charles river

FINAL REPORT

Test Facility Study No. 5002034

A 6-Week (4 doses) Intramuscular Injection Toxicity Study of mRNA-1647 in Sprague-Dawley Rats Followed by a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
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USA

TEST FACILITY:
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QUALITY ASSURANCE STATEMENT

Study Number: 5002034

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	Study Plan Amendment 1	20-Mar-2017	20-Mar-2017
23-Mar-2017	Addition of Study Plan to Provantis	23-Mar-2017	23-Mar-2017
23-Mar-2017	Study Plan Amendment 2	23-Mar-2017	23-Mar-2017
05-Apr-2017	Dose Preparation	05-Apr-2017	05-Apr-2017
06-Apr-2017	Draize Evaluation	06-Apr-2017	06-Apr-2017
18-Apr-2017	Study Plan Amendment 3	18-Apr-2017	18-Apr-2017
04-May-2017	Necropsy	04-May-2017	04-May-2017
05-May-2017	Study Plan Amendment 4	05-May-2017	05-May-2017
11-May-2017	Biochemistry	11-May-2017	11-May-2017
22-Jun-2017	Data Review - Veterinary Services	30-Jun-2017	30-Jun-2017
23-Jun-2017	Data Review - Animal Care	30-Jun-2017	30-Jun-2017
23-Jun-2017 - 27-Jun-2017	Data Review - Technical Operations	30-Jun-2017	30-Jun-2017
27-Jun-2017	Data Review - Formulations	30-Jun-2017	30-Jun-2017
27-Jun-2017 - 28-Jun-2017	Data Review - Clinical Pathology	30-Jun-2017	30-Jun-2017
27-Jun-2017	Data Review - Technical Operations	30-Jun-2017	30-Jun-2017
28-Jun-2017	Study Plan Amendment 5	28-Jun-2017	28-Jun-2017
28-Jun-2017	Data Review - Shipping/Receiving	30-Jun-2017	30-Jun-2017
28-Jun-2017	Report Preparation	30-Jun-2017	30-Jun-2017
28-Jun-2017	Data Review - Necropsy	30-Jun-2017	30-Jun-2017
28-Jun-2017 - 29-Jun-2017	Data Review - Histology	30-Jun-2017	30-Jun-2017
29-Jun-2017	Draft Phase Report - Ophthalmology	30-Jun-2017	30-Jun-2017
29-Jun-2017 - 30-Jun-2017	Draft Report - Materials and Methods	30-Jun-2017	30-Jun-2017
29-Jun-2017	Report Preparation	30-Jun-2017	30-Jun-2017
29-Jun-2017	Data Review - Shipping/Receiving	30-Jun-2017	30-Jun-2017
25-Aug-2017 - 26-Aug-2017	Final Report	28-Aug-2017	28-Aug-2017
29-Aug-2017 31-Aug-2017 - 01-Sep-2017	Data Review - Analytical Chemistry	01-Sep-2017	01-Sep-2017
29-Aug-2017 31-Aug-2017 - 01-Sep-2017	Draft Phase Report - Dose Formulation Analysis	01-Sep-2017	01-Sep-2017
18-Sep-2017	Study Plan Amendment 6	18-Sep-2017	18-Sep-2017

QUALITY ASSURANCE STATEMENT - Study Number: 5002034

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
25-Sep-2017	Final Report	26-Sep-2017	26-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.

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, anti-therapeutic antibody and PBMCs were conducted using scientifically qualified methods and in accordance with all applicable analytical procedures.
- The purity analysis of the bulk test item was conducted using a scientifically qualified methods and in accordance with 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, QC, Canada
Analytical Chemistry (Concentration, and Particle size and Purity Analysis)	[redacted] BSc Charles River Laboratories Montreal ULC Senneville, QC, Canada
Immunology (Cytokine, Alpha-2 Macroglobulin and Alpha-1 Glycoprotein Analysis)	[redacted] MSc Charles River Laboratories Montreal ULC Sherbooke, QC, Canada

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

Pathology	[redacted] DVM, DACVP, DABT Charles River Laboratories, Inc. Durham, NC, USA

