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FINAL REPORT

Test Facility Study No. 5002158

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1443 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: 5002158

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**
09-Mar-2017	Final Study Plan	10-Mar-2017	10-Mar-2017
20-Mar-2017	Addition of Study Plan to Provantis	20-Mar-2017	20-Mar-2017
20-Mar-2017	Study Plan Amendment 1	20-Mar-2017	20-Mar-2017
20-Mar-2017	Study Plan Amendment 2	20-Mar-2017	20-Mar-2017
21-Mar-2017	Dose Preparation	21-Mar-2017	21-Mar-2017
04-Apr-2017	Draize Evaluation	04-Apr-2017	04-Apr-2017
13-Apr-2017	Study Plan Amendment 3	13-Apr-2017	13-Apr-2017
28-Apr-2017	Study Plan Amendment 4	28-Apr-2017	28-Apr-2017
02-May-2017	Necropsy	02-May-2017	02-May-2017
04-May-2017	Coagulation Analysis	04-May-2017	04-May-2017
14-Jun-2017	Data Review - Necropsy	14-Jun-2017	14-Jun-2017
14-Jun-2017	Data Review - Histology	14-Jun-2017	14-Jun-2017
14-Jun-2017	Report Preparation	14-Jun-2017	14-Jun-2017
14-Jun-2017	Data Review - Shipping/Receiving	14-Jun-2017	14-Jun-2017
14-Jun-2017	Data Review - Animal Care	15-Jun-2017	15-Jun-2017
14-Jun-2017 - 15-Jun-2017	Data Review - Clinical Pathology	15-Jun-2017	15-Jun-2017
14-Jun-2017 - 15-Jun-2017	Data Review - Formulations	15-Jun-2017	15-Jun-2017
14-Jun-2017 - 15-Jun-2017	Data Review - Shipping/Receiving	15-Jun-2017	15-Jun-2017
14-Jun-2017 - 15-Jun-2017	Data Review - Technical Operations	15-Jun-2017	15-Jun-2017
14-Jun-2017	Data Review - Veterinary Services	15-Jun-2017	15-Jun-2017
14-Jun-2017	Final Phase Report - Ophthalmology	14-Jun-2017	14-Jun-2017
14-Jun-2017 - 15-Jun-2017	Report Preparation	15-Jun-2017	15-Jun-2017
15-Jun-2017	Draft Report - Materials and Methods	15-Jun-2017	15-Jun-2017
23-Jun-2017	Data Review - Bioanalysis & Immunology	27-Jun-2017	27-Jun-2017
23-Jun-2017	Final Phase Report - Immunology	27-Jun-2017	27-Jun-2017
30-Jun-2017	Study Plan Amendment 5	30-Jun-2017	30-Jun-2017
05-Jul-2017 - 07-Jul-2017	Data Review - Analytical Chemistry	07-Jul-2017	07-Jul-2017
05-Jul-2017 - 07-Jul-2017	Draft Phase Report - Dose Formulation Analysis	07-Jul-2017	07-Jul-2017
29-Aug-2017	Draft Report - Results	30-Aug-2017	30-Aug-2017
30-Aug-2017	Draft Phase Report - Deviation Log	30-Aug-2017	30-Aug-2017
30-Aug-2017	Final Report	30-Aug-2017	30-Aug-2017
18-Sep-2017	Study Plan Amendment 6	18-Sep-2017	18-Sep-2017
21-Sep-2017 - 22-Sep-2017	Final Report	22-Sep-2017	22-Sep-2017

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

QUALITY ASSURANCE STATEMENT

Study Number: 5002158

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

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Dates Findings Submitted to: Study Director Management

The Quality Assurance Statements for the work conducted at the Test Sites were reviewed and are included in the appropriate section of this report.

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

[redacted]

Quality Assurance Auditor

[redacted]

Date

COMPLIANCE STATEMENT

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

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

Exceptions from the above regulations are listed below:

- Characterization of the Test Item was performed by the Sponsor or Sponsor subcontractor according to established SOPs, controls, and approved test methodologies to ensure integrity and validity of the results generated; these analyses were not conducted in compliance with the GLP or GMP regulations.
- Analysis of cytokines, α2-macroglobulin, α1-acid glycoprotein and PBMCs were conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- Pathology peer review

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

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

[redacted] Date: [redacted]

Study Director

1. RESPONSIBLE PERSONNEL

1.1. Test Facility

Study Director [redacted], BSc

Test Facility Management [redacted], BSc

1.2. Individual Scientists (IS) at Test Facility

Ophthalmology [redacted], DMV, MS, DACVO
Consultant Ophthalmologist
Senneville (CR MTL), QC, Canada

Analytical Chemistry
(Concentration and
Particle size Analysis) [redacted], BSc
Charles River Laboratories Montreal ULC
Senneville (CR MTL), QC, Canada

Immunology
(Purity Analysis) [redacted], MSc
Charles River Laboratories Montreal ULC
Senneville (CR MTL), QC, Canada

Immunology
(Cytokine, Alpha-2
Macroglobulin and
Alpha-1 Glycoprotein
Analysis) [redacted] MSc
Charles River Laboratories Montreal ULC
Sherbrooke (CR SHB), QC, Canada

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

Pathology [redacted] DVM, MS, DACVP
Charles River Laboratories, Inc. (PAI-FDK)
Frederick, MD, USA

1.4. PI at Sponsor-designated Test Site

PBMC Analysis [redacted]
Southern Research - Cell Biology and Immunology
Birmingham, AL, USA

2. SUMMARY

The objective of this study was to determine the potential toxicity of mRNA-1443, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

The study design was as follows:

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1443	10 / 9.6	200	0.05 / 0.048	10	10	-	-
3	mRNA-1443	30 / 29	200	0.15 / 0.145	10	10	-	-
4	mRNA-1443	100 / 96	200	0.5 / 0.48	10	10	5	5

- : Not applicable
[a] Values based on Summary of Analysis (SoA) issued on 16 March 2017 / Values based on SoA issued on 30 May 2017 (Refer to memorandum in Appendix 2).

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-macroglubulin), cytokines analysis (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) on Days 1, 15, 29, 43 at 6 hours postdose and on Day 57, PBMC analysis on Day 44, gross necropsy findings, organ weights, and histopathologic examinations.

There were no mRNA-1443-related changes in body weights, food consumption, ophthalmology and no mRNA-1443-related mortalities.

The mRNA-1443 elicited minimal and variable CD4 and CD8 T cell responses to pp65.

The primary mRNA-1443-related findings were observed at the site of injection and included: at all doses, very slight to moderate edemas, increasing in incidence and/or severity with dose, occasional severe edemas observed at ≥ 29 µg/dose, and very slight erythemas noted in males at 96 µg/dose and very slight to mild erythemas noted in females at ≥ 29 µg/dose. Although incidence and severity were dose-dependent for both sexes (peaking generally 24 hours postdose and resolving 72 hours postdose), these findings were generally noted with a higher extent in female rats. Firm abnormal consistency, swelling, and dark or pale foci were seen at the injection site of males and females at all doses and correlated histopathologically with regional mixed cellular inflammation (characterized primarily by neutrophils and to a lesser extent macrophages and lymphocytes) with edema and varying degrees of erythrocytes present. Minimal to marked perineurial mixed-cell inflammation was also noted in the sciatic nerve and was considered an extension of regionally extensive acute inflammation occurring at the injection site. Dose-dependent minimal to moderate lymphoid hyperplasia, and minimal to mild medullary plasmacytosis were seen in the locoregional lymph nodes (i.e. popliteal and inguinal) of both sexes. These lymph node changes reflected a non-specific, secondary reactive immunologic response to local acute inflammation at the injection site. Inguinal and popliteal lymph nodes occasionally had locally extensive, minimal to mild peripheral (i.e. interstitial)

inflammation and edema. The peripheral interstitial edema and inflammation were likely a secondary extension of the local inflammatory response centered at the injection site. The relative proximal location of these lymph nodes likely contributed to the accumulation of inflammation and edema in and around the injection site. mRNA-1443-related microscopic changes observed in the inguinal and popliteal lymph nodes were nearly or fully resolved, and changes in the spleen and the bone marrow were completely resolved. The mixed cellular inflammation observed at injection sites, in the connective tissues surrounding the sciatic nerve and in inguinal and popliteal lymph node was replaced by an infiltrate of mononucluear cells indicative of continued resolution and healing of injection site inflammation. In addition, there was a decrease in incidence and severity of the hepatocellular microvesicular vacuolation noted at the end of the recovery phase, suggesting partial resolution. Clinical signs (i.e. edema and erythema) observed at the injection site and gross findings were no longer observed in recovery animals, indicating a complete recovery.

Systemic changes associated with inflammation were also observed in animals given ≥ 9.6 µg/dose and included: increases in splenic weights that reach statistical significance at ≥ 9.6 µg/dose in males and at 96 µg/dose in females; with no histological correlates, minimal decreased cellularity of the periarteriolar lymphoid sheath noted in both sexes; with females having slightly increased incidence vs. males, and dose-dependent minimal to mild increased myeloid hematopoiesis in the bone marrow of males at ≥ 9.6 µg/dose and females at ≥ 29 µg/dose; this change was likely a reactive response to the pronounced inflammation observed at the injection site. Clinical pathology changes suggestive of inflammation were also observed in all males and/or females given mRNA-1443 and included: minimal to moderate increases in neutrophil, eosinophil and/or large unstained cell (males only ≥ 9.6 µg/dose) counts with concomitant increases in white blood cell counts (males ≥ 29 µg/dose, females ≥ 9.6 µg/dose), minimal decreases in lymphocyte counts (males only ≥ 29 µg/dose), reticulocyte (males only ≥ 9.6 µg/dose) and platelet (females only ≥ 9.6 µg/dose) counts, minimal increases in activated partial thromboplastin time (males ≥ 29 µg/dose, females 96 µg/dose) and mild increases in fibrinogen, minimal decreases in albumin (males 96 µg/dose, females ≥ 29 µg/dose) and increases in globulin with concomitant decreases in A/G ratio (males and females ≥ 29 µg/dose). Slight increases in body temperature were generally noted 6 hours postdose and return to or close to predose value 24 hours postdose. Although all body temperatures were within normal ranges, temperatures tend to increase with dose levels. Elevations of protein and cytokine levels suggestive of inflammation were also observed. Increases in α1-acid glycoprotein, α2-macroglobulin, IP-10 and MCP-1 were noted at ≥ 9.6 µg/dose. At the end of the recovery period, all mRNA-1443-related changes return close to control values or were partially or fully recovered.

Additionally, liver sections displayed a periportal to midzonal microvesicular vacuolar change with minimal to moderate magnitude. While present in all groups including controls, this change demonstrated a slight dose-dependent increase in incidence and magnitude consistent with a Test Item exacerbation of a background lesion. This change was also observed within recovery animals, but with decreased magnitude and incidence which indicate a partial resolution.

In conclusion, administration of mRNA-1443 by intramuscular injection for 6 weeks (4 doses) was clinically well tolerated (no mortality, changes in body weight and food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 96 µg/dose. At ≥ 9.6 µg/dose, dose-dependent changes clinical signs (edema/erythema) at the

injection site, clinical pathology parameters, and cytokines/protein levels along with slight increase in body temperature were consistent with a systemic inflammatory response. Dose-dependent target organ effects were limited to the injection site, the tissues surrounding the sciatic nerve, the popliteal and inguinal lymph nodes, the spleen, the bone marrow and the liver of animals given mRNA-1443. At the end of the recovery period, all changes were partially or fully recovered.

3. INTRODUCTION

The objective of this study was to determine the potential toxicity of mRNA-1443, when given by intramuscular injection for 6 weeks (4 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

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

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

The Study Director signed the study plan on 08 Mar 2017 and dosing was initiated on 20 Mar 2017 (males) and 21 Mar 2017 (females). The in-life phase of the study was completed on 03 May 2017 (Main Study animals) and on 16 May 2017 (Recovery Study animals). The experimental start date was 08 Mar 2017, and the experimental completion date was 15 Sep 2017. The study plan, study plan amendments, and deviations are presented in Appendix 1.

