	2.697g	LIVER	12.272g
LUNG	1.571g	SPLEEN	0.868g	TESTIS	3.781g
THYMUS	0.449g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; Brain accidentally cut.	
KIDNEY; Dilatation; pelvis (TGL): Right	KIDNEY; Dilatation; unilateral; mild; pelvis (H)
LYMPH NODE, ILIAC; Enlargement (TGL): Right	LYMPH NODE, ILIAC; Increased cellularity; lymphoid; unilateral; mild (H)
SITE, INJECTION; Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4002 Group: 4 Sex: Male (continued)

Gross Pathology Observations:	Correlated with:
SITE, INJECTION (continued);	
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;	
Increased cellularity; myeloid; minimal	
EYE;	
Rosette; bilateral; minimal; retina	
KIDNEY;	
Dilatation; unilateral; mild; pelvis	KIDNEY; Dilatation; pelvis (G)
Cyst; unilateral; minimal	
Inflammation; unilateral; focal; minimal: chronic, interstitial	
LUNG;	
Macrophage aggregation; alveolar; focal; minimal	
LYMPH NODE, ILIAC;	
Increased cellularity; lymphoid; unilateral; mild	LYMPH NODE, ILIAC; Enlargement (G)
LYMPH NODE, INGUINAL;	
Increased cellularity; lymphoid; mild	
LYMPH NODE, POPLITEAL;	
Inflammation, mixed cell; minimal; perinodal	

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4002 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; mild; red pulp

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS	ESOPHAGUS
GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID	GLAND, PITUITARY
GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE		GLAND, THYROID
HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL	NERVE, OPTIC	PANCREAS	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH
TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4003 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 378g

Organ Weights:

BRAIN	1.922g	EPIDIDYMIS	0.986g	GLAND, ADRENAL	0.0734g
GLAND, PITUITARY	0.0144g	GLAND, PROSTATE	1.001g	GLAND, THYROID	0.0144g
HEART	1.334g	KIDNEY	2.787g	LIVER	12.607g
LUNG	1.583g	SPLEEN	0.829g	TESTIS	3.651g
THYMUS	0.546g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LUNG;	
Focus, dark (TGL): 1, right caudal, right accessory	LUNG; Hemorrhage; focal; minimal (H)
LYMPH NODE, INGUINAL;	
Enlargement (TGL): Right	LYMPH NODE, INGUINAL; Increased cellularity; lymphoid; mild (H)
LYMPH NODE, MANDIBULAR;	
Enlargement (TGL): Bilateral	LYMPH NODE, MANDIBULAR; Plasmacytosis; bilateral; mild (H) LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; bilateral ; moderate (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4003 Group: 4 Sex: Male (continued)

Gross Pathology Observations:	Correlated with:
SITE, INJECTION;	
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
STOMACH;	
Thick (TGL): Wall	NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal: with dilatation

LARGE INTESTINE, RECTUM;
Inflammation; focal; minimal: anorectal junction

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LUNG;
Hemorrhage; focal; minimal: chronic, with erythrophagocytosis and hemoglobin crystals ..... LUNG; Focus, dark (G)
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; mild

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4003 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; mild ..... LYMPH NODE, INGUINAL; Enlargement (G)

LYMPH NODE, MANDIBULAR;
Plasmacytosis; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)
Increased cellularity; lymphoid; bilateral; moderate ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema ..... SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Thick (G)
Hyperplasia; epidermal; minimal

SPLEEN;
Infiltration, neutrophilic; mild; red pulp
Decreased cellularity; multifocal; minimal; periarteriolar lymphoid sheath

NO CORRELATE;
No correlating lesion ..... STOMACH; Thick (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON	
LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL	NERVE, OPTIC	PANCREAS	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4003 Group: 4 Sex: Male (continued)

The following tissues were within normal limits: (continued)

SPINAL CORD, CERVICAL	SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC	STOMACH		
TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4004 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 452g

Organ Weights:

BRAIN	2.129g	EPIDIDYMIS	1.022g	GLAND, ADRENAL	0.0844g
GLAND, PITUITARY	0.0152g	GLAND, PROSTATE	1.237g	GLAND, THYROID	0.0147g
HEART	1.518g	KIDNEY	3.018g	LIVER	15.387g
LUNG	1.614g	SPLEEN	0.900g	TESTIS	3.931g
THYMUS	0.573g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LIVER;	
Focus, pale (TGL): >10, medial lobe	LIVER; Vacuolation; hepatocellular; multifocal; mild (H)
LYMPH NODE, MESENTERIC;	
Enlargement (TGL)	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4004 Group: 4 Sex: Male (continued)

Gross Pathology Observations:	Correlated with:
SITE, INJECTION (continued);	
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

EYE;
Rosette; bilateral; minimal; retina

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

GLAND, SEMINAL VESICLE;
Single cell necrosis; increased; bilateral; minimal: epithelial

GLAND, THYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

KIDNEY;
Cast; hyaline; unilateral; minimal
Hemorrhage; tubular; unilateral; focal; minimal
Basophilia; tubular; bilateral; focal; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular
Vacuolation; hepatocellular; multifocal; mild: macrovesicular, randomly distributed ..... LIVER; Focus, pale (G)
Extramedullary hematopoiesis; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4004 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; multifocal; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema, extending into perifemoral tissue ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp
Extramedullary hematopoiesis; increased; minimal

NO CORRELATE;
No correlating lesion ..... LYMPH NODE, MESENTERIC; Enlargement (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LUNG	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC	
NERVE, OPTIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	TESTIS	THYMUS
TONGUE	TRACHEA	URINARY BLADDER			

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4004 Group: 4 Sex: Male (continued)

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4005 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 396g

Organ Weights:

BRAIN	1.944g	EPIDIDYMIS	0.985g	GLAND, ADRENAL	0.0569g
GLAND, PITUITARY	0.0120g	GLAND, PROSTATE	0.811g	GLAND, THYROID	0.0143g
HEART	1.437g	KIDNEY	2.601g	LIVER	12.204g
LUNG	1.633g	SPLEEN	0.876g	TESTIS	3.998g
THYMUS	0.543g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LUNG;	
Focus, dark (TGL): 1, right middle	NO CORRELATE; No correlating lesion (H)
LYMPH NODE, MANDIBULAR;	
Focus, dark (TGL): 1, bilateral	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
THYMUS;	
Focus, dark (TGL): >10, left	THYMUS; Hemorrhage; mild (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4005 Group: 4 Sex: Male (continued)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

GLAND, SEMINAL VESICLE;
Single cell necrosis; increased; bilateral; minimal: epithelial

KIDNEY;
Basophilia; tubular; bilateral; multifocal; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; mild; periportal to midzonal: microvesicular

LUNG;
osseous metaplasia

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; mild

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; mild

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema, extending into perifemoral tissue and quadriceps femoris ..... SITE, INJECTION; Abnormal consistency; firm (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4005 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

SPLEEN;
Infiltration, neutrophilic; mild; red pulp
Increased cellularity; minimal; red pulp
Decreased cellularity; minimal; periarteriolar lymphoid sheath