1.4. PIs at Sponsor or Sponsor-designated Test Site(s)

Anti-Therapeutic Antibody Analysis	[redacted] Integrated BioTherapeutics, Inc. Rockville, MD, USA
PBMC Analysis	[redacted] Southern Research Birmingham, AL, USA

2. SUMMARY

The objectives of this study were to determine the potential toxicity of mRNA 1647, 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[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)	No. of Animals			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1647	10/8.9	200	0.05/0.045	10	10	-	-
3	mRNA-1647	30/27	200	0.15/0.14	10	10	-	-
4	mRNA-1647	100/89	200	0.5/0.45	10	10	5	5

- : Not applicable
[a] Values based on Summary of Analysis (SoA) issued on 16 Mar 2017 / Values based on SoA issued on 31 May 2017 (Refer to memorandum in Appendix 2).

The following parameters and endpoints were evaluated in this study: clinical observations consisting of twice daily examinations for mortality/moribundity and weekly detailed examinations; local irritation assessment at least 24- and 72-hour postdose on dosing days and weekly when there were no dosing and during the recovery period; weekly body weights and food consumption measurements; ophthalmic examinations once prior to dosing initiation and during Day 40 (males) or Day 39 (females) of the dosing period; body temperature on Days 1 and 43 at predose and 6 and 24 hours postdose (end of each group); clinical pathology assessment (hematology, coagulation, clinical chemistry, α1-acid glycoprotein and α2-macroglobulin) at termination; cytokine analysis (IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α and MCP-1) on Days 1, 15, 29 and 43 at 6 hours postdose and on Day 57; Anti-Therapeutic Antibody (ATA) analysis prior to dosing initiation, on Day 29 (predose), on Day 43 (postdose) and on Day 57; PBMC analysis on Day 44; gross necropsy findings, organ weights, and histopathologic examinations.

There were no mRNA-1647-related changes in food consumption and ophthalmology.

There were no mRNA-1647-related mortalities during the course of the study. One male given the Reference Item (PBS) was found dead on Day 43. The pathological evaluation revealed gross abnormal findings in the adrenal gland , kidneys , thymus; and lungs. Histopathology findings for this control male were incidental and did not explain the cause of death.

mRNA-1647-treated main study and recovery animals had significant detectable antibody responses against CMV gB protein and CMV gH pentamer complex.

mRNA-1647 elicited both CD4 and CD8 T cell responses to both CMV Pentamer and gB. T cell response (PBMC analysis) were significantly variable within each test group with data trending towards higher T cells responses at higher doses of mRNA-1647.

The primary mRNA-1647-related findings were observed at the site of injection. At all doses, increase in incidence and/or severity with dose of very slight to severe edema was noted at the injection site, following dosing of males and females (peaking 24 hours postdose, generally decreasing by 72 hours postdose). Although sporadic in occurrences, slight to moderately severe erythema was noted as well, but was only considered mRNA-1647-related at 89 µg/dose. Swelling (soft or firm), noted on the injection site following the third and/or fourth doses, together with localized skin redness at the injection site noted throughout the dosing period, were consistent with the edema and erythema findings. Macroscopically, dose-dependent firm abnormal consistency, dark foci and/or swelling at the injection site correlated with microscopic changes observed at all doses that included minimal to moderate mixed cell inflammation involving the subcutaneous tissues, skeletal muscle, and to a lesser extent the dermis, as well as minimal to moderate subcutaneous edema. Increased incidence and/or severity of minimal to marked mixed cell inflammation was seen in the popliteal and/or inguinal lymph nodes (draining) of all animals at ≥ 8.9 µg/dose which correlated macroscopically with enlargement; minimal to marked mixed cell inflammation was frequently observed in the perineurial tissue surrounding the sciatic nerve of animals given ≥ 8.9 µg/dose. Sciatic nerve and lymph node inflammatory changes were regarded as secondary to the injection site inflammation. mRNA-1647-related microscopic findings were still noted at the injection site and sciatic nerve of recovery animals; minimal to mild mononuclear cell infiltration and minimal mixed cell inflammation were seen respectively in the injection site and on the sciatic nerves of males and/or females given 89 µg/dose. The absence of mixed cell inflammation and edema, with a shift to minimal to mild mononuclear cell infiltration, at the intramuscular injections sites and a reduced incidence and/or severity of perineurial mixed cell inflammation associated with the sciatic nerves were however all indicative of a partial recovery. Clinical signs (i.e. edema, swelling, erythema and reddening of the skin) observed at the injection site and gross pathology findings as well as microscopic findings observed at the inguinal and popliteal lymph nodes were no longer observed in recovery animals, indicating a complete recovery for these changes.