4. MATERIALS AND METHODS

4.1. Test and Reference Items

4.1.1. Test Item

Identification:	mRNA-1443
Batch (Lot) No.:	MTDP17017
Retest Date:	The end of use bulk Test Item analysis demonstrated that the Test Item was suitable for use during the study period.
Concentration:	2.6 / 2.5* mg/mL
Physical Description:	White to off-white lipid nanoparticle dispersion
Storage Conditions:	Kept in a freezer set to maintain -20°C
Supplier:	Moderna Therapeutics, Inc.

* Concentration based on SoA released on 16 Mar 2017 / Concentration based on SoA released on 30 May 2017 (Refer to memorandum in Appendix 2).

4.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Batch (Lot) No.:	1809319 1759866
Expiration Date:	Jul 2018 Feb 2018
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C
Supplier:	Gibco

4.3. Test Item Characterization

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

4.4. Analysis of the Test Item

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

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

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

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

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

4.5. Reserve Samples

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

4.6. Test and Reference Item Inventory and Disposition

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

4.7. Dose Formulation and Analysis

4.7.1. Preparation of Reference Item

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

The Reference Item, Phosphate-buffered Saline (PBS) pH 7.2, was dispensed on days of dosing (i.e. Days 1, 15, 29 and 43) for administration to Group 1 control animals and was used as required to dilute the bulk Test Item for administration to Groups 2 to 4 animals. The aliquots were stored in a refrigerator set to maintain 4°C until use. They were removed from the refrigerator and allowed to warm to room temperature for at least 30 minutes before dosing.

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

4.7.2. Preparation of Test Item

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

Test Item formulations were diluted with PBS pH 7.2, as necessary for administration. The dosing formulations were prepared on each days of dosing (i.e. Days 1, 15, 29 and 43) and were stored in a refrigerator set to maintain 4°C. The dose formulations were allowed to warm to room temperature for at least 30 minutes prior to dosing. Stock vials were used only once.

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

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

4.7.3. Sample Collection and Analysis

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

Text Table 2
Dose Formulation Sample Collection Schedule

Interval[b]	Homogeneity	Concentration	Sampling From
Day 1	All groups[a]	All groups	Dosing container
Day 43	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.

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

4.7.3.1. Analytical Method

Analyses were performed by IEX-HPLC using a validated analytical procedure (CR MTL Study No. 1801913).

4.7.3.2. Concentration and Homogeneity Analysis

On the first and the last preparation of the study, duplicate sets of samples (0.5 mL) 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 in an appropriate sized glass container from the top,

middle and bottom strata of the dosing container for each concentration. On days where only concentration analysis was required, the formulation was only sampled from the middle stratum.

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.

4.7.3.3. Stability Analysis

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

4.8. Test System

4.8.1. Receipt

On 08 Mar 2017, 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, the animals were 7 weeks old and males weighed between 223 and 260 grams and females weighed between 188 and 232 grams.

4.8.2. Justification for Test System and Number of Animals

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

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

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

4.8.3. Animal Identification

Each animal was identified using a subcutaneously implanted electronic identification chip.

4.8.4. Environmental Acclimation

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

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

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

No animal were replaced before or after the initiation of dosing. All spare animals were released from the study on Day 4.

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

4.8.6. Husbandry

4.8.6.1. Housing

Animals were group housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions were maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The 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. Control group animals were housed on a separate rack from the Test Item-dosed animals.

4.8.6.2. Environmental Conditions

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

4.8.6.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 (14% protein) was provided ad libitum throughout the study, except during designated procedures. Wet pellet were provided for few days to one animal as warranted by clinical sign.

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

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

4.8.6.4. Water

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

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

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

4.8.6.5. Animal Enrichment

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

4.8.6.6. Veterinary Care

Veterinary care was available throughout the course of the study, and animals were examined by the veterinary staff as warranted by clinical signs or other changes. All veterinary examinations were documented in the study records. No veterinary treatments were necessary during the course of the study.

Reaction to non-toxic pen used for marking the injection area was suspected for control female No. 1508 on Day 25. Consequently, no marking of the injection site was performed for this animal after that day, except on the terminal necropsy day.

4.9. Experimental Design

Text Table 3
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1443	10 / 9.6	200	0.05 / 0.048	10	10	-	-
3	mRNA-1443	30 / 29	200	0.15 / 0.145	10	10	-	-
4	mRNA-1443	100 / 96	200	0.5 / 0.48	10	10	5	5

- : Not applicable
[a] Values based on SoA issued on 16 March 2017 / Values based on SoA issued on 30 May 2017 (Refer to memorandum in Appendix 2).

4.9.1. Administration of Test Materials

The Test and Reference Items were administered to the appropriate animals via intramuscular injection into the lateral compartment of the thigh on Days 1, 15, 29 and 43. The injection site was alternated on each dosing occasion (Site 1 left thigh and Site 2 right thigh). The volume for each dose was administered using a syringe/needle within the demarcated area. The first day of dosing was designated as Day 1.

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

A low incidence of dosing reflux and/or spillage was observed for individual animals. As these events occurred only once (twice for one animal) per affected animal and were scattered in all dosing groups, including controls, they were considered to have no impact on overall animals exposure and on the study outcome.

4.9.2. Justification of Route and Dose Levels

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

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

4.10. In-life Procedures, Observations, and Measurements

4.10.1. Mortality/Moribundity Checks

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

4.10.2. Clinical Observations

4.10.2.1. Detailed Clinical Observations

The animals were removed from the cage, and a detailed clinical observation was performed weekly starting on Day -1.

4.10.3. Local Irritation Assessment

All animals had the dose injection site examined for signs of erythema/edema at least 24 and 72 hours postdose (end of each group). Examinations were also performed weekly when there was no dosing and during the recovery period. Following Day 43 dosing, no assessment was performed on Main Study animals at 72 hours postdose as these animals were sent to necropsy on Day 44.

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

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

4.10.4. Body Weights

Animals were weighed individually weekly, starting on Day -1. A fasted weight was recorded on the day of necropsy.

4.10.5. Food Consumption

Food consumption was quantitatively measured weekly starting on Day -5 (refer to Appendix 1) and continuing weekly throughout the dosing and recovery periods.

4.10.6. Ophthalmic Examinations

Animals had funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations once prior to randomization (all animals) and on Day 42 for males and Day 41 for females. As there were no Test Item-related ophthalmoscopic findings toward the end of the dosing period, examinations were not performed during the recovery phase. The mydriatic used was atropine 0.126%.

4.10.7. Body Temperature

Rectal body temperature was recorded on un-sedated animals on Days 1 and 43 at predose and 6 and 24 hours postdose (end of each group).

4.11. Laboratory Evaluations

4.11.1. Clinical Pathology

4.11.1.1. Sample Collection

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

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

Text Table 4
Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	α1-acid glycoprotein/ α2-macroglubulin
1 to 4[a]	Day 44	X	X	X	X
1 and 4	Day 57	X	X	X	X

X = Sample collected
[a] Samples were only collected from those animals scheduled for euthanasia on Day 44.

4.11.1.2. Hematology

Blood samples (target volume of 0.5 mL collected in a tube containing K_3EDTA as anticoagulant) were analyzed for the parameters specified in Text Table 5.

Text Table 5
Hematology Parameters

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

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

4.11.1.3. 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 the plasma was analyzed for the parameters listed in Text Table 6.

Text Table 6
Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

4.11.1.4. Clinical Chemistry

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

Text Table 7
Clinical Chemistry Parameters

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

4.11.1.5. α1-acid Glycoprotein and α2-macroglobulin Analysis

Blood (target volume of 0.7 mL collected in a serum separator tube) was obtained via abdominal aorta following isoflurane anesthesia before scheduled necropsy for all animals.

Blood samples were allowed to clot at ambient room temperature until centrifugation which was carried out as soon as practical. The samples were centrifuged for [redacted] in a refrigerated centrifuge (set to maintain [redacted] at [redacted]. Samples were processed to serum by the Immunology Department. Serum was aliquoted into 1 x 75 µL aliquot for α2-macroglobulin and

2 x 75 µL aliquot and a leftover (when available) for α1-acid glycoprotein. All samples were stored in a freezer set to maintain -20°C, pending analysis.

Analysis for α1-acid glycoprotein and α2-macroglobulin was conducted using a qualified ELISA method by the Immunology Department. The procedure to be followed along with the assay acceptance criteria was detailed in the appropriate analytical procedure. Samples were analyzed in duplicate.

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

4.11.2. Laboratory Investigation (Cytokine Analysis)

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

Text Table 8
Sample Collection Schedule

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**K_3EDTA**
Centrifugation setting			[redacted]	[redacted]
Timepoints			**Sample Type**	
Day	**Hrs**	**Animal Nos.**	IFN-α*	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	1011 to1015 4011 to 4015 1511 to 1515 4511 to 4515	X	X
15	6		X	X
29	6		X	X
43	6		X	X
57	N/A		X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR-SHB	CR-SHB

X = Sample collected; N/A = not applicable

* The assay validation of IFN-α did not work appropriately and serum samples analysis was not conducted.

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

The samples were analyzed by the Immunology department. Analysis for IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1 were conducted using a multiplex Luminex method. The procedures followed during the course of this study along with the assays acceptance criteria were detailed in the appropriate analytical procedure. Samples were analyzed in duplicate.

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

4.11.3. Anti Therapeutic Antibody (ATA) Analysis

Before the initiation of dosing and on Day 29 (before dose administration), a target blood volume of 0.5 mL was collected in a serum separator tube by jugular venipuncture from the appropriate animals.

Samples were mixed gently and allowed to clot at room temperature until centrifugation, which was carried out as soon as practical. The samples were centrifuged for [redacted] in a refrigerated centrifuge (set to maintain [redacted] at [redacted] The resultant serum was separated, transferred to uniquely labeled clear polypropylene tubes, frozen immediately over dry ice and transferred to a freezer set to maintain -80°C.

ATA samples were ultimately not analyzed and were discarded prior to report finalization, following Study Director approval.

4.11.4. PBMC Analysis

On Day 44, blood (target volume of 0.5 mL collected in a tube containing Sodium Heparin as anticoagulant) was obtained by jugular venipuncture from the appropriate animals. Samples were shipped at controlled temperature set to maintain 21°C via overnight courier to Southern Research, Birmingham, AL, USA, for whole blood stimulation and cytokine analysis.

The PBMC samples were analyzed using a qualified method.

4.12. Terminal Procedures

Terminal procedures are summarized in Text Table 9.

Text Table 9
Terminal Procedures

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology	Histopathology
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	44	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	57	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.

4.12.1. Unscheduled Deaths

No animals died during the course of the study.

4.12.2. Scheduled Euthanasia

Main study and recovery animals surviving until scheduled euthanasia had a terminal body weight recorded, samples for laboratory evaluation were collected (as appropriate), and were

euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. The animals were euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, were necropsied throughout the day. Animals were fasted overnight before their scheduled necropsy.

4.12.3. Necropsy

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

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

4.12.4. Organ Weights

The organs identified in Text Table 10 were weighed at necropsy for all scheduled euthanasia animals. Paired organs were weighed together. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight were calculated.

Text Table 10
Organs Weighed at Necropsy

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

[a] Paired organ weight.

4.12.5. Tissue Collection and Preservation

Representative samples of the tissues identified in Text Table 11 were collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated.

Text Table 11
Tissue Collection and Preservation

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

[a] Preserved in Davidson's fixative.
[b] Preserved in Modified Davidson's fixative.
[c] Thigh site used for the last injection.
[d] Lymph node draining the last administration site used (unilateral examination).
[e] Seven Brain levels examined to include olfactory bulb (examined in Body cavity, nasal section level 4).
[f] Level 4 processed to slide for evaluation of olfactory bulb. Nasal structures were not examined.
[g] Biceps femoris for all recovery animals (refer to Appendix 1).

4.12.6. 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.

4.12.7. Histopathology

Histopathological evaluation was performed by a board-certified veterinary pathologist. Injection site, liver, spleen, bone marrow, sciatic nerve and popliteal and inguinal lymph nodes were identified by the study pathologist during microscopic evaluation as potential target tissues. They were evaluated and reported.