THYMUS;
Hemorrhage; mild: one lobe ..... THYMUS; Focus, dark (G)

NO CORRELATE;
No correlating lesion ..... LUNG; Focus, dark (G)
LYMPH NODE, MANDIBULAR; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LUNG	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL
NERVE, OPTIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	TESTIS	TONGUE
TRACHEA	URINARY BLADDER				

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4006 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 396g

Organ Weights:

BRAIN	2.151g	EPIDIDYMIS	1.073g	GLAND, ADRENAL	0.0635g
GLAND, PITUITARY	0.0126g	GLAND, PROSTATE	0.998g	GLAND, THYROID	0.0136g
HEART	1.367g	KIDNEY	2.871g	LIVER	11.845g
LUNG	1.514g	SPLEEN	1.046g	TESTIS	3.967g
THYMUS	0.514g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS;	
Lung situs inversus	
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4006 Group: 4 Sex: Male (continued)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

EYE;
Rosette; unilateral; minimal; retina

HEART;
Infiltration, mononuclear cell; focal; minimal: with myofiber degeneration

KIDNEY;
Basophilia; tubular; bilateral; multifocal; minimal

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; mild

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4006 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);
Inflammation, mixed cell; minimal; muscular (continued) ..... SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; mild; red pulp
Increased cellularity; minimal; red pulp
Decreased cellularity; minimal; periarteriolar lymphoid sheath

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LUNG	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL	NERVE, OPTIC	PANCREAS	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH
TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4007 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 391g

Organ Weights:

BRAIN	1.976g	EPIDIDYMIS	1.009g	GLAND, ADRENAL	0.0671g
GLAND, PITUITARY	0.0118g	GLAND, PROSTATE	1.033g	GLAND, THYROID	0.0214g
HEART	1.327g	KIDNEY	2.765g	LIVER	13.698g
LUNG	1.572g	SPLEEN	0.740g	TESTIS	4.089g
THYMUS	0.517g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS;	
Brain accidentally cut.	
LUNG;	
Focus, dark (TGL): 1, edge, right middle	NO CORRELATE; No correlating lesion (H)
LYMPH NODE, ILIAC;	
Enlargement (TGL): Right	LYMPH NODE, ILIAC; Increased cellularity; lymphoid; mild (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4007 Group: 4 Sex: Male (continued)

Gross Pathology Observations:	Correlated with:
SITE, INJECTION (continued);	
Abnormal consistency; firm (TGL) (continued)	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
SPLEEN;	
Irregular surface (TGL)	SPLEEN; Increased cellularity; mild; red pulp (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

KIDNEY;
Basophilia; tubular; unilateral; focal; minimal

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; mild ..... LYMPH NODE, ILIAC; Enlargement (G)

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; minimal

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4007 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);	
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema and microabscesses	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
SPLEEN;	
Infiltration, neutrophilic; minimal; red pulp	
Increased cellularity; mild; red pulp	SPLEEN; Irregular surface (G)
NO CORRELATE;	
No correlating lesion	LUNG; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON	
LARGE INTESTINE, RECTUM		LUNG	LYMPH NODE, MANDIBULAR		
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC
NERVE, SCIATIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	TESTIS	THYMUS
TONGUE	TRACHEA	URINARY BLADDER			

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4008 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 338g<

Organ Weights:

BRAIN	1.902g	EPIDIDYMIS	1.042g	GLAND, ADRENAL	0.0485g
GLAND, PITUITARY	0.0094g	GLAND, PROSTATE	0.941g	GLAND, THYROID	0.0144g
HEART	1.215g	KIDNEY	2.359g	LIVER	12.331g
LUNG	1.360g	SPLEEN	0.819g	TESTIS	3.451g
THYMUS	0.237g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS;	
Adrenal gland left accidentally cut; Larynx accidentally cut.	
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4008 Group: 4 Sex: Male (continued)

Gross Pathology Observations:	Correlated with:
SITE, INJECTION (continued);	
Thick (TGL) (continued)	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

GLAND, SEMINAL VESICLE;
Single cell necrosis; increased; bilateral; minimal: epithelial

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; mild

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;

Degeneration/necrosis; focal; minimal; myofiber	
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; dermal; mild	
Hyperplasia; epidermal; minimal	

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4008 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp
Increased cellularity; mild; red pulp

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
KIDNEY	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LIVER	LUNG	LYMPH NODE, MANDIBULAR	
LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL	NERVE, OPTIC	PANCREAS	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH
TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4009 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 428g

Organ Weights:

BRAIN	2.217g	EPIDIDYMIS	1.079g	GLAND, ADRENAL	0.0577g
GLAND, PITUITARY	0.0163g	GLAND, PROSTATE	1.012g	GLAND, THYROID	0.0188g
HEART	1.625g	KIDNEY	2.870g	LIVER	14.694g
LUNG	1.652g	SPLEEN	1.076g	TESTIS	3.760g
THYMUS	0.475g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; Lymph node lesion submitted with pancreas; Lymph node mandibular left submitted cass B	
LIVER; Focus, pale (TGL): 1, fissure, right medial	LIVER; Tension lipidosis; minimal (H)
LUNG; Focus, dark (TGL): 3, right caudal	LUNG; Hemorrhage; multifocal; minimal (H)
LYMPH NODE; Enlargement (TGL): Pancreatic	LYMPH NODE; Increased cellularity; lymphoid; mild (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4009 Group: 4 Sex: Male (continued)

Gross Pathology Observations:	Correlated with:
LYMPH NODE, MANDIBULAR;	
Enlargement (TGL): Bilateral	LYMPH NODE, MANDIBULAR; Plasmacytosis; unilateral; minimal (H)
	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; bilateral ; mild (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
THYMUS;	
Focus, dark (TGL): >10	THYMUS; Hemorrhage; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

BONE, FEMUR;
Inflammation, mixed cell; minimal; joint

HEART;
Infiltration, mononuclear cell; focal; minimal: with myofiber degeneration

KIDNEY;
Basophilia; tubular; bilateral; multifocal; minimal
Cyst; unilateral; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4009 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

LARGE INTESTINE, RECTUM;
Inflammation; focal; minimal: anorectal junction

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular
Extramedullary hematopoiesis; minimal
Tension lipidosis; minimal ..... LIVER; Focus, pale (G)

LUNG;
Hemorrhage; multifocal; minimal: acute and chronic, with inflammatory cells, erythrophagocytosis and hemoglobin crystals — LUNG; Focus, dark (G)
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE;
Increased cellularity; lymphoid; mild: pancreatic ..... LYMPH NODE; Enlargement (G)