mRNA-1647-related systemic changes associated with inflammation were also observed in animals given ≥ 27 µg/dose and included minimally increased hematopoiesis of the myeloid lineage in the bone marrow. This change was likely a reactive response to the pronounced inflammation observed at the injection site. Other systemic findings included increases in absolute and/or relative spleen weights without correlating histopathology, and minimal to mild decreased cellularity of the splenic periarteriolar lymphoid sheath. Clinical pathology changes suggestive of inflammation were also observed in males and/or females given mRNA-1647 at all doses (unless noted otherwise) and included: minimal to moderate increases in neutrophil, eosinophil and large unstained cell counts with concomitant increases in white blood cell counts, minimal decreases in lymphocyte counts and platelet counts (females at 89 µg/dose), minimal increases in activated partial thromboplastin time and mild increases in fibrinogen, minimal increases in globulin, minimal decreases in albumin, with concomitant decreases in A/G ratio. Increase in body temperature postdose (89 µg/dose), along with increases in acute phase protein Alpha-1-Glycoprotein and Alpha-2-Macroglobulin and elevations of cytokine levels IP-10

(89 µg/dose) and MCP-1, were all suggestive of inflammation. At the end of the 2-week recovery period, Alpha-2-Macroglobulin levels were still higher than controls, but to a lesser extent, the incidence and severity of increased absolute and/or relative spleen weights was reduced, as well as the decrease in cellularity of the periarteriolar lymphoid sheath in the spleen, suggesting only a partial recovery for these aforementioned findings. All other mRNA-1647-related systemic changes returned close to control values and, as such, were considered fully recovered.

When compared to controls, following each dose, a tendency towards lower mean body weight gains was noted in males given ≥ 8.9 µg/dose and in females given 89 µg/dose; these changes sometimes reached statistical significance. The changes were only cumulative in males. There were no clear association of the body weight changes with food consumption or clinical observations. The body weight changes were generally comparable or rebounded during the 2-week recovery period.

In conclusion, administration of mRNA-1647 by intramuscular injection for 6 weeks (4 doses) was clinically well tolerated (no mortality, major decreases in body weight and no changes in food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 89 µg/dose. Starting at 8.9 µg/dose, generally dose-dependent changes in clinical signs at the injection site, clinical pathology parameters, cytokines and acute protein levels were consistent with an inflammatory response at the injection site. Dose-related target organ effects were limited to the injection site, the bone marrow, the inguinal and popliteal lymph nodes, the connective tissue surrounding the sciatic nerve and the spleen of animals given mRNA-1647. At the end of the 2-week recovery period, all changes were partially or fully recovered.

3. INTRODUCTION

The objectives of this study were to determine the potential toxicity of mRNA 1647, 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 Nov 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 22 Mar 2017 (males) and on 23 Mar 2017 (females). The in-life phase of the study was completed on 05 May 2017 (main study animals) and on 18 May 2017 (recovery study animals), the date of the last necropsy. The experimental start date was 08 Mar 2017, and the experimental completion date is 20 Sep 2017 (signature of the pathology report). The study plan, study plan amendments, and deviations are presented in Appendix 1.

4. MATERIALS AND METHODS

4.1. Test Item

Identification:	mRNA-1647
Batch (Lot) No.:	MTDP17015
Retest Date:	An end-of-use analysis of the bulk Test Item was performed to demonstrate the stability of the Test Item during the dosing period.
Physical Description:	White to off-white lipid nanoparticle dispersion
Concentration:	2.7 / 2.4*mg/mL
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 31 May 2017

4.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS) pH 7.2
Batch (Lot) No.:	1809319 1854892 1759866 1830677
Expiration Date:	Jul 2018 Dec 2018 Feb 2018 Sep 2018
Physical Description:	Liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C

4.3. Test and Reference Item Characterization

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

4.4. Analysis of Test Item

A sample (2 vials) of the Test Item were 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 analytical laboratory at the Test Facility for purity analysis.