4.12.8. Peer Review

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

4.12.9. Bone Marrow Smear Analysis

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

5. CONSTRUCTED VARIABLES

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

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

6. STATISTICAL ANALYSIS

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

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

Text Table 12
Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Body Temperature	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
α2-macroglobulin	X
α1-acid glycoprotein	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons were made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

6.1. Parametric/Non-Parametric

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

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

7. COMPUTERIZED SYSTEMS

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

Text Table 13
Critical Computerized Systems

System Name	Version	Description of Data Collected and/or Analyzed
Provantis	8	In-life; clinical pathology; postmortem
Dispense	8	Test Material receipt, accountability
In-house reporting software Nevis (using SAS)	Nevis 2 (SAS 9.2)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO2, as appropriate
Johnson Controls Metasys	MVE 7.0/4.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms

8. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, documentation, study plan, samples, specimens, and final reports from this study were archived at CR MTL archive by no later than the date of final report issue unless otherwise specified in the study plan. At least one year after issue of the draft report, the Sponsor will be contacted to determine disposition of materials associated with the study.

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

All records, retained samples and specimens, and reports generated from phases or segments performed by Test Facility-designated subcontractors were returned to the Test Facility for archiving.

All records and reports generated from Sponsor-designated subcontractors were archive at the Southern Research's Archive.

9. RESULTS

9.1. Dose Formulation Analyses

(Appendix 3)

Dose formulation concentration results were within specification except for Day 1, Group 2 (i.e. mean: 126%). Following investigation, the cause of out of specification results could not be determined. However, this was considered to have had no impact on the overall integrity of the study since the concentration results obtained were slightly over the concentration acceptance criteria. In addition, the same procedures of preparation were performed for all occasions and on Day 43, all concentrations were within specifications.

Homogeneity testing showed that the formulation technique used produced homogeneous preparations.

9.2. End of Use Bulk Test Item Analysis

(Appendix 2 and Appendix 19)

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

The end of use bulk Test Item analysis demonstrates a purity of 78.3%, which is similar to the original results provided by the Sponsor on the Certificate of Analysis (i.e. ≥ 65%).

9.3. Mortality

(Appendix 4)

There were no mortalities during the course of the study.

9.4. Clinical Observations

(Table 1, Appendix 5, and Appendix 6)

There were no significant mRNA-1443-related clinical signs observed during the course of this study.

9.5. Local Irritation Assessment

(Appendix 7)

Edema and, less frequently, erythema, were noted at the injection site following dosing of males and females given ≥ 9.6 µg/dose. The edema severity scores ranged from very slight to moderate, with occasional severe edema noted at ≥ 29 µg/dose. Very slight erythemas were noted in males at 96 µg/dose while scores ranged from very slight to mild erythema in females at ≥ 29 µg/dose. The apex of severity was generally noted 24 hours postdose and decreased 72 hours postdose. Although incidence and severity were dose-dependent for both sexes, these findings were generally noted with a higher extent in female rats.

Very slight to slight edema and/or erythema were still observed 72 hours post last dose (i.e. Day 43) but they were no longer observed at the end of the recovery period, and as such, they were considered completely reversed.

9.6. Body Weights and Body Weight Gains

(Figure 1, Figure 2, Table 2, Table 3, Appendix 8, and Appendix 9)

There were no significant mRNA-1443-related changes in body weights during the course of this study.

9.7. Food Consumption

(Table 4 and Appendix 10)

There were no significant mRNA-1443-related changes in food consumption during the course of this study.

9.8. Ophthalmic Examinations

(Appendix 17)

There were no mRNA-1443-related ocular changes observed during the course of the study. The findings noted were age-related or incidental in origin and expected in this population of animals.

9.9. Body Temperature

(Table 5 and Appendix 11)

Slight increases in body temperature were generally noted 6 hours postdose and return to or close to predose value 24 hours postdose. Although all body temperatures were generally within normal ranges (i.e. 36.0°C to 38.0°C), temperatures tend to increase with dose levels. On Day 43, predose body temperatures were higher than postdose temperatures, except for animals dosed at 96 µg where postdose temperatures were higher.

9.10. Hematology

(Table 6 and Appendix 12)

mRNA-1443-related hematology changes were noted for males and females at ≥ 9.6 µg/dose and included increases in neutrophil (NEUT), eosinophil (EOS) and/or large unstained cell (LUC) counts (with concomitant increases in white blood cell (WBC) counts) and decreases in lymphocyte (LYMPH), reticulocyte (RETIC) and platelet (PLT) counts. These changes are illustrated in Text Table 14.

Text Table 14
Hematology Changes in Rats Administered mRNA-1443

Dose (µg/dose)	9.6		29		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
WBC						
Day 44	-	1.3	1.3	1.4	**2.0**	**2.0**
Day 57					1.3	-
NEUT						
Day 44	1.6	1.7	**3.3**	**3.6**	**9.0**	**6.8**
Day 57					-	0.74
LYMPH						
Day 44	-	-	0.91	-	0.87	-
Day 57					1.4	-
EOS						
Day 44	1.8	**2.4**	**2.0**	**3.3**	**2.8**	**4.1**
Day 57					1.4	0.69
LUC						
Day 44	1.8	-	1.6	-	**2.7**	-
Day 57					-	-
RETIC						
Day 44	0.90	-	**0.85**	-	**0.82**	-
Day 57					-	-
PLT						
Day 44	-	**0.84**	-	0.93	-	**0.77**
Day 57					-	0.93

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

Minimal increases in WBC counts (up to 2.0X controls) were noted in males and females given ≥ 9.6 µg/dose, mainly due to minimal to moderate increases in NEUT and EOS (up to 9.0X and 2.8X controls for males and 6.8X and 4.1X controls for females, respectively), and/or LUC (up to 2.7X controls for males only). Minimal decreases in LYMPH were noted for males only at ≥ 29 µg/dose (down to 0.87X controls).

Minimal decreases in RETIC were noted in males at ≥ 9.6 µg/dose (down to 0.82X controls) and minimal decreases in PLT were noted in females at ≥ 9.6 µg/dose (down to 0.77X controls).

Of the above changes noted during the dosing period, a partial to full recovery of the findings were noted following the recovery period.

Any other differences in hematology parameters, including those attaining statistical significance, were judged to be due to individual or biological variation or lacked true dose relationship and therefore were considered not mRNA-1443-related.

9.11. Coagulation

(Table 7 and Appendix 13)

mRNA-1443-related increases in activated partial thromboplastin time (APTT) and in fibrinogen (FIB) were noted in males and females given ≥ 9.6 µg/dose. The changes are illustrated in Text Table 15.

Text Table 15
Coagulation Changes in Rats Administered mRNA-1443

Dose (µg/dose)	9.6		29		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
APTT						
Day 44	-	-	**1.1**	-	**1.2**	**1.1**
Day 57					-	-
FIB						
Day 44	**1.6**	1.5	**2.0**	**2.1**	**2.5**	**2.4**
Day 57					-	-

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

Minimal increases in APTT were noted for males at ≥ 29 µg/dose (up to 1.2X controls) and females at 96 µg/dose (1.1X controls). Mild increases in FIB were noted for males and females given ≥ 9.6 µg/dose (up to 2.5X and 2.4X controls, respectively). At the end of the recovery period, values were fully recovered.

Any other differences in the coagulation parameters were judged to be due to individual or biological variability or lacked true dose relationship and therefore were considered not mRNA-1443-related.

9.12. Clinical Chemistry

(Table 8 and Appendix 14)

mRNA-1443-related decreases in albumin (ALB) and increases in globulin (GLOB) were noted for males and females and were reflected by decrease in A/G ratio. These changes are illustrated in Text Table 16.

Text Table 16
Clinical Chemistry Changes in Rats Administered mRNA-1443

Dose (µg/dose)	9.6		29		96	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
ALB						
Day 44	-	-	-	**0.89**	**0.89**	**0.87**
Day 57					-	-
GLOB						
Day 44	-	-	**1.2**	**1.2**	**1.3**	**1.3**
Day 57					-	-
A/G Ratio						
Day 44	-	-	**0.78**	**0.72**	**0.70**	**0.67**
Day 57					-	-

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

Minimal decreases in ALB were noted for males given 96 µg/dose (0.89X controls) and females given ≥ 29 µg/dose (down to 0.87X controls). Minimal increases in GLOB were noted for males and females given ≥ 29 µg/dose (up to1.3X controls, for both sexes) and affected the A/G ratio

(down to 0.70X and 0.67X controls for males and females, respectively). At the end of the recovery period, values were fully recovered.

Any other differences in the clinical chemistry parameters, including those attaining statistical significance, were judged to be due to individual or biological variability or lacked true dose relationship and therefore were considered not mRNA-1443-related.

9.12.1. α1-acid Glycoprotein and α2-macroglobulin Analysis

(Table 9 and Appendix 15)

On Day 44, dose-dependent increases in α2-macroglobulin and α1-acid Glycoprotein were noted for males and females. These changes were statistically significant at ≥ 29 µg/dose in both genders. At the end of the recovery period (i.e. Day 57), all values returned close to control group suggesting a full recovery.

9.13. Laboratory Investigations (Cytokine Analysis)

(Table 10, Appendix 16, and Appendix 20)

When compared to the control group, higher concentrations of IP-10 were observed in animals at 96 µg/dose with the highest concentrations being generally observed on Days 29 and 43, 6 hours post dose, in both genders. These changes were statistically significant at 6 hours post dose on Days 29 and 43 for males and on Day 29 only for females. In addition, statistically significant increases in MCP-1 were also observed in females on Days 1, 15, 29 and 43, at 6 hours postdose.

At the end of the recovery period (i.e. Day 57), the concentrations of IP-10 and MCP-1 in the treated groups were generally very similar to the control group concentration suggesting full recovery.

No mRNA-1443-related changes were observed in IL-1β, IL-6, MIP1-α and TNF-α levels.

9.14. PBMC Analysis

(Appendix 18)

The T cell responses were evaluated by assessment of Interferon gamma (INFγ) producing T cells by intracellular cytokine staining and flow cytometric analysis. A summary of INFγ production responses are detailed in the following table.

Summary of Results - pp65 Specific INFγ Response

	Group	Test material	N	Dose level (µg)	pp65 specific CD4+ T cells Range (%)*;	Mean (%);	SD	pp65 specific CD8+ T cells Range (%)*;	Mean (%);	SD
Males	1	Reference	10	0	0.00 - 0.18;	0.00;	0.13	0.00 - 0.00;	0.00;	0.07
	2	mRNA-1443	10	9.6	0.00 - 0.27;	0.00;	0.12	0.00 - 1.07;	0.12;	0.34
	3	mRNA-1443	10	29	0.00 - 0.22;	0.00;	0.20	0.00 - 0.57;	0.00;	0.45
	4	mRNA-1443	9	96	0.00 - 0.10;	0.00;	0.11	0.00 - 0.41;	0.00;	0.37
Females	1	Reference	10	0	0.00 - 0.48;	0.00;	0.25	0.00 - 0.18;	0.01;	0.09
	2	mRNA-1443	10	9.6	0.00 - 0.62;	0.00;	0.56	0.00 - 0.22;	0.01;	0.11
	3	mRNA-1443	10	29	0.00 - 0.48;	0.00;	0.34	0.00 - 0.17;	0.01;	0.10
	4	mRNA-1443	10	96	0.00 - 0.68;	0.09;	0.38	0.00 - 0.55;	0.00;	0.43

*For purpose of Range and Mean calculation, values < 0.00 following Unstimulated Control subtraction were set to 0.00 for reporting.

The mRNA-1443 elicited minimal CD4 and CD8 T cell responses to pp65. Minimal and varying T cell responses for pp65 peptide library were noted at all dose levels. In male rats dosed with 96 µg/dose, the range of pp65-specific CD4 and CD8 T cells secreting IFN-α were 0 to 0.10% and 0 to 0.41%, respectively. In female rats that received 96 µg/dose, the range of pp65-specific CD4 and CD8 T cells were 0 to 0.68% and 0 to 0.55%, respectively.

In males at 29 µg/dose, the range of pp65-specific CD4 and CD8 T cells secreting IFN-α were 0 to 0.22% and 0 to 0.57%, respectively. In females at 29 µg/dose, the range of pp65-specific CD4 and CD8 T cells were 0 to 0.48% and 0 to 0.17%, respectively.