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; mild

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; mild

LYMPH NODE, MANDIBULAR;
Plasmacytosis; unilateral; minimal ..... LYMPH NODE, MANDIBULAR; Enlargement (G)
Increased cellularity; lymphoid; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4009 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);	
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema and hemorrhage	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema and hemorrhage	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
SPLEEN;	
Infiltration, neutrophilic; mild; red pulp	
Extramedullary hematopoiesis; increased; minimal	
THYMUS;	
Hemorrhage; minimal: one lobe	THYMUS; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE, STERNUM	BRAIN	EPIDIDYMIS	ESOPHAGUS	EYE
GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID	GLAND, PITUITARY
GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE		GLAND, THYROID
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LYMPH NODE, MESENTERIC	
MUSCLE, SKELETAL	NERVE, OPTIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	TESTIS	TONGUE
TRACHEA	URINARY BLADDER				

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4010 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 18DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 18DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 367g<

Organ Weights:

BRAIN	1.945g	EPIDIDYMIS	0.915g	GLAND, ADRENAL	0.0535g
GLAND, PITUITARY	0.0096g	GLAND, PROSTATE	0.894g	GLAND, THYROID	0.0155g
HEART	1.323g	KIDNEY	2.337g	LIVER	14.343g
LUNG	1.415g	SPLEEN	0.787g	TESTIS	3.578g
THYMUS	0.476g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4010 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

GLAND, SEMINAL VESICLE;
Single cell necrosis; increased; bilateral; minimal: epithelial

KIDNEY;
Basophilia; tubular; unilateral; multifocal; minimal
Cyst; unilateral; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; mild; periportal to midzonal: microvesicular

LUNG;
Hemorrhage; focal; minimal: chronic, with inflammatory cells, erythrophagocytosis and hemoglobin crystals

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; minimal
Erythrocytosis; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4010 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);
Inflammation, mixed cell; dermal; minimal
Hyperplasia; epidermal; minimal

SPLEEN;
Infiltration, neutrophilic; mild; red pulp
Decreased cellularity; multifocal; mild; periarteriolar lympho-id sheath

TESTIS;
Atrophy; tubular; unilateral; minimal

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, ILIAC	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL
NERVE, OPTIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	THYMUS	TONGUE
TRACHEA	URINARY BLADDER				

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4011 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 410g

Organ Weights:

BRAIN	2.104g	EPIDIDYMIS	1.200g	GLAND, ADRENAL	0.0464g
GLAND, PITUITARY	0.0128g	GLAND, PROSTATE	0.936g	GLAND, THYROID	0.0122g
HEART	1.490g	KIDNEY	2.894g	LIVER	11.236g
LUNG	1.369g	SPLEEN	0.834g	TESTIS	3.946g
THYMUS	0.384g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Adrenal left accidentally cut; Tongue accidentally cut; Pituit-
ary accidentally cut.

LIVER;
Focus, pale (TGL): 1, fissure, right medial. ..... NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PROSTATE;
Infiltration, mononuclear cell; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4011 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

HEART;
Infiltration, mononuclear cell; multifocal; minimal

KIDNEY;
Cast; hyaline; unilateral; minimal
Basophilia; tubular; bilateral; focal; minimal

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; focal; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

PANCREAS;
Inflammation; focal; minimal; islet of langerhans

SITE, INJECTION;
Inflammation, mixed cell; minimal; subcutis/perimuscular
Infiltration, mononuclear cell; multifocal; minimal; muscular
Hyperplasia; epidermal; focal; minimal
Inflammation; dermal; focal; minimal: subepidermal

NO CORRELATE;
No correlating lesion ..... LIVER; Focus, pale (G)

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4011 Group: 4 Sex: Male (continued)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR	
LYMPH NODE, MESENTERIC		NERVE, OPTIC	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4012 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 404g

Organ Weights:

BRAIN	2.083g	EPIDIDYMIS	1.225g	GLAND, ADRENAL	0.0602g
GLAND, PITUITARY	0.0110g	GLAND, PROSTATE	0.925g	GLAND, THYROID	0.0189g
HEART	1.263g	KIDNEY	2.531g	LIVER	10.577g
LUNG	1.429g	SPLEEN	0.632g	TESTIS	3.850g
THYMUS	0.392g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; pituitary accidentally cut.	
LIVER; Focus, pale (TGL): 1, fissure, right medial.	NO CORRELATE; No correlating lesion (H)
LYMPH NODE, ILIAC; Enlargement (TGL): Right.	LYMPH NODE, ILIAC; Increased cellularity; lymphoid; unilateral; minimal (H)
LYMPH NODE, INGUINAL; Focus, dark (TGL): 1, left.	LYMPH NODE, INGUINAL; Erythrocytosis; unilateral; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4012 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

GLAND, PROSTATE;
Infiltration, mononuclear cell; mild

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular
Infiltration, mononuclear cell; multifocal; minimal: with single cell necrosis

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; unilateral; minimal ..... LYMPH NODE, ILIAC; Enlargement (G)

LYMPH NODE, INGUINAL;
Erythrocytosis; unilateral; minimal ..... LYMPH NODE, INGUINAL; Focus, dark (G)

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Inflammation, mixed cell; minimal; subcutis/perimuscular

NO CORRELATE;
No correlating lesion ..... LIVER; Focus, pale (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	HEART	KIDNEY	LARGE INTESTINE, CECUM		
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LUNG	
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL	
MUSCLE, SKELETAL	NERVE, OPTIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS
THYMUS	TONGUE	TRACHEA	URINARY BLADDER		

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4012 Group: 4 Sex: Male (continued)

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4013 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 387g

Organ Weights:

BRAIN	1.847g	EPIDIDYMIS	1.211g	GLAND, ADRENAL	0.0497g
GLAND, PITUITARY	0.0123g	GLAND, PROSTATE	0.916g	GLAND, THYROID	0.0111g
HEART	1.343g	KIDNEY	2.567g	LIVER	11.942g
LUNG	1.265g	SPLEEN	0.735g	TESTIS	3.547g
THYMUS	0.286g				

Gross Pathology Observations: Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Prostate submitted in 2 pieces.

LIVER;
Focus, pale (TGL): 1, fissure, right medial. ..... NO CORRELATE; No correlating lesion (H)

LYMPH NODE, MANDIBULAR;
Enlargement (TGL): Right. ..... NO CORRELATE; No correlating lesion (H)
Focus, dark (TGL): 1 to 5, bilateral. ..... NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4013 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

HEART;
Infiltration, mononuclear cell; multifocal; minimal: with myofiber degeneration

KIDNEY;
Basophilia; tubular; unilateral; multifocal; minimal

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal
Thrombus; focal; minimal: acute

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; minimal; subcutis/perimuscular
Infiltration, mononuclear cell; multifocal; minimal; muscular

NO CORRELATE;
No correlating lesion ..... LIVER; Focus, pale (G)
LYMPH NODE, MANDIBULAR; Enlargement (G)
LYMPH NODE, MANDIBULAR; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		GLAND, THYROID	LARGE INTESTINE, CECUM		
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, ILIAC
LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL
NERVE, OPTIC	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TESTIS

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4013 Group: 4 Sex: Male (continued)

The following tissues were within normal limits: (continued)

THYMUS	TONGUE	TRACHEA	URINARY BLADDER

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4014 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 448g<

Organ Weights:

BRAIN	2.082g	EPIDIDYMIS	1.228g	GLAND, ADRENAL	0.0526g
GLAND, PITUITARY	0.0149g	GLAND, PROSTATE	0.933g	GLAND, THYROID	0.0175g
HEART	1.683g	KIDNEY	3.062g	LIVER	13.558g
LUNG	1.705g	SPLEEN	0.930g	TESTIS	3.799g
THYMUS	0.489g				

Gross Pathology Observations:

Correlated with:

Tissues submitted Into 10% neutral buffered formalin except eyes
and optic nerves submitted in Davidson`s and testes in modified
Davidson`s Fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

LYMPH NODE, MANDIBULAR;
Discoloration, mottled (TGL): Right ..... LYMPH NODE, MANDIBULAR; Erythrocytosis; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, THYROID;
Inflammation; unilateral; focal; mild: granulomatous, with
foreign bodies

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4014 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

KIDNEY;
Basophilia; tubular; unilateral; multifocal; minimal

LARGE INTESTINE, RECTUM;
Inflammation; minimal

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; minimal

LYMPH NODE, MANDIBULAR;
Erythrocytosis; minimal ..... LYMPH NODE, MANDIBULAR; Discoloration, mottled (G)

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; minimal; subcutis/perimuscular
Infiltration, mononuclear cell; focal; minimal; muscular

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		
GLAND, SEMINAL VESICLE		HEART	LARGE INTESTINE, CECUM		
LARGE INTESTINE, COLON		LIVER	LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC	
LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC	PANCREAS	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4015 Group: 4 Sex: Male Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 425g

Organ Weights:

BRAIN	2.188g	EPIDIDYMIS	1.197g	GLAND, ADRENAL	0.0539g
GLAND, PITUITARY	0.0121g	GLAND, PROSTATE	1.078g	GLAND, THYROID	0.0173g
HEART	1.325g	KIDNEY	2.742g	LIVER	12.539g
LUNG	1.601g	SPLEEN	0.716g	TESTIS	3.528g
THYMUS	0.310g				

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s and testes in modified Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, MANDIBULAR;	
Enlargement (TGL): Bilateral	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; bilateral ; mild (H)
Focus, dark (TGL): 2 to 4, bilateral	LYMPH NODE, MANDIBULAR; Erythrocytosis; unilateral; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

EYE;
Rosette; bilateral; minimal; retina

KIDNEY;
Dilatation; unilateral; minimal; pelvis

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4015 Group: 4 Sex: Male (continued)

Histo Pathology Observations:

LUNG;
   osseous metaplasia
   Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
   Inflammation, mixed cell; minimal; perinodal

LYMPH NODE, MANDIBULAR;
   Increased cellularity; lymphoid; bilateral; mild ..... LYMPH NODE, MANDIBULAR; Enlargement (G)
   Erythrocytosis; unilateral; minimal ..... LYMPH NODE, MANDIBULAR; Focus, dark (G)

NERVE, SCIATIC;
   Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
   Inflammation, mixed cell; minimal; subcutis/perimuscular
   Infiltration, mononuclear cell; multifocal; minimal; muscular

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	EPIDIDYMIS
ESOPHAGUS	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, PROSTATE	GLAND, SALIVARY, MANDIBULAR		GLAND, SEMINAL VESICLE	
GLAND, THYROID	HEART	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON	
LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC	
LYMPH NODE, POPLITEAL		MUSCLE, SKELETAL	NERVE, OPTIC	PANCREAS	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	TESTIS	THYMUS	TONGUE	TRACHEA	URINARY BLADDER

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4501 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 293g

Organ Weights:

BRAIN	1.721g	GLAND, ADRENAL	0.0736g	GLAND, PITUITARY	0.0144g
GLAND, THYROID	0.0130g	HEART	1.056g	KIDNEY	1.898g
LIVER	9.486g	LUNG	1.281g	OVARY	0.112g
SPLEEN	0.739g	THYMUS	0.446g	UTERUS	0.536g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4501 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Erythrocytosis; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; multifocal; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema, extending into perifemoral tissue ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; dermal; minimal
Hyperplasia; epidermal; minimal

SPLEEN;
Infiltration, neutrophilic; mild; red pulp
Increased cellularity; minimal; red pulp

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4501 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

THYMUS;
Tingible body macrophages; increased; minimal

UTERUS;
uterine body not in section

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	ESOPHAGUS	EYE
GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID	GLAND, PITUITARY
GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	KIDNEY	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		NERVE, OPTIC
OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	TONGUE	TRACHEA
URINARY BLADDER	UTERUS	VAGINA			

The following tissues have not been examined:

CERVIX; NOT PRESENT IN WET TISSUES.

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4502 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 218g

Organ Weights:

BRAIN	1.848g	GLAND, ADRENAL	0.0738g	GLAND, PITUITARY	0.0142g
GLAND, THYROID	0.0102g	HEART	1.005g	KIDNEY	1.644g
LIVER	6.938g	LUNG	1.130g	OVARY	0.108g
SPLEEN	0.584g	THYMUS	0.297g	UTERUS	0.414g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
SITE, INJECTION;	
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4502 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

KIDNEY;
Basophilia; tubular; bilateral; multifocal; minimal

LIVER;
Hypertrophy; minimal; kupffer cell

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal
Inflammation, neutrophilic; multifocal; minimal: with necrosis

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

MUSCLE, SKELETAL;
Degeneration/necrosis; multifocal; minimal; myofiber
Infiltration, mononuclear cell; multifocal; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

PANCREAS;
Atrophy; acinar; focal; minimal: lobular

SITE, INJECTION;

Inflammation, mixed cell; mild; subcutis/perimuscular: with edema, extending into perifemoral tissue and inguinal skin/-mammary gland	SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; minimal; muscular: with edema	SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)

Hyperplasia; epidermal; minimal

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4502 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		NERVE, OPTIC	OVARY
SKIN	SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		
SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

The following tissues have not been examined:

LYMPH NODE, INGUINAL; NOT PRESENT IN WET TISSUES.

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4503 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 234g<

Organ Weights:

BRAIN	1.919g	GLAND, ADRENAL	0.0701g	GLAND, PITUITARY	0.0167g		
GLAND, THYROID	0.0177g	HEART	0.918g	KIDNEY	1.661g		
LIVER	8.055g	LUNG	1.166g	OVARY	0.091g		
SPLEEN	0.534g	THYMUS	0.428g	UTERUS	0.494g		

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, MANDIBULAR;	
Enlargement (TGL): Bilateral	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4503 Group: 4 Sex: Female (continued)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

KIDNEY;
Inflammation; unilateral; minimal; pelvis: with transitional epithelium hyperplasia
Basophilia; tubular; unilateral; focal; minimal

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LUNG;
Macrophage aggregation; alveolar; focal; minimal

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; mild
Inflammation, neutrophilic; multifocal; minimal: with necrosis

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal
Inflammation, neutrophilic; focal; minimal: with necrosis

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4503 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);	
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema, extending into quadriceps femoris and perifemoral tissue	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp
Increased cellularity; minimal; red pulp