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

4.5. Reserve Samples

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

4.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, and storage and disposition of Test and Reference Items were maintained. With the exception of reserve samples, all unused Test and Reference Items were returned to the Sponsor after completion of dosing.

4.7. Dose Formulation and Analysis

(Appendix 3)

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.

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

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.

4.7.3.1. Analytical Method

Analyses described below were performed by IEX-HPLC using a validated analytical procedure (CR-MTL Study No.1802050).

4.7.3.2. Concentration and Homogeneity Analysis

On Days 1 and 43 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 except for Group 1 dosing formulation and on day 43 where only concentration analysis were required; the formulation was then only sampled from the middle stratum.

Concentration results were considered acceptable if mean sample concentration results were within or equal to ± 15% of theoretical concentration. Each individual sample concentration result was considered acceptable if it was within or equal to ± 20%. After acceptance of the analytical results, backup samples were discarded.

Homogeneity results were considered acceptable if 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 was 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 March 2017, one hundred and twenty Crl:CD(SD) Sprague-Dawley rat (60 males and 60 females) were received from Charles River Canada Inc., St. Constant, QC, Canada. The animals were 08 weeks old and males weighed between 235 and 297 grams and females weighed between 195 and 248 grams at initiation of dosing.

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 14 days was allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment (refer to Appendix 1).

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

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

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

The alternate animals were used as replacements on the study within approximately 4 days.

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 all along the study. The rooms 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, except when interrupted for designated procedures.

4.8.6.3. Food

PMI Nutrition International Certified Rodent Chow No. 5CR4 (14% protein) was provided ad libitum throughout the study, except during designated procedures. The same diet in meal form was provided to one female animal from Group 4 as warranted by clinical signs (broken/damaged incisors). On few occasions, wet pellets were also provided to Group 4 animals as warranted by clinical signs.

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 are 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).

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

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

4.8.6.5. 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 (Skin scab) to non-toxic pen used for marking the injection area was observed for control Animals Nos. 1510 and 1514 on Day 21 and 38, respectively. Consequently, no marking of the injection site was performed for these animals after that day.

4.9. Experimental Design

Text Table 3
Experimental Design

Group No.	Test Material	Dose Level[a] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[a] (mg/mL)	Animals No.			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	1001-1010	1501-1510	1011-1015	1511, 1612, 1513-1515
2	mRNA-1647	10/8.9	200	0.05/0.045	2001, 2102, 2003-2010	2501-2510	-	-
3	mRNA-1647	30/27	200	0.15/0.14	3001, 3002, 3103, 3004-3010	3501-3503, 3604, 3505-3510	-	-
4	mRNA-1647	100/89	200	0.5/0.45	4001-4010	4501-4510	4011-4015	4511-4515

- : Not applicable
[a] Values based on SoA issued on 16 Mar 2017 / Values based on SoA issued on 31 May 2017.

Prior to the start of dosing, animals were rejected from the study due to compromising background ophthalmic findings and were replaced with spare animals. The final allocation of animals is listed under Text Table 3. All animals remaining unassigned to groups after Day 4 (males) or 3 (females) were released from the study and their disposition, documented.

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; site 2= right). 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 (refer to Section 4.8.6.6 for exceptions). Hair may have been clipped or shaved, if required, to improve visualization of the injection sites. The injection site was documented in the raw data for each dose administered.

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 to be 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 during the dosing and recovery periods, beginning during Week -1.

4.10.3. Local Irritation Assessment

On days of dosing and at least 24 and 72 hours postdose (end of each group), all animals had the dose injection site examined for signs of erythema/edema. 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 during Day -1. A fasted weight was recorded on the day of necropsy. Terminal body weight was not collected from animals found dead.

4.10.5. Food Consumption

Food consumption was quantitatively measured starting on Day -9 and weekly throughout the dosing and recovery periods (refer to Appendix 1 for additional details).