In males at 9.6 µg/dose, the range of pp65-specific CD4 and CD8 T cells secreting IFN-α were 0 to 0.27% and 0 to 1.07%, respectively. In females at 9.6 µg/dose, the range of pp65-specific CD4 and CD8 T cells were 0 to 0.62% and 0 to 0.22%, respectively.

Overall, the analysis revealed that minimal noted antigen-specific response to the pp-65 peptide library was seen during the study.

9.15. Gross Pathology

9.15.1. Terminal Euthanasia Animals (Day 44)

(Appendix 21).

Test Item-related gross pathology findings are summarized in Text Table 17.

Text Table 17
Summary of Gross Pathology Findings – Terminal Euthanasia (Day 44)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**9.6**	**29**	**96**	**0**	**9.6**	**29**	**96**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Injection Site (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency; firm	0	2	9	10	0	2	10	10
Swelling	0	1	4	7	0	0	1	2
Focus; dark	0	0	3	1	0	0	1	1
Focus; pale	0	0	0	1	0	0	0	0
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	2	2	2	0	0	0	1
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	3	5	0	1	2	4

At the injection site, firm abnormal consistency was seen in males and females at ≥ 9.6 µg/dose with a dose-related increase in frequency; this change correlated microscopically with mixed cell inflammation. Swelling was also observed in males at ≥ 9.6 µg/dose and females at ≥ 29 µg/dose. At the injection site, dark foci were also observed in males and females at ≥ 29 µg/dose which correlated histopathologically with mixed cell inflammation with hemorrhage. In addition, one male at 96 µg/dose (No. 4004) was noted with pale foci at the injection site.

Enlargement of the popliteal and inguinal lymph nodes was seen in some treated rats which usually correlated histologically with perinodal mixed cell inflammation.

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-1443.

9.15.2. Recovery Euthanasia Animals (Day 57)

(Appendix 21)

At the end of the recovery period, no mRNA-1443-related gross findings were noted. The 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-1443.

9.16. Organ Weights

9.16.1. Terminal Euthanasia Animals (Day 44)

(Appendix 21)

mRNA-1443-related organ weight changes are summarized in Text Table 18.

Text Table 18
Summary of Organ Weight Data – Terminal Euthanasia (Day 44)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**9.6**	**29**	**96**	**9.6**	**29**	**96**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Spleen (No. Weighed)[a]	(10)	(10)	(10)	(10)	(10)	(10)
% diff Group 1	**16.5343**	15.7402	**22.8217**	14.0207	13.9037	20.0535
% of body weight	**21.13059**	**20.11467**	**31.40503**	9.34063	13.78629	**20.28219**
% of brain weight	14.89285	**18.35570**	**24.47485**	15.32076	13.87448	**20.57586**

[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.

Statistically significant increased splenic weights were noted in males at ≥ 9.6 µg/dose and females at 96 µg/dose. There were no gross or microscopic changes that correlated to the above weight changes.

No other mRNA-1443-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective controls. However, there were no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or related to difference of sexual maturity and unrelated to administration of mRNA-1443.

9.16.2. Recovery Euthanasia Animals (Day 57)

(Appendix 21)

mRNA-1443-related organ weight changes noted at the terminal euthanasia were not observed at the end of the recovery period (i.e. Day 57). There were isolated organ weight values that were statistically different from their respective controls. However, there were no patterns, trends or correlating data to suggest these values were toxicologically relevant. Thus, the organ weight differences observed were considered incidental and/or related to difference of sexual maturity and unrelated to administration of mRNA-1443.

9.17. Histopathology

9.17.1. Terminal Euthanasia (Day 44)

(Appendix 21)

mRNA-1443-related microscopic findings are summarized in Text Table 19.

Text Table 19
Summary of Microscopic Findings – Terminal Euthanasia (Day 44)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**9.6**	**29**	**96**	**0**	**9.6**	**29**	**96**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injection	10	10	10	10	10	10	10	10
Inflammation, mixed cell	(3)[a]	(10)	(10)	(10)	(1)	(10)	(10)	(10)
Minimal	3	1	0	0	0	2	0	0
Mild	0	3	0	0	1	7	0	0
Moderate	0	6	4	0	0	1	7	0
Marked	0	0	6	10	0	0	3	10
Liver	10	10	10	10	10	10	10	10
Vacuolation, microvesicular, periportal to midzonal	(1)	(6)	(9)	(9)	(5)	(8)	(8)	(9)
Minimal	1	6	6	4	5	5	5	5
Mild	0	0	3	4	0	3	2	3
Moderate	0	0	0	1	0	0	1	1
Spleen	10	10	10	10	10	10	10	10
Decreased cellularlity, lymphoid, periarteriolar sheath	(0)	(2)	(1)	(1)	(0)	(1)	(1)	(4)
Minimal	0	2	1	1	0	1	1	4
Lymph node, inguinal	10	10	10	10	10	9	9	10
Inflammation, mixed cell; perinodal	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(0)
Mild	0	0	0	1	0	0	0	0
Plasmacytosis	(0)	(1)	(0)	(7)	(0)	(0)	(0)	(3)
Minimal	0	1	0	5	0	0	0	3
Mild	0	0	0	2	0	0	0	0
Hyperplasia; lymphoid	(1)	(6)	(4)	(5)	(0)	(5)	(7)	(4)
Minimal	1	2	2	3	0	3	2	3
Mild	0	3	1	2	0	1	5	1
Moderate	0	1	1	0	0	1	0	0
Lymph node, popliteal	9	10	10	10	10	10	10	10
Inflammation, mixed cell; perinodal	(0)	(9)	(10)	(6)	(0)	(9)	(9)	(7)
Minimal	0	3	6	1	0	5	3	2
Mild	0	6	2	4	0	4	5	4
Moderate	0	0	2	1	0	0	1	1
Plasmacytosis	(1)	(0)	(0)	(3)	(1)	(1)	(1)	(5)
Minimal	1	0	0	3	1	1	1	2
Mild	0	0	0	0	0	0	0	3
Hyperplasia; lymphoid	(0)	(9)	(8)	(5)	(0)	(8)	(9)	(8)
Minimal	0	6	5	3	0	3	6	5
Mild	0	3	3	2	0	5	3	3
Sciatic nerve	10	10	10	10	10	10	10	10
Inflammation, mixed cell; perineurial	(0)	(10)	(10)	(10)	(5)	(10)	(9)	(10)
Minimal	0	1	4	0	5	0	4	2
Mild	0	5	3	8	0	6	3	7
Moderate	0	3	3	2	0	3	2	1
Marked	0	1	0	0	0	1	0	0
Bone marrow	10	10	10	10	10	10	10	10
Increased hematopoiesis; myeloid	(0)	(2)	(2)	(5)	(1)	(0)	(4)	(4)
Minimal	0	2	2	4	1	0	4	4
Mild	0	0	0	1	0	0	0	0

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

At the injection site, a dose-dependent, minimal to marked mixed cellular inflammation accompanied by edema was noted in males and females at ≥ 9.6 µg/dose. This change was characterized by a stereotypic acute inflammatory milieu comprising increased clear space expanding the interstitium (i.e. edema) accompanied by numerous neutrophils variably admixed with foamy macrophages, lymphocytes, and rare plasma cells and hemosiderophages, as well as variable quantities of extravasated erythrocytes (i.e. hemorrhage).

In the sciatic nerve, a dose-dependent, minimal to marked mixed cellular inflammation of the perineurial tissue was observed and was variably accompanied by edema. Of note, the sciatic nerve contained no changes within the nerve fibers, inflammation did not broach the epidneurium, and inflammation/edema was generally of a lesser severity than the injection site proper.

Similar to the sciatic nerve, minimal to moderate mixed cellular inflammation surrounded the inguinal and/or popliteal lymph node in males and females at ≥ 9.6 µg/dose. These changes were reflected by perinodal interstitial mixed cell inflammation variably accompanied by small amounts of edema. Inflammation did not extend into the lymph node capsule. The inguinal lymph node site generally had less incidence and severity of peripheral inflammation vs. the popliteal site.

Intrinsic lymph node changes included lymphoid hyperplasia and medullary plasmacytosis; these changes were orderly and of a character and magnitude that would be expected of reactive lymph nodes that are a non-specific and appropriate secondary consequence of injection site inflammation. These non-specific reactive changes were observed in relevant locoregional injection site lymph nodes (i.e. inguinal, popliteal) at a higher rate and slightly higher magnitude than controls.

In the spleen of males and females at ≥ 9.6 µg/dose, slightly increased incidence of a minimally decreased cellularity of the periarteriolar lymphoid sheath was noted. Although males did not display any evident dose-dependent trend, increased incidence in females at 96 µg/dose may indicate a dose-dependent effect. Microscopically, this change was characterized by subtle attrition of periarteriolar lymphocytes and variably accompanied by a slight increase in tingible body macrophages.

In the bone marrow of males at ≥ 9.6 µg/dose and females at ≥ 29 µg/dose, increased incidence of minimal to mild increased myeloid hematopoiesis (i.e. myeloid hyperplasia) with a distinctive appearance were noted. Incidence in males and females generally trends upward with increasing dose, suggesting a dose-dependent effect. Microscopically, this change was consistently characterized by multifocal aggregates of precursor cells predominantly composed of early myeloid lineage and typically found adjacent to the cortex and/or trabeculae.

Liver of control and treated males and females display microvescular hepatocelluar vacuolation without nuclear displacement throughout periportal to midzonal regions. However, this change demonstrated a dose-dependent increase in incidence and magnitude at ≥ 9.6 µg/dose in both genders, consistent with a Test Item exacerbation of a background lesion.

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-1443.

9.17.2. Recovery Euthanasia (Day 57)

(Appendix 21)

Microscopic findings noted at the terminal euthanasia were observed at the end of the recovery period (i.e. Day 57) and are summarized in Text Table 20.

Text Table 20
Summary of Microscopic Findings – Recovery Euthanasia (Day 57)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**9.6**	**29**	**96**	**0**	**9.6**	**29**	**96**
No. Animals Examined	**5**	**-**	**-**	**5**	**5**	**-**	**-**	**5**
Injection site	5	-	-	5	5	-	-	5
Infiltration, mononuclear cell	(1)[a]	-	-	(4)	(0)	-	-	(4)
Minimal	1	-	-	4	0	-	-	4
Liver	5	-	-	5	5	-	-	5
Vacuolation, microvesicular, periportal to midzonal	(0)	-	-	(1)	(2)	-	-	(4)
Minimal	0	-	-	0	2	-	-	1
Mild	0	-	-	1	0	-	-	3
Lymph node, inguinal	5	-	-	5	5	-	-	5
Plasmacytosis	(1)	-	-	(2)	(0)	-	-	(0)
Minimal	1	-	-	2	0	-	-	0
Hyperplasia; lymphoid	(2)	-	-	(3)	(1)	-	-	(1)
Minimal	2	-	-	2	1	-	-	1
Mild	0	-	-	1	0	-	-	0
Lymph node, popliteal	5	-	-	5	5	-	-	5
Infiltration, mononuclear cell; perinodal	(0)	-	-	(1)	(0)	-	-	(1)
Minimal	0	-	-	1	0	-	-	1
Plasmacytosis	(2)	-	-	(3)	(0)	-	-	(2)
Minimal	2	-	-	2	0	-	-	0
Mild	0	-	-	1	0	-	-	2
Hyperplasia; lymphoid	(1)	-	-	(3)	(0)	-	-	(5)
Minimal	0	-	-	3	0	-	-	5
Mild	1	-	-	0	0	-	-	0
Sciatic nerve	5	-	-	5	5	-	-	5
Infiltration, mononuclear cell; perineurial	(0)	-	-	(5)	(1)	-	-	(4)
Minimal	0	-	-	5	1	-	-	2
Mild	0	-	-	0	0	-	-	2

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

At the injections site, there was a resolution of edema and acute mixed cellular inflammation in animals at 96 µg/dose at the end of the recovery period (i.e. Day 57) when compared with main animals at 96 µg/dose on Day 44. When present, the interstitial to perivascular inflammatory population was minimal and comprises a mixture of lymphocytes and macrophages with rare plasma cells and is consistent with a healing process.