NO CORRELATE;	
No correlating lesion	LYMPH NODE, MANDIBULAR; Enlargement (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL
NERVE, OPTIC	OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA		

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4504 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 246g<

Organ Weights:

BRAIN	1.871g	GLAND, ADRENAL	0.0613g	GLAND, PITUITARY	0.0151g
GLAND, THYROID	0.0137g	HEART	1.038g	KIDNEY	1.591g
LIVER	7.464g	LUNG	1.056g	OVARY	0.096g
SPLEEN	0.611g	THYMUS	0.254g	UTERUS	0.904g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, ILIAC;	
Enlargement (TGL): Left	LYMPH NODE, ILIAC; Increased cellularity; lymphoid; unilateral; minimal (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4504 Group: 4 Sex: Female (continued)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

KIDNEY;
Basophilia; tubular; bilateral; multifocal; minimal

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LUNG;
osseous metaplasia
Macrophage aggregation; alveolar; focal; minimal

LYMPH NODE, ILIAC;
Increased cellularity; lymphoid; unilateral; minimal ..... LYMPH NODE, ILIAC; Enlargement (G)

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Hyperplasia; epidermal; minimal

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4504 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

SPLEEN;
Infiltration, neutrophilic; mild; red pulp
Decreased cellularity; minimal; periarteriolar lymphoid sheath

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL
NERVE, OPTIC	OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA		

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4505 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 220g<

Organ Weights:

BRAIN	1.862g	GLAND, ADRENAL	0.0654g	GLAND, PITUITARY	0.0160g
GLAND, THYROID	0.0126g	HEART	0.975g	KIDNEY	1.817g
LIVER	7.721g	LUNG	1.006g	OVARY	0.101g
SPLEEN	0.590g	THYMUS	0.334g	UTERUS	0.461g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.	
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS;	
Brain accidentally cut; Pituitary accidentally cut; Ovary right submitted in 2 pieces	
LYMPH NODE, ILIAC;	
Enlargement (TGL): Right	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4505 Group: 4 Sex: Female (continued)

Gross Pathology Observations:	Correlated with:
SPLEEN;	
Irregular surface (TGL)	NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

KIDNEY;
Hemorrhage; tubular; unilateral; multifocal; minimal
Basophilia; tubular; unilateral; focal; minimal
Cyst; unilateral; mild

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; mild; periportal to midzonal: microvesicular

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
Inflammation, mixed cell; mild; perinodal: with edema
Inflammation, neutrophilic; multifocal; moderate: with necrosis

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4505 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);	
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema and hemorrhage, extending into perifemoral tissue	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Thick (G)
Hyperplasia; epidermal; minimal	
SPLEEN;	
Infiltration, neutrophilic; minimal; red pulp	
Increased cellularity; minimal; red pulp	
NO CORRELATE;	
No correlating lesion	LYMPH NODE, ILIAC; Enlargement (G) SPLEEN; Irregular surface (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LYMPH NODE, INGUINAL	
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL	NERVE, OPTIC
OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	THYMUS	TONGUE
TRACHEA	UTERUS				

The following tissues have not been examined:

LARGE INTESTINE, RECTUM; NOT PRESENT IN WET TISSUES.
URINARY BLADDER; NOT PRESENT IN WET TISSUES.
VAGINA; NOT PRESENT IN WET TISSUES.

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4506 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 208g<

Organ Weights:

BRAIN	1.812g	GLAND, ADRENAL	0.0658g	GLAND, PITUITARY	0.0133g
GLAND, THYROID	0.0121g	HEART	0.828g	KIDNEY	1.430g
LIVER	6.848g	LUNG	1.003g	OVARY	0.103g
SPLEEN	0.621g	THYMUS	0.272g	UTERUS	0.817g

Gross Pathology Observations:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Correlated with:

SITE, INJECTION;
Swelling (TGL): right ..... SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)
Thick (TGL): right ..... SITE, INJECTION; Inflammation, mixed cell; mild; subcutis/perimuscular (H)
SITE, INJECTION; Inflammation, mixed cell; minimal; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4506 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LYMPH NODE, ILIAC;
Inflammation, mixed cell; focal; minimal; perinodal
Inflammation, neutrophilic; multifocal; minimal: with necrosis

LYMPH NODE, INGUINAL;
Inflammation, neutrophilic; focal; minimal: with necrosis

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; mild; subcutis/perimuscular: with edema ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; minimal; muscular: with edema ..... SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; mild; red pulp

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	KIDNEY
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LUNG	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL
NERVE, OPTIC	OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4506 Group: 4 Sex: Female (continued)

The following tissues were within normal limits: (continued)

SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA		

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4507 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 273g

Organ Weights:

BRAIN	1.945g	GLAND, ADRENAL	0.0639g	GLAND, PITUITARY	0.0164g
GLAND, THYROID	0.0177g	HEART	1.083g	KIDNEY	1.975g
LIVER	8.988g	LUNG	1.275g	OVARY	0.091g
SPLEEN	0.651g	THYMUS	0.505g	UTERUS	0.625g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, ILIAC; Enlargement (TGL): Bilateral	LYMPH NODE, ILIAC; Increased cellularity; lymphoid; bilateral; minimal (H)
SITE, INJECTION; Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4507 Group: 4 Sex: Female (continued)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

KIDNEY;
Cyst; unilateral; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LUNG;
Hemorrhage; focal; minimal: acute

LYMPH NODE, ILIAC;
Inflammation, mixed cell; bilateral; minimal; perinodal
Increased cellularity; lymphoid; bilateral; minimal ..... LYMPH NODE, ILIAC; Enlargement (G)
Inflammation, neutrophilic; unilateral; multifocal; mild: with necrosis

LYMPH NODE, INGUINAL;
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; focal; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4507 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);	
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Hyperplasia; epidermal; minimal	
SPLEEN;	
Infiltration, neutrophilic; mild; red pulp	
Increased cellularity; minimal; red pulp	

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		NERVE, OPTIC	OVARY
PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM	
SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4508 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 243g

Organ Weights:

BRAIN	1.975g	GLAND, ADRENAL	0.0772g	GLAND, PITUITARY	0.0121g
GLAND, THYROID	0.0082g	HEART	1.041g	KIDNEY	1.689g
LIVER	8.280g	LUNG	1.188g	OVARY	0.099g
SPLEEN	0.561g	THYMUS	0.251g	UTERUS	0.601g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LYMPH NODE, ILIAC;	
Enlargement (TGL): Right	NO CORRELATE; No correlating lesion (H)
LYMPH NODE, INGUINAL;	
Enlargement (TGL): Right	NO CORRELATE; No correlating lesion (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/per-imuscular (H) SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4508 Group: 4 Sex: Female (continued)

Gross Pathology Observations:	Correlated with:
SITE, INJECTION (continued);	
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

KIDNEY;
Basophilia; tubular; bilateral; multifocal; minimal

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LUNG;
Hemorrhage; focal; minimal: acute

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Inflammation, neutrophilic; multifocal; mild: with necrosis