4.10.6. Ophthalmic Examinations

Animals had funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations once prior to dosing (all animals) and on Day 40 for males and Day 39 for females. As there were no Test Item-related ophthalmoscopic findings at 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). After first dose administration, body temperature of Group 4 female animals was monitored until 48 post dose, after which body temperature normal range (36.0°C to 38.0°C) was recovered.

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-macroglobulin
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 EDTA as anticoagulant) were analyzed for the parameters specified in Text Table 5.

Text Table 5
Hematology Parameters

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

A blood smear was prepared from each hematology sample. Blood smears were labeled, stained, and stored. 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 plasma was analyzed for the parameters listed in Text Table 6.

Text Table 6
Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality

4.11.1.4. Clinical Chemistry

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

Text Table 7
Clinical Chemistry Parameters

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

4.11.1.5. 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 10 minutes in a refrigerated centrifuge (set to maintain 4°C) at 2400 g. Samples were processed to serum by the Immunology Department. Serum were 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 (Cytokines Analysis)

Blood was collected from the jugular vein of recovery animals. After collection, 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)** (refer to Appendix 1 for one exception)	**EDTA**
Centrifugation setting			[redacted]	[redacted]
Timepoints			**Sample Type**	
Day	**Hrs**	**Males/ Females No.**	IFN-α*	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	1011-1015, 4011-4015	X	X
15	6		X	X
29	6	1511, 1612, 1513-1515, 4511-4515	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 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 to be 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.

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

4.11.3. Anti-Therapeutic Antibody (ATA) Analysis

Before the initiation of dosing, on Day 29 (before dose administration, all animals), on Day 43 (post dose administration, main animals only) and on Day 57 (recovery animals), 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 ambient room temperature until centrifugation, which was carried out as soon as practical. The samples were centrifuged for 10 minutes in a refrigerated centrifuge (set to maintain 4°C) at 1200 g. 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 until shipment on dry ice to Integrated BioTherapeutics, Inc., Rockville, MA, USA for analysis.

The samples were analyzed for rat anti-CMV antibodies using a qualified ELISA method.

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

4.12. 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 main animals only. Samples were shipped at controlled temperature set to maintain 21°C via overnight courier to Southern research, Birmingham, AL, for whole blood stimulation and cytokine analysis.

The PBMC samples were analyzed using a qualified method.

An Immunology Report for PBMC analysis is included as an appendix to the Final Report.

4.13. 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]
Unscheduled Deaths				X	X	-	Full Tissue[a]	Full Tissue[a]

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

4.13.1. Unscheduled Deaths

A complete necropsy was conducted for one control animal assigned to recovery study that died during dosing, and specified tissues were saved. Animal was refrigerated before necropsy to minimize autolysis.

4.13.2. 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.

4.13.3. Necropsy

Main study and recovery animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices;

cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues.

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

4.13.4. Organ Weights

The organs identified in Text Table 10 were weighed at necropsy for all scheduled euthanasia animals. Organ weights were not recorded for animal found dead. Paired organs were weighed together. In the event of gross abnormalities, in addition to the combined weight, the weight of each organ of a pair may be taken and entered as a tissue comment. Organ to body weight ratio (using the terminal body weight) and organ to brain weight ratios were calculated.

Text Table 10
Organs Weighed at Necropsy

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

[a] Paired organ weight.

4.13.5. 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	Lung
Bone marrow smear	Lymph node, mandibular
Bone marrow	Lymph node, mesenteric
Bone, femur	Lymph node, Inguinal[e]
Bone, sternum	Lymph node, Popliteal[e]
Brain[d]	Small intestine, duodenum
Cervix	Small intestine, ileum
Epididymis	Small intestine, jejunum
Esophagus	Muscle, skeletal
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] Seven brain levels examined included olfactory bulb (Examine in Body cavity, nasal section level 4).
[e] Lymph node draining the last administration site used (unilateral examination).

4.13.6. Histology

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

4.13.7. Histopathology

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

4.13.8. Peer Review

(Appendix 20)

A pathology peer review was conducted by a Sponsor-designated pathologist; [redacted] PhD from Experimental Pathology Laboratories, Inc., Research Triangle Park, NC 27709, USA.