In the sciatic nerve, minimal to mild infiltration of mononuclear cells was noted in both sexes. This change suggests a partial recovery from the mixed cellular inflammation observed by the end of the Recovery period.

In the inguinal/popliteal lymph nodes, perinodal mixed-cell inflammation was absent in males and females at 96 µg/dose following recovery. As part of the resolving/resolved acute

inflammation, a minimal mononuclear cell infiltration was occasionally present within the interstitium and/or perivascularly, albeit with much decreased frequency and incidence when compared with initial perinodal inflammation on Day 44.

Intrinsic lymph node changes including lymphoid hyperplasia and medullary plasmacytosis had decreased incidence and magnitude following recovery and were consistent with a resolving/resolved inflammatory response.

In the liver of control and treated males and females, microvescular hepatocellular vacuolation were noted throughout the periportal to midzonal regions. This change occurred at decreased incidence and magnitude when compared with Main Study (i.e. Day 44) animals indicating improvement. Amongst recovery animals, this change was observed in two control females (minimal), and one male (mild) and four (1 minimal, 3 mild) females at 96 µg/dose. However, the higher incidence in the 96 µg/dose recovery animals suggests that this Test Item effect has not fully resolved.

Microscopic findings noted in the bone marrow and the spleen at terminal euthanasia were no longer observed at the end of the recovery period and therefore were considered completely recovered.

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-1443.

10. CONCLUSION

In conclusion, administration of mRNA-1443 by intramuscular injection for 6 weeks (4 doses) was clinically well tolerated (no mortality, changes in body weight and food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 96 µg/dose. At ≥ 9.6 µg/dose, dose-dependent changes clinical signs (edema/erythema) at the injection site, clinical pathology parameters, and cytokines/protein levels along with slight increase in body temperature were consistent with a systemic inflammatory response. Dose-dependent target organ effects were limited to the injection site, the tissues surrounding the sciatic nerve, the popliteal and inguinal lymph nodes, the spleen, the bone marrow and the liver of animals given mRNA-1443. At the end of the recovery period, all changes were partially or fully recovered.

Figure 1

Summary of Body Weights - Males

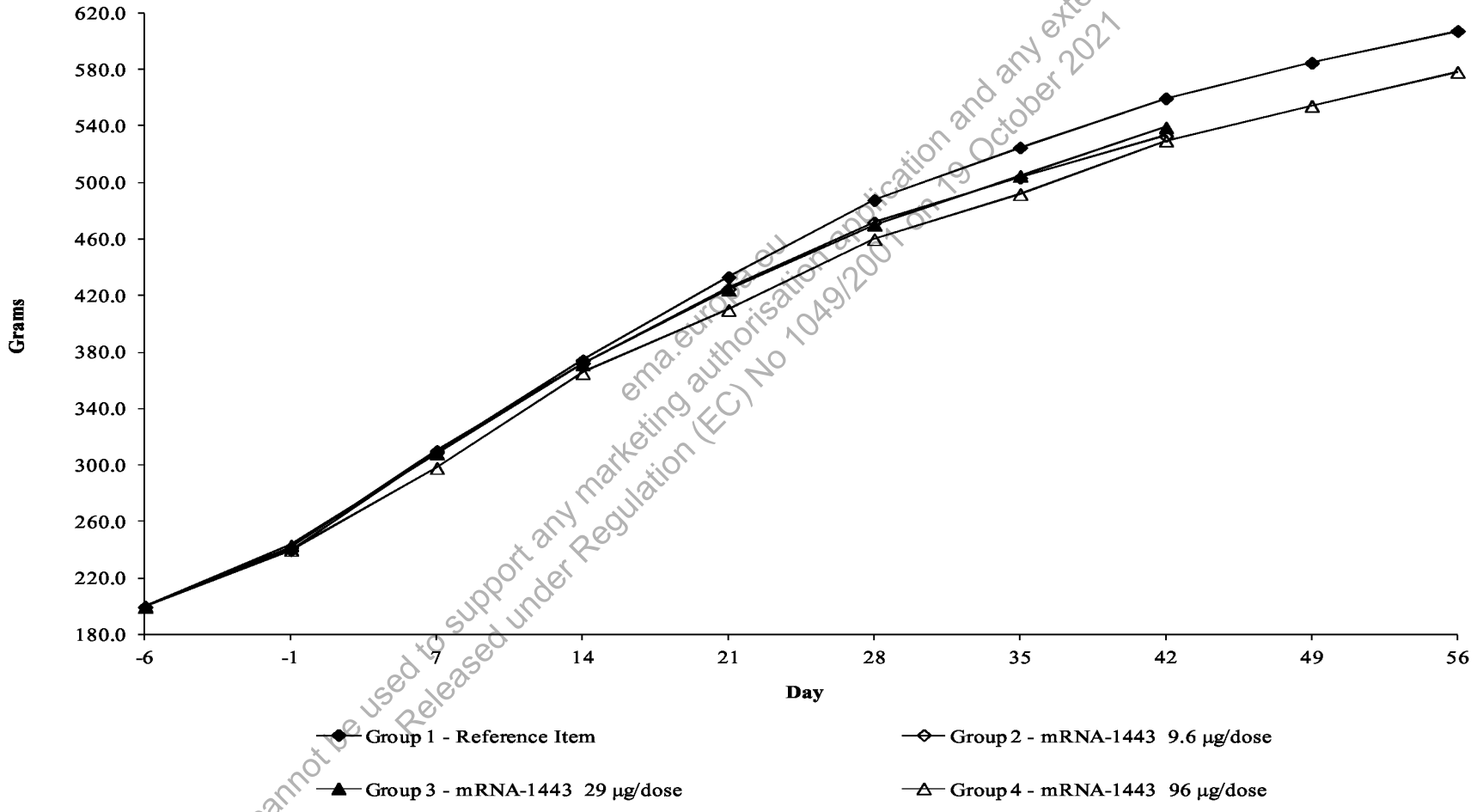

Figure 2

Summary of Body Weights - Females

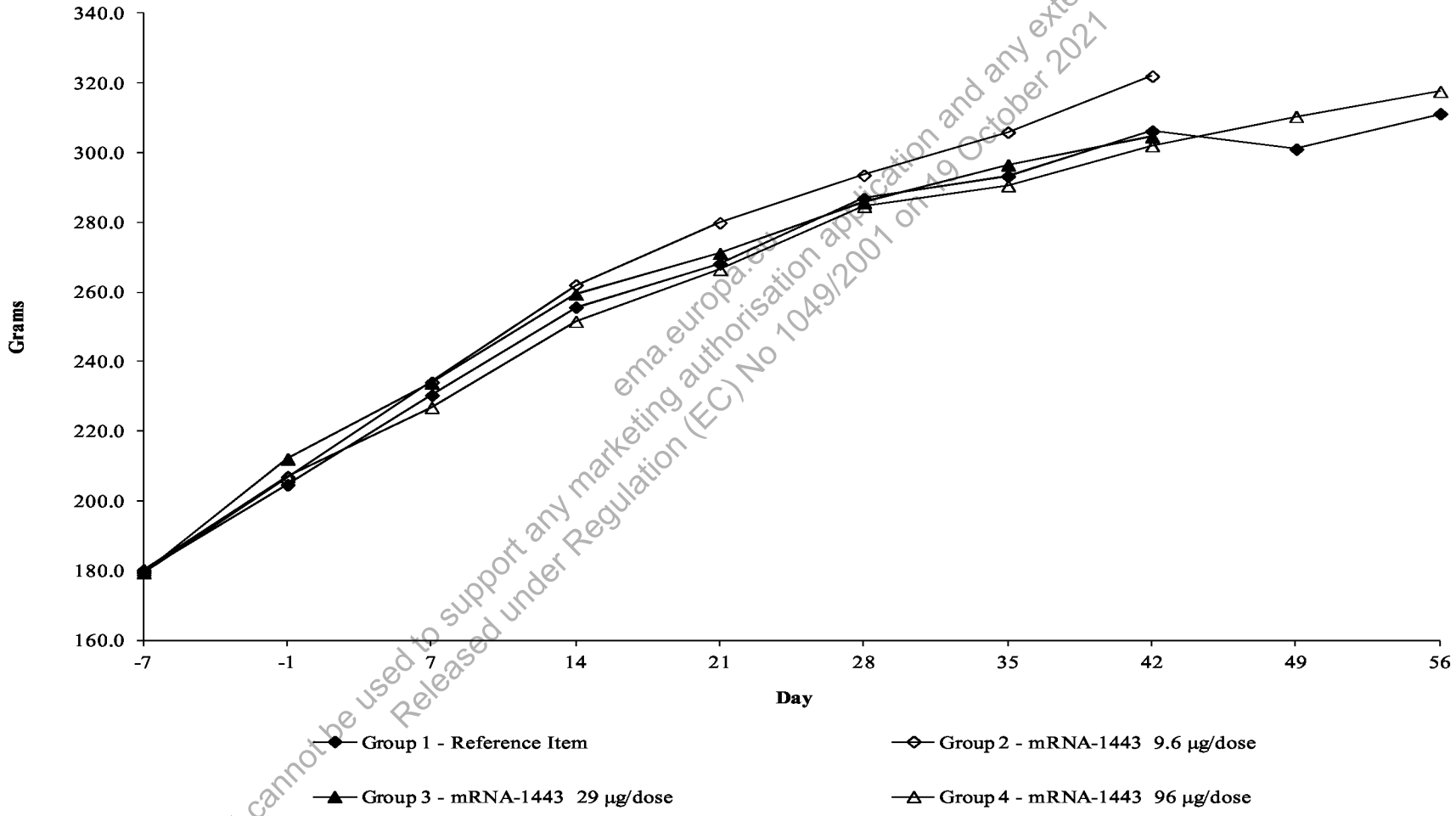

Table 1

Summary of Clinical Observations

5002158

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	9.6 ug/dose	29 ug/dose	96 ug/dose
Skin, Red				
Number of Observations	.	1	.	2
Number of Animals	.	1	.	1
Days from - to	.	28 28	.	14 21
Skin, Lesion w/ Discharge				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	-1 -1	.
Skin, Scab				
Number of Observations	9	6	7	2
Number of Animals	6	4	4	2
Days from - to	-1 44	21 44	28 44	35 35
Fur, Staining, Black				
Number of Observations	3	.	.	.
Number of Animals	1	.	.	.
Days from - to	-1 14	.	.	.
Fur, Staining, Red				
Number of Observations	24	13	9	19
Number of Animals	8	5	5	11
Days from - to	-1 57	7 44	28 44	14 57
Fur, Staining, Yellow				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	28 28
Fur, Thin Cover				
Number of Observations	3	.	3	2
Number of Animals	2	.	1	1
Days from - to	14 28	.	35 44	56 57

Table 1

Summary of Clinical Observations

5002158

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	9.6 ug/dose	29 ug/dose	96 ug/dose
Auditory Canal, Discharge Liq				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Mouth, Discharge Liquid				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Muzzle, Discharge Liquid				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Sneezing				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Breathing, Deep				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Breathing, Labored				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.
Skin Staining				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	29 29	.	.	.

Table 1

Summary of Clinical Observations

5002158

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	9.6 ug/dose	29 ug/dose	96 ug/dose
Pinna Partly Missing				
Number of Observations	4	.	.	.
Number of Animals	1	.	.	.
Days from - to	-11 44	.	.	.

Table 1

Summary of Clinical Observations

5002158

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	9.6 ug/dose	29 ug/dose	96 ug/dose
Skin, Red				
Number of Observations	2	.	.	1
Number of Animals	2	.	.	1
Days from - to	28 49	.	.	-1 -1
Skin, Dry				
Number of Observations	3	.	.	1
Number of Animals	1	.	.	1
Days from - to	21 44	.	.	-1 -1
Skin, Scab				
Number of Observations	5	3	.	7
Number of Animals	4	3	.	3
Days from - to	-1 49	14 28	.	14 44
Fur, Staining, Red				
Number of Observations	23	11	15	31
Number of Animals	9	6	7	11
Days from - to	7 57	14 44	14 44	21 57
Fur, Thin Cover				
Number of Observations	3	2	.	1
Number of Animals	2	1	.	1
Days from - to	42 44	42 44	.	56 56
Pinna Partly Missing				
Number of Observations	.	.	8	.
Number of Animals	.	.	1	.
Days from - to	.	.	-1 44	.
Mass Present				
Number of Observations	.	5	.	.
Number of Animals	.	1	.	.
Days from - to	.	21 44	.	.