LYMPH NODE, INGUINAL;
Inflammation, mixed cell; minimal; perinodal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

MUSCLE, SKELETAL;
Degeneration/necrosis; multifocal; minimal; myofiber
Infiltration, mononuclear cell; multifocal; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4508 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; mild

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Abnormal consistency; firm (G)
SITE, INJECTION; Swelling (G)
SITE, INJECTION; Thick (G)
Hyperplasia; epidermal; minimal

SPLEEN;
Infiltration, neutrophilic; minimal; red pulp
Increased cellularity; mild; red pulp

NO CORRELATE;
No correlating lesion ..... LYMPH NODE, ILIAC; Enlargement (G)
LYMPH NODE, INGUINAL; Enlargement (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PITUITARY
GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	LARGE INTESTINE, CECUM	
LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM		LYMPH NODE, MANDIBULAR	
LYMPH NODE, MESENTERIC		NERVE, OPTIC	OVARY	PANCREAS	SKIN
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH
THYMUS	TONGUE	TRACHEA	URINARY BLADDER	UTERUS	VAGINA

The following tissues have not been examined:

GLAND, PARATHYROID; NOT PRESENT IN SECTION.

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4508 Group: 4 Sex: Female (continued)

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4509 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 230g<

Organ Weights:

BRAIN	1.953g	GLAND, ADRENAL	0.0729g	GLAND, PITUITARY	0.0157g
GLAND, THYROID	0.0135g	HEART	0.929g	KIDNEY	1.750g
LIVER	7.625g	LUNG	1.024g	OVARY	0.069g
SPLEEN	0.631g	THYMUS	0.260g	UTERUS	1.086g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LUNG; Focus, dark (TGL): 1, right caudal.	LUNG; Hemorrhage; focal; minimal (H)
LYMPH NODE, ILIAC; Enlargement (TGL): Left.	LYMPH NODE, ILIAC; Increased cellularity; lymphoid; mild (H)
LYMPH NODE, MANDIBULAR; Enlargement (TGL): Right.	LYMPH NODE, MANDIBULAR; Plasmacytosis; moderate (H) LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; moderate (H)
LYMPH NODE, POPLITEAL; Enlargement (TGL): Right.	NO CORRELATE; No correlating lesion (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4509 Group: 4 Sex: Female (continued)

Gross Pathology Observations:	Correlated with:
SITE, INJECTION;	
Thick (TGL): Right.	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

KIDNEY;
Basophilia; tubular; unilateral; multifocal; minimal
Cyst; unilateral; mild

LIVER;
Hypertrophy; mild; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LUNG;	
Hemorrhage; focal; minimal: acute	LUNG; Focus, dark (G)
Macrophage aggregation; alveolar; focal; minimal	
LYMPH NODE, ILIAC;	
Increased cellularity; lymphoid; mild	LYMPH NODE, ILIAC; Enlargement (G)
LYMPH NODE, INGUINAL;	
Increased cellularity; lymphoid; minimal	
LYMPH NODE, MANDIBULAR;	
Plasmacytosis; moderate	LYMPH NODE, MANDIBULAR; Enlargement (G)

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4509 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, MANDIBULAR (continued);
Increased cellularity; lymphoid; moderate ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; moderate

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema, extending into perifemoral tissue ..... SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema ..... SITE, INJECTION; Thick (G)

SPLEEN;
Infiltration, neutrophilic; mild; red pulp
Increased cellularity; minimal; red pulp
Decreased cellularity; multifocal; minimal; periarteriolar lymphoid sheath

NO CORRELATE;
No correlating lesion ..... LYMPH NODE, POPLITEAL; Enlargement (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL	NERVE, OPTIC	OVARY	PANCREAS
SKIN	SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		
SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4509 Group: 4 Sex: Female (continued)

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4510 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 19DEC2018 Study Day No. (Week): 30 (5) Mode of Death: TERMINAL EUTHANASIA
Date of Necropsy: 19DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 211g

Organ Weights:

BRAIN	1.727g	GLAND, ADRENAL	0.0809g	GLAND, PITUITARY	0.0105g
GLAND, THYROID	0.0170g	HEART	1.149g	KIDNEY	1.534g
LIVER	7.235g	LUNG	1.351g	OVARY	0.115g
SPLEEN	0.670g	THYMUS	0.230g	UTERUS	0.712g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LUNG; Focus, dark (TGL): >10, left lobe, right caudal, right accessory	LUNG; Hemorrhage; multifocal; moderate (H)
LYMPH NODE, ILIAC; Enlargement (TGL): Bilateral	LYMPH NODE, ILIAC; Increased cellularity; lymphoid; bilateral; mild (H)
LYMPH NODE, INGUINAL; Enlargement (TGL): Right	LYMPH NODE, INGUINAL; Inflammation, neutrophilic; multifocal; moderate (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4510 Group: 4 Sex: Female (continued)

Gross Pathology Observations:	Correlated with:
LYMPH NODE, POPLITEAL;	
Enlargement (TGL): Right	LYMPH NODE, POPLITEAL; Inflammation, mixed cell; mild; perinodal (H)
SITE, INJECTION;	
Abnormal consistency; firm (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Swelling (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)
Thick (TGL): Right	SITE, INJECTION; Inflammation, mixed cell; moderate; subcutis/perimuscular (H)
	SITE, INJECTION; Inflammation, mixed cell; mild; muscular (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

BONE MARROW;
Increased cellularity; myeloid; minimal

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

KIDNEY;
Basophilia; tubular; bilateral; focal; minimal
Cyst; unilateral; mild

LARGE INTESTINE, RECTUM;
Inflammation; focal; minimal

LIVER;
Hypertrophy; minimal; kupffer cell
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4510 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

LIVER (continued);
Necrosis; hepatocellular; multifocal; minimal

LUNG;
Hemorrhage; multifocal; moderate: acute and chronic, with inflammatory cells, erythrophagocytosis, pigment, hemoglobin crystals and perivascular mixed cell infiltration ..... LUNG; Focus, dark (G)

LYMPH NODE, ILIAC;
Inflammation, mixed cell; bilateral; minimal; perinodal
Increased cellularity; lymphoid; bilateral; mild ..... LYMPH NODE, ILIAC; Enlargement (G)
Inflammation, neutrophilic; unilateral; multifocal; mild: with necrosis

LYMPH NODE, INGUINAL;
Inflammation, mixed cell; moderate; perinodal
Inflammation, neutrophilic; multifocal; moderate: microabscesses, with necrosis ..... LYMPH NODE, INGUINAL; Enlargement (G)

LYMPH NODE, MANDIBULAR;
Increased cellularity; lymphoid; mild

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; mild; perinodal ..... LYMPH NODE, POPLITEAL; Enlargement (G)
Inflammation, neutrophilic; focal; minimal: with necrosis

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; multifocal; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal: extending into nerve