The peer review statement was included as an appendix to the Final Report.

4.13.9. Bone Marrow Smear Analysis

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

5. CONSTRUCTED VARIABLES

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

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

6. STATISTICAL ANALYSIS

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

Text Table 12
Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Hematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Cytokines	X
Body Temperature	X
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 parametric assumption at the 5% significance level. 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.

All significant pairwise comparisons were reported at the 0.1, 1, and 5% significance levels.

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 and/or formulation activities
In-house reporting software Nevis (using SAS)	Nevis 2 (SAS 9.2)	Statistical analyses of numerical in-life, clinical pathology and postmortem data
Mesa Laboratories AmegaView CMS	v3.0 Build 1208.8	Continuous Monitoring System. Monitoring of standalone fridges, freezers, incubators, and selected laboratories to measure temperature, relative humidity, and CO_2, as appropriate
Johnson Controls Metasys	MVE 7.0 and 4.0	Building Automation System. Control of HVAC and other building systems, as well as temperature/humidity control and trending in selected laboratories and animal rooms
Empower 3 (Waters Corporation)	Build 3471 SR1	Data acquisition for dose formulation analysis, including regression analysis and measurement of concentration and recovery of dose formulations using HPLC
Bio Plex Manager (Bio-Rad)	6.1	Cytokine data collection
Softmax Pro GxP	5.4.6	Cytokine data collection
Watson LIMS	7.4.2 SP1	Sample tracking/analysis/regression - biomarkers
Dynamics (Wyatt)	7.1.9.3	Data acquisition for particle size analysis for the test item using DLS

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 CRL-MTL 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 Archival location and duration are detailed in the applicable PI report(s) or details regarding the retention of the materials were provided to the Study Director for inclusion in the Final Report.

All records, retained samples and specimens, and reports generated from phases or segments performed by Sponsor-designated subcontractors were returned to the Test Facility for archiving Archival location and duration are detailed in the applicable PI report(s) or details regarding the retention of the materials were provided to the Study Director for inclusion in the Final Report.

9. RESULTS

9.1. Dose Formulation Analyses

(Appendix 3)

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

9.2. End of Use Bulk Test Item Analysis

(Appendix 3)

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

9.3. Mortality

(Appendix 4)

There were no mRNA-1647-related mortalities during the course of the study.

One male (No. 1014) given the Reference Item was found dead on Day 43. The pathological evaluation revealed a small, dark discoloration, and soft abnormal consistency of the right adrenal gland without histopathology correlates; a dark discoloration of the corticomedullary junction of the kidneys without histopathology correlates; a dark focus and dark discoloration of the thymus (incidental thymic hemorrhage); and a failure of the lungs to collapse (lung congestion). Histopathology findings for this control male were incidental and did not explain the cause of death for this animal.

9.4. Clinical Observations

(Table 1 and Appendix 5)

On the day following the last dosing occasion, a dose-related (in severity) soft swelling was noted on the last injection site (i.e. the right hindlimb). Firm swelling (severe) was also noted at the injection site of individual males and females given 89 µg/dose. The firm swelling was noted two days following the third dose and, for one male only, 1 day following the last dose. In addition, skin redness at the injection site, was noted at a higher incidence throughout the dosing period for animals given 89 µg/dose.

Given the absence of swelling or redness at the injection site 3 days following the last dose and throughout the recovery period, these clinical observations were considered fully reversed.

9.5. Local Irritation Assessment

(Appendix 5)

Slight to severe edema was noted at the injection site following dosing of males and females given ≥ 8.9 µg/dose. The incidence and severity of these findings were dose-dependent. The apex of severity was noted 24 hours postdose and generally decreased 72 hours postdose.

Sporadic, slight to (rare) moderately severe erythema, noted at the injection site, was considered mRNA-1647-related only at 89 µg/dose and occurred generally following the third and fourth (last) doses.