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day -6	-1	7	14	21	28	35
1M	Mean	199.4	239.7	309.0	374.3	433.2	487.7	525.0
	SD	7.6	11.1	17.9	25.4	31.6	34.3	35.7
	N	15	15	15	15	15	15	15
2M	Mean	199.7	241.8	309.9	372.1	424.8	471.8	503.6
	SD	4.6	8.0	13.1	17.6	20.9	22.8	26.9
	N	10	10	10	10	10	10	10
	%Diff G1	0.2	0.9	0.3	-0.6	-1.9	-3.3	-4.1
3M	Mean	200.0	243.2	308.2	371.2	424.1	470.2	504.7
	SD	5.0	11.6	20.8	29.0	37.0	43.5	53.0
	N	10	10	10	10	10	10	10
	%Diff G1	0.3	1.4	-0.3	-0.8	-2.1	-3.6	-3.9
4M	Mean	199.4	239.9	297.9	365.2	409.9	459.9	491.9
	SD	7.4	10.4	18.5	28.8	37.4	43.3	50.0
	N	15	15	15	15	15	15	15
	%Diff G1	0.0	0.1	-3.6	-2.4	-5.4	-5.7	-6.3

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day 42	Day 49	Day 56
1M	Mean	559.7	585.0	607.4
	SD	38.2	46.3	46.0
	N	15	5	5
2M	Mean	533.1	--	--
	SD	31.7	--	--
	N	10	--	--
	%Diff G1	-4.7	--	--
3M	Mean	539.1	--	--
	SD	55.5	--	--
	N	10	--	--
	%Diff G1	-3.7	--	--
4M	Mean	529.8	554.4	578.4
	SD	56.1	41.7	41.5
	N	15	5	5
	%Diff G1	-5.3	-5.2	-4.8

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day -7	-1	7	14	21	28	35
1F	Mean	180.1	204.7	230.4	255.7	268.1	286.8	293.3
	SD	8.0	11.2	13.4	15.4	18.3	19.1	18.8
	N	15	15	15	15	15	15	15
2F	Mean	179.5	206.9	234.1	262.0	279.9	293.5	305.9
	SD	5.9	9.9	15.1	18.8	24.6	26.7	30.1
	N	10	10	10	10	10	10	10
	%Diff G1	-0.4	1.1	1.6	2.5	4.4	2.3	4.3
3F	Mean	179.4	212.1	233.9	259.4	271.1	285.7	296.5
	SD	5.7	8.1	11.4	13.0	19.9	22.4	24.4
	N	10	10	10	10	10	10	10
	%Diff G1	-0.4	3.6	1.5	1.5	1.1	-0.4	1.1
4F	Mean	180.3	207.0	226.9	251.6	266.5	284.6	290.5
	SD	7.8	12.3	17.6	23.3	24.4	26.7	26.0
	N	15	15	15	15	15	15	15
	%Diff G1	0.1	1.1	-1.5	-1.6	-0.6	-0.8	-1.0

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day 42	Day 49	Day 56
1F	Mean	306.2	301.0	311.2
	SD	21.7	11.4	8.5
	N	15	5	5
2F	Mean	322.0	--	--
	SD	31.8	--	--
	N	10	--	--
	%Diff G1	5.2	--	--
3F	Mean	304.6	--	--
	SD	24.9	--	--
	N	10	--	--
	%Diff G1	-0.5	--	--
4F	Mean	302.0	310.4	317.6
	SD	28.8	18.6	20.0
	N	15	5	5
	%Diff G1	-1.4	3.1	2.1

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day Change -6 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1M	Mean	40.3	69.3	65.3	58.9	54.5	37.3	34.7
	SD	5.3	9.3	9.7	8.4	7.7	5.2	7.7
	N	15	15	15	15	15	15	15
2M	Mean	42.1	68.1	62.2	52.7	47.0a	31.8	29.5
	SD	7.1	6.9	6.3	5.1	4.9	6.2	9.9
	N	10	10	10	10	10	10	10
3M	Mean	43.2	65.0	63.0	52.9	46.1a	34.5	34.4
	SD	7.8	10.4	9.1	8.4	7.5	10.0	4.2
	N	10	10	10	10	10	10	10
4M	Mean	40.5	57.9b	67.3	44.7c	49.9	32.1	37.9
	SD	5.7	9.2	11.2	10.2	8.7	7.9	7.9
	N	15	15	15	15	15	15	15

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

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day Change -1 - 42	Change 42 - 49	Change 49 - 56	Change 42 - 56
1M	Mean	319.9	20.8	22.4	43.2
	SD	33.0	4.0	4.2	2.6
	N	15	5	5	5
2M	Mean	291.3	--	--	--
	SD	27.0	--	--	--
	N	10	--	--	--
3M	Mean	295.9	--	--	--
	SD	45.0	--	--	--
	N	10	--	--	--
4M	Mean	289.9	21.2	24.0	45.2
	SD	47.9	5.9	4.9	6.5
	N	15	5	5	5

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day Change -7 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1F	Mean	24.5	25.7	25.3	12.5	18.7	6.5	12.9
	SD	6.8	8.5	3.8	5.1	7.3	8.2	6.7
	N	15	15	15	15	15	15	15
2F	Mean	27.4	27.2	27.9	17.9	13.6	12.4	16.1
	SD	8.6	8.9	6.3	8.0	6.0	6.1	5.7
	N	10	10	10	10	10	10	10
3F	Mean	32.7	21.8	25.5	11.7	14.6	10.8	8.1
	SD	9.5	9.9	7.8	10.1	5.9	7.5	8.8
	N	10	10	10	10	10	10	10
4F	Mean	26.7	19.9	24.7	14.9	18.1	5.9	11.5
	SD	7.5	8.0	8.2	4.3	8.5	9.0	9.2
	N	15	15	15	15	15	15	15

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day Change -1 - 42	Change 42 - 49	Change 49 - 56	Change 42 - 56
1F	Mean	101.5	3.4	10.2	13.6
	SD	16.2	4.7	7.0	9.8
	N	15	5	5	5
2F	Mean	115.1	--	--	--
	SD	25.3	--	--	--
	N	10	--	--	--
3F	Mean	92.5	--	--	--
	SD	24.8	--	--	--
	N	10	--	--	--
4F	Mean	95.0	10.4	7.2	17.6
	SD	21.0	7.0	11.0	16.2
	N	15	5	5	5

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day (From/To) -5/1	1/8	8/15	15/22	22/29	29/36	36/43
1M	Mean	30.27	31.11	34.52	35.89	36.27	36.60	36.43
	SD	1.84	1.40	1.94	2.44	2.08	1.91	1.36
	N	15	15	15	15	15	15	15
2M	Mean	30.10	31.33	33.98	34.74	34.13	34.33	34.23
	SD	1.07	0.74	0.72	0.48	1.22	1.74	1.78
	N	10	10	10	10	10	10	10
	%Diff G1	-0.57	0.72	-1.56	-3.20	-5.91	-6.20	-6.03
3M	Mean	29.98	30.92	34.39	34.54	35.05	34.66	34.60
	SD	2.47	2.23	2.11	2.31	2.45	2.49	2.24
	N	10	10	10	10	10	10	10
	%Diff G1	-0.97	-0.60	-0.38	-3.75	-3.37	-5.30	-5.01
4M	Mean	28.85	27.91	33.82	32.37	34.96	33.25	35.29
	SD	1.46	1.30	1.84	2.48	2.37	2.50	2.98
	N	15	15	15	15	15	15	15
	%Diff G1	-4.69	-10.27	-2.03	-9.81	-3.62	-9.14	-3.13

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day (From/To) 43/50	50/56
1M	Mean	35.32	36.64
	SD	0.44	0.60
	N	5	5
2M	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
3M	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
4M	Mean	33.66	36.48
	SD	1.04	0.93
	N	5	5
	%Diff G1	-4.70	-0.44

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day (From/To) -5/1	1/8	8/15	15/22	22/29	29/36	36/43
1F	Mean	19.91	21.43	21.87	22.86	22.30	21.59	22.38
	SD	1.02	1.18	1.19	1.42	1.31	0.90	1.29
	N	15	15	15	15	15	15	15
2F	Mean	21.83	22.27	23.50	24.42	24.24	24.17	24.58
	SD	0.62	1.14	1.36	2.01	2.09	1.86	2.04
	N	10	10	10	10	10	10	10
	%Diff G1	9.63	3.94	7.44	6.82	8.70	11.93	9.83
3F	Mean	21.21	21.74	21.66	22.23	22.27	22.08	22.07
	SD	1.66	1.54	1.03	1.49	1.87	1.59	1.63
	N	10	10	10	10	10	10	10
	%Diff G1	6.51	1.46	-0.98	-2.76	-0.13	2.25	-1.39
4F	Mean	19.90	20.78	21.86	22.27	22.73	21.67	22.91
	SD	0.58	0.96	0.91	0.43	0.82	0.63	1.32
	N	15	15	15	15	15	15	15
	%Diff G1	-0.07	-3.02	-0.06	-2.60	1.91	0.34	2.38

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		Day (From/To) 43/50	50/56
1F	Mean	20.68	21.80
	SD	0.38	0.82
	N	5	5
2F	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
3F	Mean	--	--
	SD	--	--
	N	--	--
	%Diff G1	--	--
4F	Mean	21.66	23.56
	SD	0.22	0.60
	N	5	5
	%Diff G1	4.74	8.07

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1 (pr)	Day 1 (p)	Day 2	Day 43 (pr)	Day 43 (p)	Day 44
1M	Mean	36.76	36.09	36.85	37.11	37.06	36.83
	SD	0.71	0.43	0.35	0.61	0.64	0.66
	N	15	15	15	15	15	15
2M	Mean	36.95	36.63a	36.79	37.65	36.95	36.77
	SD	0.41	0.72	0.25	0.71	0.54	0.24
	N	10	10	10	10	10	10
	%Diff G1	0.52	1.51	-0.17	1.46	-0.30	-0.15
3M	Mean	37.27	37.41c	36.74	38.38c	37.28	37.22
	SD	0.68	0.43	0.32	0.54	0.70	0.59
	N	10	10	10	10	10	10
	%Diff G1	1.39	3.67	-0.31	3.43	0.59	1.07
4M	Mean	36.91	37.74c	37.46c	37.49	38.15c	37.85c
	SD	0.67	0.47	0.51	0.78	0.95	0.53
	N	15	15	15	15	15	15
	%Diff G1	0.42	4.58	1.65	1.04	2.93	2.77

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

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1 (pr)	Day 1 (p)	Day 2	Day 43 (pr)	Day 43 (p)	Day 44
1F	Mean	36.85	37.00	37.12	38.13	37.51	36.81
	SD	0.69	0.53	0.41	0.62	0.58	0.60
	N	15	15	15	15	15	15
2F	Mean	36.75	37.23	36.80	38.17	37.46	36.81
	SD	0.49	0.45	0.47	0.39	0.75	0.60
	N	10	10	10	10	10	10
	%Diff G1	-0.26	0.62	-0.86	0.11	-0.14	-0.01
3F	Mean	37.29	37.48a	36.88	38.41	37.97	36.79
	SD	0.52	0.48	0.63	0.43	0.71	0.38
	N	10	10	10	10	10	10
	%Diff G1	1.20	1.30	-0.65	0.74	1.22	-0.06
4F	Mean	37.07	37.77c	37.35	38.55	38.71c	37.27
	SD	0.58	0.33	0.64	0.40	0.46	0.65
	N	15	15	15	15	15	15
	%Diff G1	0.60	2.09	0.63	1.12	3.18	1.23