SITE, INJECTION;
Degeneration/necrosis; multifocal; minimal; myofiber

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4510 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION (continued);	
Inflammation, mixed cell; moderate; subcutis/perimuscular: with edema, extending into perifemoral tissue and quadriceps femoris	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; mild; muscular: with edema	SITE, INJECTION; Abnormal consistency; firm (G) SITE, INJECTION; Swelling (G) SITE, INJECTION; Thick (G)
Inflammation, mixed cell; dermal; minimal	
Hyperplasia; epidermal; minimal	
SPLEEN;	
Infiltration, neutrophilic; minimal; red pulp	
Increased cellularity; minimal; red pulp	

The following tissues were within normal limits:

ARTERY, AORTA	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX	ESOPHAGUS
EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LYMPH NODE, MESENTERIC	
NERVE, OPTIC	OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		STOMACH	THYMUS	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA		

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4511 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 247g

Organ Weights:

BRAIN	1.754g	GLAND, ADRENAL	0.0616g	GLAND, PITUITARY	0.0157g
GLAND, THYROID	0.0128g	HEART	0.928g	KIDNEY	1.637g
LIVER	7.794g	LUNG	1.145g	OVARY	0.129g
SPLEEN	0.459g	THYMUS	0.286g	UTERUS	0.370g

Gross Pathology Observations:	Correlated with:
Tissues submitted Into 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s Fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
LUNG; Focus, dark (TGL): 1, right caudal	LUNG; Hemorrhage; focal; minimal (H)
LYMPH NODE, INGUINAL; Focus, dark (TGL): 10, left	NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:	
GLAND, PARATHYROID; ONE OF A PAIR AVAILABLE FOR EVALUATION.	
LUNG; Hemorrhage; focal; minimal: acute, with erythrophagocytosis ...	LUNG; Focus, dark (G)

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4511 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, INGUINAL;
Inflammation, mixed cell; unilateral; minimal; perinodal

MUSCLE, SKELETAL;
Infiltration, mononuclear cell; focal; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; minimal; subcutis/perimuscular
Infiltration, mononuclear cell; multifocal; minimal; muscular

SKIN;
Inflammation; dermal; focal; minimal: chronic, with epidermal hyperplasia

THYMUS;
Hemorrhage; minimal: in thyroid section

NO CORRELATE;
No correlating lesion ..... LYMPH NODE, INGUINAL; Focus, dark (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
KIDNEY	LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		
LARGE INTESTINE, RECTUM		LIVER	LYMPH NODE, ILIAC	LYMPH NODE, MANDIBULAR	
LYMPH NODE, MESENTERIC		LYMPH NODE, POPLITEAL		NERVE, OPTIC	OVARY
PANCREAS	SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		
SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC
SPLEEN	STOMACH	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4511 Group: 4 Sex: Female (continued)

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4512 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 251g

Organ Weights:

BRAIN	1.860g	GLAND, ADRENAL	0.0669g	GLAND, PITUITARY	0.0177g
GLAND, THYROID	0.0155g	HEART	1.080g	KIDNEY	1.775g
LIVER	7.812g	LUNG	1.143g	OVARY	0.087g
SPLEEN	0.492g	THYMUS	0.355g	UTERUS	0.409g

Gross Pathology Observations: Correlated with:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

LIVER;
Focus, pale (TGL): 1, fissure, right medial ..... NO CORRELATE; No correlating lesion (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:

GLAND, PARATHYROID;
ONE OF A PAIR AVAILABLE FOR EVALUATION.

KIDNEY;
Cast; hyaline; unilateral; minimal
Inflammation; unilateral; focal; minimal: chronic, interstitial

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Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4512 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular

LUNG;
osseous metaplasia
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; minimal; subcutis/perimuscular
Infiltration, mononuclear cell; focal; minimal; muscular

NO CORRELATE;
No correlating lesion ..... LIVER; Focus, pale (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC	
MUSCLE, SKELETAL	NERVE, OPTIC	OVARY	PANCREAS	SKIN	
SMALL INTESTINE, DUODENUM		SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM	
SPINAL CORD, CERVICAL		SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN
STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER	UTERUS
VAGINA					

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4513 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 247g

Organ Weights:

BRAIN	1.938g	GLAND, ADRENAL	0.0631g	GLAND, PITUITARY	0.0177g
GLAND, THYROID	0.0114g	HEART	0.895g	KIDNEY	1.673g
LIVER	7.291g	LUNG	1.034g	OVARY	0.084g
SPLEEN	0.517g	THYMUS	0.291g	UTERUS	1.003g

Gross Pathology Observations: Correlated with:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

GENERAL OBSERVATIONS;
Pituitary accidentally cut.

LYMPH NODE, MANDIBULAR;
Enlargement (TGL): Bilateral. ..... LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; minimal (H)

Any remaining study plan required tissues, which have been examined, have no visible

Histo Pathology Observations: lesions

KIDNEY;
Cast; hyaline; unilateral; minimal

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4513 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

LIVER;
Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular
Extramedullary hematopoiesis; minimal

LUNG;
Macrophage aggregation; alveolar; multifocal; minimal

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; mild

LYMPH NODE, MANDIBULAR;
Increased cellularity; lymphoid; minimal ..... LYMPH NODE, MANDIBULAR; Enlargement (G)

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

MUSCLE, SKELETAL;
Degeneration/necrosis; focal; minimal; myofiber
Infiltration, mononuclear cell; focal; minimal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Degeneration/necrosis; focal; minimal; myofiber
Inflammation, mixed cell; minimal; subcutis/perimuscular
Infiltration, mononuclear cell; multifocal; mild; muscular

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, PARATHYROID
GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART	
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC		NERVE, OPTIC	OVARY	PANCREAS

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4513 Group: 4 Sex: Female (continued)

The following tissues were within normal limits: (continued)

SKIN	SMALL INTESTINE, DUODENUM	SMALL INTESTINE, ILEUM			
SMALL INTESTINE, JEJUNUM	SPINAL CORD, CERVICAL	SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		
SPLEEN	STOMACH	THYMUS	TONGUE	TRACHEA	URINARY BLADDER
UTERUS	VAGINA				

The following tissues have not been examined:

GLAND, MAMMARY; NOT PRESENT IN SECTION.