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

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1M	Mean	9.447	1.274	7.657	0.282	0.085	0.017	0.129
	SD	2.590	0.648	2.004	0.117	0.024	0.011	0.060
	N	10	10	10	10	10	10	10
2M	Mean	10.602	2.000	7.853	0.353	0.152	0.020	0.227
	SD	3.116	0.637	2.436	0.105	0.031	0.011	0.109
	N	10	10	10	10	10	10	10
	%Diff G1	12.226	56.986	2.560	25.177	78.824	17.647	75.969
3M	Mean	11.923	4.252b	6.995	0.273	0.172a	0.020	0.211
	SD	2.505	1.498	1.834	0.107	0.060	0.008	0.067
	N	10	10	10	10	10	10	10
	%Diff G1	26.209	233.752	-8.646	-3.191	102.353	17.647	63.566
4M	Mean	18.818f	11.404c	6.639	0.234	0.240c	0.025	0.349f
	SD	3.082	3.929	1.893	0.102	0.105	0.015	0.120
	N	10	10	10	10	10	10	8
	%Diff G1	99.196	795.133	-13.295	-17.021	182.353	47.059	170.349

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

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.837	14.27	43.08	55.00	18.22	33.13	12.48
	SD	0.308	0.54	1.60	1.30	0.60	0.46	0.65
	N	10	10	10	10	10	10	10
2M	Mean	7.878	13.99	41.85	53.09b	17.78	33.46	12.41
	SD	0.357	0.70	2.06	0.69	0.34	0.52	0.64
	N	10	10	10	10	10	10	10
	%Diff G1	0.523	-1.96	-2.86	-3.47	-2.41	1.00	-0.56
3M	Mean	7.788	13.83	41.70	53.53a	17.76	33.15	12.60
	SD	0.415	0.70	2.50	1.36	0.38	0.52	0.39
	N	10	10	10	10	10	10	10
	%Diff G1	-0.625	-3.08	-3.20	-2.67	-2.52	0.06	0.96
4M	Mean	8.075	14.09	42.97	53.22b	17.46b	32.79	13.45c
	SD	0.451	0.77	2.32	0.90	0.38	0.37	0.33
	N	10	10	10	10	10	10	10
	%Diff G1	3.037	-1.26	-0.26	-3.24	-4.17	-1.03	7.77

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

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1120.6	238.18
	SD	107.9	34.31
	N	10	10
2M	Mean	1121.1	213.58
	SD	129.9	26.11
	N	10	10
	%Diff G1	0.0	-10.33
3M	Mean	1019.3	201.37a
	SD	175.8	11.88
	N	10	10
	%Diff G1	-9.0	-15.45
4M	Mean	1061.7	196.20b
	SD	100.1	30.46
	N	10	10
	%Diff G1	-5.3	-17.63

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

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	Mean	5.567	0.926	4.359	0.138	0.068	0.006	0.070
	SD	2.216	0.689	1.536	0.066	0.024	0.005	0.046
	N	10	10	10	10	10	10	10
2F	Mean	7.284	1.603	5.270	0.133	0.165a	0.009	0.102
	SD	2.047	0.554	1.605	0.064	0.053	0.006	0.066
	N	10	10	10	10	10	10	10
	%Diff G1	30.842	73.110	20.899	-3.623	142.647	50.000	45.714
3F	Mean	8.004	3.359f	4.212	0.110	0.227c	0.006	0.090
	SD	2.409	1.207	1.520	0.034	0.075	0.007	0.061
	N	10	10	10	10	10	10	10
	%Diff G1	43.776	262.743	-3.372	-20.290	233.824	0.000	28.571
4F	Mean	10.868f	6.310f	4.047	0.126	0.277c	0.012	0.097
	SD	2.513	1.333	1.334	0.076	0.102	0.004	0.051
	N	10	10	10	10	10	10	10
	%Diff G1	95.222	581.425	-7.158	-8.696	307.353	100.000	38.571

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

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.457	13.50	40.25	54.00	18.14	33.58	11.33
	SD	0.215	0.31	1.04	1.30	0.40	0.46	0.22
	N	10	10	10	10	10	10	10
2F	Mean	7.399	13.58	40.41	54.61	18.35	33.63	11.20
	SD	0.314	0.63	1.81	1.23	0.44	0.20	0.50
	N	10	10	10	10	10	10	10
	%Diff G1	-0.778	0.59	0.40	1.13	1.16	0.15	-1.15
3F	Mean	7.158	13.01a	38.78a	54.16	18.19	33.59	11.82a
	SD	0.163	0.38	1.11	0.74	0.38	0.51	0.42
	N	10	10	10	10	10	10	10
	%Diff G1	-4.010	-3.63	-3.65	0.30	0.28	0.03	4.32
4F	Mean	7.363	13.42	39.86	54.17	18.25	33.65	12.32c
	SD	0.319	0.38	1.20	1.82	0.60	0.28	0.35
	N	10	10	10	10	10	10	10
	%Diff G1	-1.261	-0.59	-0.97	0.31	0.61	0.21	8.74

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

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1155.8	202.09
	SD	112.7	31.48
	N	10	10
2F	Mean	970.3a	207.10
	SD	148.6	29.60
	N	10	10
	%Diff G1	-16.0	2.48
3F	Mean	1071.8	191.92
	SD	173.2	25.17
	N	10	10
	%Diff G1	-7.3	-5.03
4F	Mean	887.6c	184.22
	SD	142.2	35.06
	N	10	10
	%Diff G1	-23.2	-8.84

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

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1M	Mean	9.192	1.204	7.520	0.198	0.072	0.022	0.178
	SD	0.687	0.588	0.796	0.090	0.037	0.004	0.070
	N	5	5	5	5	5	5	5
4M	Mean	12.290	1.372	10.320	0.308	0.098	0.026	0.164
	SD	3.447	0.595	2.822	0.086	0.023	0.015	0.036
	N	5	5	5	5	5	5	5
	%Diff G1	33.703	13.953	37.234	55.556	36.111	18.182	-7.865

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.610	14.40	40.98	53.92	18.92	35.06	13.16
	SD	0.643	1.23	2.97	2.15	1.15	0.89	0.86
	N	5	5	5	5	5	5	5
4M	Mean	7.990	14.62	42.56	53.34	18.36	34.44	14.04
	SD	0.566	0.58	1.93	1.93	0.67	0.71	0.29
	N	5	5	5	5	5	5	5
	%Diff G1	4.993	1.53	3.86	-1.08	-2.96	-1.77	6.69

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1003.8	242.88
	SD	187.0	47.23
	N	5	5
4M	Mean	1201.6	243.54
	SD	79.2	24.07
	N	5	5
	%Diff G1	19.7	0.27

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	Mean	4.554	0.776	3.488	0.124	0.094	0.006	0.066
	SD	1.476	0.260	1.492	0.025	0.023	0.005	0.015
	N	5	5	5	5	5	5	5
4F	Mean	4.053	0.573	3.228	0.125	0.065	0.003	0.058
	SD	1.543	0.096	1.327	0.097	0.034	0.005	0.029
	N	4	4	4	4	4	4	4
	%Diff G1	-11.012	-26.224	-7.468	0.806	-30.851	-58.333	-12.879

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.252	13.28	38.68	53.34	18.34	34.34	11.38
	SD	0.372	0.48	1.64	0.89	0.68	0.78	0.26
	N	5	5	5	5	5	5	5
4F	Mean	7.068	13.20	38.53	54.53	18.70	34.33	12.73c
	SD	0.189	0.36	1.44	1.21	0.36	0.56	0.29
	N	4	4	4	4	4	4	4
	%Diff G1	-2.544	-0.60	-0.40	2.22	1.96	-0.04	11.82

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

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1080.2	165.32
	SD	181.5	43.83
	N	5	5
4F	Mean	1009.3	193.65
	SD	36.2	34.22
	N	4	4
	%Diff G1	-6.6	17.14

Table 7

Summary of Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	16.64	15.92	281.9
	SD	0.66	0.76	14.3
	N	10	10	10
2M	Mean	16.29	16.77	445.9c
	SD	0.40	0.75	30.9
	N	10	10	10
	%Diff G1	-2.10	5.34	58.2
3M	Mean	16.13	17.73c	550.4c
	SD	0.82	1.09	56.3
	N	9	9	9
	%Diff G1	-3.04	11.39	95.3
4M	Mean	16.24	18.75c	701.8c
	SD	0.56	1.01	39.3
	N	10	10	10
	%Diff G1	-2.40	17.78	149.0

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

Table 7

Summary of Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	16.92	16.04	214.3
	SD	0.48	1.04	23.9
	N	10	10	10
2F	Mean	16.99	15.93	327.4
	SD	0.50	0.59	41.1
	N	10	10	10
	%Diff G1	0.41	-0.69	52.8
3F	Mean	17.00	16.81	455.1c
	SD	0.45	0.74	48.5
	N	10	10	10
	%Diff G1	0.47	4.80	112.4
4F	Mean	17.65d	18.30f	508.9c
	SD	0.89	0.70	29.1
	N	10	10	10
	%Diff G1	4.31	14.09	137.5

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

Table 7

Summary of Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	18.72	16.08	298.8
	SD	1.29	0.34	93.8
	N	5	5	5
4M	Mean	18.92	15.58	272.8
	SD	0.38	0.47	33.5
	N	5	5	5
	%Diff G1	1.07	-3.11	-8.7

Table 7

Summary of Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	18.04	15.54	201.8
	SD	0.62	1.42	17.3
	N	5	5	5
4F	Mean	17.40	14.98	194.5
	SD	1.10	0.81	27.7
	N	4	4	4
	%Diff G1	-3.55	-3.64	-3.6

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1M	Mean	90.0	32.6	115.6	2.0	414.5	0.063	13.6
	SD	22.9	4.1	21.7	0.0	229.2	0.016	2.1
	N	10	10	10	10	10	10	10
2M	Mean	79.0	38.8	119.2	2.0	290.2	0.051	12.9
	SD	21.7	6.8	13.9	0.0	221.2	0.026	1.7
	N	10	10	10	10	10	10	10
	%Diff G1	-12.2	19.0	3.1	0.0	-30.0	-19.048	-5.1
3M	Mean	101.1	42.4b	106.3	2.0	494.3	0.061	14.3
	SD	24.3	6.4	17.1	0.0	279.9	0.019	2.9
	N	10	10	10	10	10	10	10
	%Diff G1	12.3	30.1	-8.0	0.0	19.3	-3.175	5.1
4M	Mean	99.8	32.6	103.2	2.0	605.2	0.069	13.9
	SD	26.5	7.4	17.4	0.0	388.5	0.025	2.2
	N	10	10	10	10	10	10	10
	%Diff G1	10.9	0.0	-10.7	0.0	46.0	9.524	2.2

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

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	Mean	0.38	149.3	70.2	70.0	5.97	3.81	2.16
	SD	0.04	25.8	13.6	30.5	0.16	0.13	0.14
	N	10	10	10	10	10	10	10
2M	Mean	0.32b	127.1	61.6	66.8	5.91	3.58c	2.33
	SD	0.04	17.9	10.7	26.5	0.14	0.12	0.09
	N	10	10	10	10	10	10	10
	%Diff G1	-15.79	-14.9	-12.3	-4.6	-1.01	-6.04	7.87
3M	Mean	0.39	139.7	65.5	67.7	6.04	3.48c	2.56c
	SD	0.03	21.9	16.0	32.7	0.27	0.11	0.21
	N	10	10	10	10	10	10	10
	%Diff G1	2.63	-6.4	-6.7	-3.3	1.17	-8.66	18.52
4M	Mean	0.40	153.2	65.4	71.1	6.12	3.38c	2.74c
	SD	0.05	27.0	12.9	18.7	0.23	0.13	0.18
	N	10	10	10	10	10	10	10
	%Diff G1	5.26	2.6	-6.8	1.6	2.51	-11.29	26.85

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

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.77	10.52	7.71	142.3	5.31	102.9
	SD	0.16	0.22	0.47	1.3	0.41	1.2
	N	10	10	10	10	10	10
2M	Mean	1.55c	10.64	7.92	142.3	5.07	103.0
	SD	0.07	0.21	0.71	1.2	0.26	1.5
	N	10	10	10	10	10	10
	%Diff G1	-12.43	1.14	2.72	0.0	-4.52	0.1
3M	Mean	1.38c	10.61	7.82	141.7	5.30	102.2
	SD	0.11	0.38	0.64	0.9	0.24	1.4
	N	10	10	10	10	10	10
	%Diff G1	-22.03	0.86	1.43	-0.4	-0.19	-0.7
4M	Mean	1.24c	10.50	8.53a	141.1	5.44	101.0a
	SD	0.10	0.21	0.66	1.2	0.31	2.1
	N	10	10	10	10	10	10
	%Diff G1	-29.94	-0.19	10.64	-0.8	2.45	-1.8