Cause of death: None

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4514 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Palpable Mass Details:
None

Terminal Body Weight: 246g<

Organ Weights:

BRAIN	1.842g	GLAND, ADRENAL	0.0583g	GLAND, PITUITARY	0.0151g
GLAND, THYROID	0.0108g	HEART	1.351g	KIDNEY	1.734g
LIVER	7.279g	LUNG	1.227g	OVARY	0.115g
SPLEEN	0.541g	THYMUS	0.370g	UTERUS	0.597g

Gross Pathology Observations:	Correlated with:
Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson`s fixative. EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION	
GENERAL OBSERVATIONS; Adrenal left accidentally cut; Oviduct lesion submitted cass A; Lymph node lesion submitted with pancreas.	
GLAND, ADRENAL; Focus, dark (TGL): 2 to 5, bilateral.	NO CORRELATE; No correlating lesion (H)
LIVER; Focus, pale (TGL): 1, fissure, right medial.	LIVER; Tension lipidosis; minimal (H)
LYMPH NODE; Enlargement (TGL): Pancreatic.	NO CORRELATE; No correlating lesion (H)
Focus, dark (TGL): >10, pancreatic.	LYMPH NODE; Erythrocytosis; minimal (H)

Codes Used: (TGL) = Trackable Gross Lesion, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4514 Group: 4 Sex: Female (continued)

Gross Pathology Observations:	Correlated with:
LYMPH NODE, MANDIBULAR;	
Enlargement (TGL): Right.	LYMPH NODE, MANDIBULAR; Increased cellularity; lymphoid; minimal (H)
OVIDUCT;	
Cyst, pale (TGL): 1, right.	OVIDUCT; Dilatation; moderate (H)

Any remaining study plan required tissues, which have been examined, have no visible lesions

Histo Pathology Observations:	
KIDNEY;	
Basophilia; tubular; unilateral; multifocal; minimal	
LIVER;	
Tension lipidosis; minimal	LIVER; Focus, pale (G)
LUNG;	
osseous metaplasia	
Macrophage aggregation; alveolar; multifocal; minimal	
LYMPH NODE;	
Erythrocytosis; minimal: pancreatic	LYMPH NODE; Focus, dark (G)
LYMPH NODE, MANDIBULAR;	
Increased cellularity; lymphoid; minimal	LYMPH NODE, MANDIBULAR; Enlargement (G)
LYMPH NODE, POPLITEAL;	
Inflammation, mixed cell; minimal; perinodal	
NERVE, SCIATIC;	
Inflammation, mixed cell; perineurial; minimal	
OVIDUCT;	
Dilatation; moderate: with inflammation	OVIDUCT; Cyst, pale (G)

Codes Used: (TGL) = Trackable Gross Lesion, (G) = Gross Finding, (H) = Histo Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4514 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

SITE, INJECTION;
Inflammation, mixed cell; minimal; subcutis/perimuscular
Infiltration, mononuclear cell; multifocal; minimal; muscular

NO CORRELATE;
No correlating lesion ..... GLAND, ADRENAL; Focus, dark (G)
LYMPH NODE; Enlargement (G)

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, ILIAC	LYMPH NODE, INGUINAL	LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL	NERVE, OPTIC
OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM		
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	THYMUS
TONGUE	TRACHEA	URINARY BLADDER	UTERUS	VAGINA	

Cause of death: None

Codes Used: (G) = Gross Finding

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4515 Group: 4 Sex: Female Species: Rat Strain: Sprague Dawley

Test Material: mRNA-1893 Dose: 96 ug/dose Route: Intramuscular, Injection Study Type: REPEAT DOSE TOXICITY
Date of Death : 31DEC2018 Study Day No. (Week): 43 (7) Mode of Death: RECOVERY EUTHANASIA
Date of Necropsy: 31DEC2018 ** NECROPSY COMPLETE **

** EXAMINATION COMPLETE **

Terminal Body Weight: 251g<

Organ Weights:

BRAIN	1.765g	GLAND, ADRENAL	0.0653g	GLAND, PITUITARY	0.0188g
GLAND, THYROID	0.0131g	HEART	1.105g	KIDNEY	1.430g
LIVER	6.699g	LUNG	1.077g	OVARY	0.103g
SPLEEN	0.468g	THYMUS	0.461g	UTERUS	0.482g

Gross Pathology Observations:

Tissues submitted in 10% neutral buffered formalin except eyes and
optic nerves submitted in Davidson`s fixative.
EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Any remaining study plan required tissues, which have been examined, have no visible
lesions
Histo Pathology Observations:

KIDNEY;
- Basophilia; tubular; unilateral; focal; minimal
- Cyst; unilateral; mild

LIVER;
- Vacuolation; hepatocellular; multifocal; minimal; periportal to midzonal: microvesicular
- Infiltration, mononuclear cell; focal; minimal

LUNG;
- Macrophage aggregation; alveolar; multifocal; minimal

Appendix 18

Individual Macroscopic and Microscopic Pathology

5002400

Animal Ref.: 4515 Group: 4 Sex: Female (continued)

Histo Pathology Observations:

LYMPH NODE, ILIAC;
Inflammation, mixed cell; minimal; perinodal
Increased cellularity; lymphoid; minimal

LYMPH NODE, POPLITEAL;
Inflammation, mixed cell; minimal; perinodal

NERVE, SCIATIC;
Inflammation, mixed cell; perineurial; minimal

SITE, INJECTION;
Inflammation, mixed cell; minimal; subcutis/perimuscular
Inflammation, mixed cell; multifocal; minimal; muscular

THYMUS;
Hemorrhage; minimal

The following tissues were within normal limits:

ARTERY, AORTA	BONE MARROW	BONE, FEMUR	BONE, STERNUM	BRAIN	CERVIX
ESOPHAGUS	EYE	GALT	GLAND, ADRENAL	GLAND, HARDERIAN	GLAND, MAMMARY
GLAND, PARATHYROID	GLAND, PITUITARY	GLAND, SALIVARY, MANDIBULAR		GLAND, THYROID	HEART
LARGE INTESTINE, CECUM		LARGE INTESTINE, COLON		LARGE INTESTINE, RECTUM	
LYMPH NODE, INGUINAL	LYMPH NODE, MANDIBULAR		LYMPH NODE, MESENTERIC		MUSCLE, SKELETAL
NERVE, OPTIC	OVARY	PANCREAS	SKIN	SMALL INTESTINE, DUODENUM	
SMALL INTESTINE, ILEUM		SMALL INTESTINE, JEJUNUM		SPINAL CORD, CERVICAL	
SPINAL CORD, LUMBAR	SPINAL CORD, THORACIC		SPLEEN	STOMACH	TONGUE
TRACHEA	URINARY BLADDER	UTERUS	VAGINA		

Cause of death: None

Appendix 19

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PEER-REVIEW STATEMENT

Study Number: 5002400

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

EXPERIMENTAL DESIGN:

Text Table 1
Experimental Design

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

PURPOSE: The purpose of this peer review was to assess the overall quality and consistency of the microscopic data and determine the validity of the study pathologist's conclusions.

METHODS:

1. Study plan and amendments, narrative pathology report, histology records, clinical observations, and organ weight data were reviewed
2. Review of all tissues of animal numbers: 1002, 1006, 1009, 4003, 4006, 4010, 1503,1507, 4501, 4505, and 4509.
3. The following organs from all animals in all Groups were reviewed: Spleen, Seminal vesicles, Liver, Bonne Marrow, Sciatic Nerve, Iliac, Inguinal and Popliteal Lymph Nodes and Injection Sites.
4. Following review of the histological sections and corresponding histopathology-related study data, findings were discussed with the study pathologist.

Appendix 19

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RESULTS:

Differences of opinion were resolved and mutual agreement on terminology and diagnoses were achieved. The histopathology tables and corresponding narrative contained in the pathology report reflect diagnoses and conclusions agreed to by the peer reviewer and study pathologist

(b) (6)

Date : September 6 2019

(b) (6)

Date : 11 September 2019