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

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1F	Mean	93.3	31.2	61.1	2.0	381.2	0.081	13.9
	SD	22.0	5.8	16.0	0.0	250.1	0.037	1.4
	N	10	10	10	10	10	10	10
2F	Mean	103.3	31.3	61.8	2.0	501.1	0.060	16.0
	SD	14.9	5.1	11.8	0.0	235.6	0.015	2.5
	N	10	10	10	10	10	10	10
	%Diff G1	10.7	0.3	1.1	0.0	31.5	-25.926	15.1
3F	Mean	117.6	39.6	62.1	2.0	499.2	0.062	15.7
	SD	45.3	23.6	12.2	0.0	346.7	0.018	2.8
	N	10	10	10	10	10	10	10
	%Diff G1	26.0	26.9	1.6	0.0	31.0	-23.457	12.9
4F	Mean	116.6	47.1	69.0	2.0	470.7	0.098	16.0
	SD	28.6	31.4	14.7	0.0	390.8	0.029	2.4
	N	10	10	10	10	10	10	10
	%Diff G1	25.0	51.0	12.9	0.0	23.5	20.988	15.1

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	Mean	0.41	156.1	75.6	50.3	6.52	4.61	1.91
	SD	0.06	30.8	11.6	11.1	0.37	0.37	0.17
	N	10	10	10	10	10	10	10
2F	Mean	0.40	128.4	83.0	55.3	6.23	4.15b	2.08
	SD	0.05	22.4	22.7	30.3	0.29	0.30	0.20
	N	10	10	10	10	10	10	10
	%Diff G1	-2.44	-17.7	9.8	9.9	-4.45	-9.98	8.90
3F	Mean	0.47a	126.6	77.4	42.6	6.41	4.09b	2.32c
	SD	0.05	14.9	12.1	8.1	0.29	0.30	0.15
	N	10	10	10	10	10	10	10
	%Diff G1	14.63	-18.9	2.4	-15.3	-1.69	-11.28	21.47
4F	Mean	0.48a	134.6	67.7	52.0	6.47	4.03b	2.44c
	SD	0.06	13.7	22.5	16.9	0.44	0.35	0.13
	N	10	10	10	10	10	10	10
	%Diff G1	17.07	-13.8	-10.4	3.4	-0.77	-12.58	27.75

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

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.45	10.63	6.95	141.7	4.73	103.4
	SD	0.30	0.25	1.19	1.3	0.25	2.1
	N	10	10	10	10	10	10
2F	Mean	2.02	10.73	7.85	142.4	4.73	103.7
	SD	0.30	0.41	0.69	0.8	0.32	1.8
	N	10	10	10	10	10	10
	%Diff G1	-17.55	0.94	12.95	0.5	0.00	0.3
3F	Mean	1.77c	10.69	7.46	142.1	4.77	103.7
	SD	0.21	0.24	0.80	1.4	0.22	1.6
	N	10	10	10	10	10	10
	%Diff G1	-27.76	0.56	7.34	0.3	0.85	0.3
4F	Mean	1.65c	10.76	7.31	142.1	4.80	103.1
	SD	0.10	0.44	1.25	0.9	0.30	1.4
	N	10	10	10	10	10	10
	%Diff G1	-32.65	1.22	5.18	0.3	1.48	-0.3

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

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1M	Mean	101.2	60.4	132.8	2.0	496.8	0.090	18.0
	SD	37.7	9.8	21.7	0.0	438.4	0.034	2.7
	N	5	5	5	5	5	5	5
4M	Mean	77.0	36.4b	110.2	2.0	426.8	0.082	16.4
	SD	30.0	9.3	26.1	0.0	488.3	0.020	3.0
	N	5	5	5	5	5	5	5
	%Diff G1	-23.9	-39.7	-17.0	0.0	-14.1	-8.889	-8.9

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

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	Mean	0.36	226.8	78.4	143.2	5.86	3.72	2.14
	SD	0.05	37.8	12.5	69.6	0.17	0.26	0.34
	N	5	5	5	5	5	5	5
4M	Mean	0.32	191.6	72.2	88.2	5.98	3.88	2.10
	SD	0.04	33.1	13.0	16.0	0.24	0.16	0.24
	N	5	5	5	5	5	5	5
	%Diff G1	-11.11	-15.5	-7.9	-38.4	2.05	4.30	-1.87

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.78	10.72	7.32	139.4	5.44	100.8
	SD	0.35	0.19	0.63	1.1	0.38	1.5
	N	5	5	5	5	5	5
4M	Mean	1.90	10.92	7.56	140.0	5.20	101.4
	SD	0.24	0.40	0.66	0.7	0.31	1.1
	N	5	5	5	5	5	5
	%Diff G1	6.74	1.87	3.28	0.4	-4.41	0.6

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1F	Mean	126.8	42.0	48.8	2.0	863.8	0.068	15.8
	SD	19.8	8.7	11.0	0.0	236.3	0.024	2.7
	N	5	5	5	5	5	5	5
4F	Mean	89.6a	39.4	57.2	2.0	197.2c	0.062	14.8
	SD	27.4	10.3	14.7	0.0	44.0	0.026	1.3
	N	5	5	5	5	5	5	5
	%Diff G1	-29.3	-6.2	17.2	0.0	-77.2	-8.824	-6.3

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

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	Mean	0.42	137.8	74.2	73.4	6.40	4.58	1.82
	SD	0.04	25.8	11.2	44.0	0.31	0.36	0.11
	N	5	5	5	5	5	5	5
4F	Mean	0.40	144.8	77.6	51.2	6.30	4.38	1.92
	SD	0.07	18.7	19.5	8.5	0.41	0.39	0.08
	N	5	5	5	5	5	5	5
	%Diff G1	-4.76	5.1	4.6	-30.2	-1.56	-4.37	5.49

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.54	11.02	6.06	139.6	4.70	101.6
	SD	0.30	0.24	0.92	0.9	0.14	1.3
	N	5	5	5	5	5	5
4F	Mean	2.28	10.86	6.58	139.8	4.66	102.6
	SD	0.22	0.43	0.78	0.4	0.24	2.1
	N	5	5	5	5	5	5
	%Diff G1	-10.24	-1.45	8.58	0.1	-0.85	1.0

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	68.251	19.900
	SD	14.318	4.283
	N	10	10
2	Mean	166.674	28.669
	SD	39.974	16.938
	N	10	10
	% Diff (G1)	144	44
3	Mean	294.610 F	158.635 E
	SD	55.663	130.148
	N	10	10
	% Diff (G1)	332	697
4	Mean	467.607 F	1180.908 F
	SD	51.225	516.141
	N	10	10
	% Diff (G1)	585	5834

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Females

Group 1 - Reference Item
Group 2 - mRNA-1443 9.6 µg/dose
Group 3 - mRNA-1443 29 µg/dose
Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	39.036	23.679
	SD	24.230	6.360
	N	10	10
2	Mean	130.096	32.994
	SD	33.274	21.332
	N	10	10
	% Diff (G1)	233	39
3	Mean	251.813 F	52.681
	SD	58.668	24.036
	N	10	10
	% Diff (G1)	545	122
4	Mean	449.381 F	261.184 F
	SD	93.459	158.723
	N	10	10
	% Diff (G1)	1E3	1003

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 57
Males

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	144.768	20.964
	SD	137.871	6.791
	N	5	5
4	Mean	88.570	36.180
	SD	22.372	15.887
	N	5	5
	% Diff (G1)	-39	73

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 57
Females

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	50.728	27.554
	SD	6.036	19.138
	N	5	5
4	Mean	58.860	36.956
	SD	5.834	19.806
	N	5	5
	% Diff (G1)	16	34

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IL-1β (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	144.712	48.938	21.000	18.972	20.558
	SD	190.687	77.310	21.734	19.162	20.142
	N	5	5	5	5	5
4	Mean	5.850	93.748	5.850	11.078	91.646
	SD	0.000	134.613	0.000	11.690	131.767
	N	5	5	5	5	5
	% Diff (G1)	-96	92	-72	-42	346

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IL-6 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	176.000	176.000	176.000	176.000	176.000
	SD	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5
4	Mean	176.000	176.000	176.000	444.630	176.000
	SD	0.000	0.000	0.000	371.335	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	153	0

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

TNF-α (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	1.470	2.490	2.490	2.372	2.430
	SD	0.000	2.281	2.281	2.017	2.147
	N	5	5	5	5	5
4	Mean	2.710	2.710	3.052	3.828	1.470
	SD	2.773	2.773	3.537	3.356	0.000
	N	5	5	5	5	5
	% Diff (G1)	84	9	23	61	-40

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IP-10 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	201.838	146.606	110.802	167.726	209.122
	SD	87.765	49.771	36.821	160.721	295.657
	N	5	5	5	5	5
4	Mean	170.262	222.820	308.492 d	484.112 a	100.256
	SD	42.451	102.577	198.023	149.175	23.377
	N	5	5	5	5	5
	% Diff (G1)	-16	52	178	189	-52

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

MIP-1-α (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	5.850	5.850	5.850	5.850	5.850
	SD	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5
4	Mean	5.850	5.850	5.850	5.850	5.850
	SD	0.000	0.000	0.000	0.000	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	0	0

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

MCP-1 (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	303.614	295.866	439.954	280.644	174.794
	SD	148.431	130.748	122.121	194.300	143.055
	N	5	5	5	5	5
4	Mean	465.994	328.254	467.394	450.566	70.500
	SD	102.423	151.067	103.422	103.609	0.000
	N	5	5	5	5	5
	% Diff (G1)	53	11	6	61	-60

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IL-1β (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	33.063	15.046	5.850	16.698	16.956
	SD	54.425	20.563	0.000	24.257	24.834
	N	4	5	5	5	5
4	Mean	12.602	5.850	9.962	5.850	38.250
	SD	15.098	0.000	9.195	0.000	72.449
	N	5	5	5	5	5
	% Diff (G1)	-62	-61	70	-65	126

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IL-6 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	176.000	176.000	176.000	176.000	176.000
	SD	0.000	0.000	0.000	0.000	0.000
	N	4	5	5	5	5
4	Mean	176.000	176.000	176.000	317.472	176.000
	SD	0.000	0.000	0.000	316.341	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	80	0

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

TNF-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	1.470	1.470	1.470	1.470	1.470
	SD	0.000	0.000	0.000	0.000	0.000
	N	4	5	5	5	5
4	Mean	1.470	1.470	1.470	3.856	1.470
	SD	0.000	0.000	0.000	3.267	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	162	0

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

IP-10 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	108.658	99.730	84.002	82.884	80.284
	SD	19.848	21.463	26.730	17.756	9.052
	N	4	5	5	5	5
4	Mean	122.778	196.752	522.986 d	566.746	87.108
	SD	21.355	172.662	359.718	487.335	39.147
	N	5	5	5	5	5
	% Diff (G1)	13	97	523	584	8

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

MIP-1-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	5.850	5.850	5.850	5.850	5.850
	SD	0.000	0.000	0.000	0.000	0.000
	N	4	5	5	5	5
4	Mean	5.850	5.850	5.850	9.546	5.850
	SD	0.000	0.000	0.000	8.265	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	0	0	63	0

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)

Table 10

Summary of Cytokine Values

MCP-1 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1443 96 µg/dose

Group	Summary Information	Day 1 - 6 h Post Dose	15 - 6 h Post Dose	29 - 6 h Post Dose	43 - 6 h Post Dose	57
1	Mean	70.500	236.046	326.604	158.990	128.104
	SD	0.000	155.429	176.570	121.308	128.806
	N	4	5	5	5	5
4	Mean	519.054 b	440.528 d	544.322 a	439.100 d	70.500
	SD	251.811	76.306	90.075	64.682	0.000
	N	5	5	5	5	5
	% Diff (G1)	636	87	67	176	-45

Significantly different from control group (Group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (*t*-test)
d - $P \leq 0.05$ e - $P \leq 0.01$ f - $P \leq 0.001$ (Wilcoxon)