Edema and erythema were no longer observed one week into 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 6 and Appendix 7)

When compared to controls, following each dose, a tendency towards lower mean body weight gains was noted in males given ≥ 8.9 µg/dose and in females given 89 µg/dose; these changes sometimes reached statistical significance. The changes were only cumulative in males and were down to 0.86X controls from Day -1 to 42. The body weight changes were generally comparable or rebounded during the 2-week recovery period.

9.7. Food Consumption

(Table 4 and Appendix 8)

Given the variability in weekly food consumption results, the occasional weekly changes, with no clear dose-relationship, were considered not mRNA-1647-related.

9.8. Opthalmology

(Appendix 15)

There were no mRNA-1647-related ocular changes observed during the course of the study. The findings noted were age-related or incidental in origin and to be expected in this population of animals.

9.9. Body Temperature

(Table 5 and Appendix 9)

In general body temperatures were within normal ranges of 36-38°C . When compared to control animals and pre-dose body temperature measurements, the mean body temperature appeared minimally increased in males and females given 89 µg/dose, 6 and/or 24 hours post Day 1 and Day 43 doses. These statistically-significant changes were considered mRNA-1647-related.

9.10. Hematology

(Table 6 and Appendix 10)

mRNA-1647-related hematology changes were noted for males and females starting at 8.9 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) and platelet (PLT) counts. These changes are illustrated in Text Table 14.

Text Table 14
Hematology Changes

Dose (µg/dose)	8.9		27		89	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
WBC						
Day 44	-	1.2	1.3	**1.4**	**1.8**	**1.8**
Day 57					1.1	1.1
NEUT						
Day 44	1.8	4.6	**4.4**	**6.2**	**7.2**	**8.9**
Day 57					0.63	0.95
LYMPH						
Day 44	0.84	0.73	0.74	0.73	0.77	0.83
Day 57					1.2	1.2
EOS						
Day 44	**2.6**	**4.0**	**2.8**	**3.9**	**3.8**	**6.5**
Day 57					1.0	1.2
LUC						
Day 44	**2.2**	1.9	**2.2**	2.1	1.8	2.0
Day 57					1.1	0.81
PLT						
Day 44	-	-	-	-	-	**0.82**
Day 57					-	1.1

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

Mild to moderate increases in WBC counts (up to 1..8X controls for both genders) were noted in males given ≥ 27 µg/dose and females given ≥ 8.9 µg/dose, mainly due to minimal to moderate increases in NEUT, LUC (up to 7.2X and 2.2X controls for males and 8.9X and 2.1X controls for females) and/or EOS (up to 3.8X controls for males and up to 6.5X controls for females). Minimal decreases in LYMPH counts were noted for males and females at ≥ 8.9 µg/dose (down to 0.74X and 0.73X controls, respectively).

Minimal decreases in PLT were noted in females given 89 µg/dose (0.82X controls).

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

Any other differences in hematology parameters, including those attaining statistical significance, were judged to be due to individual or biological variation or lacked true dose relationship and therefore were considered not mRNA-1647-related.

9.11. Coagulation

(Table 7 and Appendix 11)

mRNA-1647-related increases in activated partial thromboplastin time (APTT) and in fibrinogen (FIB) were noted in males and females given ≥ 8.9 µg/dose. The changes are illustrated in Text Table 15.

Text Table 15
Coagulation Changes

Dose (µg/dose)	8.9		27		89	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
APTT						
Day 44	1.1	**1.2**	**1.1**	**1.2**	**1.2**	**1.2**
Day 57					0.99	0.96
FIB						
Day 44	**1.7**	**1.7**	**1.9**	**1.9**	**2.1**	**2.1**
Day 57					0.95	1.1

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

Minimal increases in APTT were noted for males and females given ≥ 8.9 µg/dose (up to 1.2X controls for both genders). Mild increases in FIB were noted for males and females given ≥ 8.9 µg/dose (up to 2.1X controls for both genders). At the end of the 2-week recovery period, changes 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-1647-related.

9.12. Clinical Chemistry

(Table 8 and Appendix 12)

mRNA-1647-related decreases in albumin (ALB) and increases in globulin (GLOB) were noted for males and females; these changes were reflected by overall decrease in A/G ratio. The changes are illustrated in Text Table 16.

Text Table 16
Clinical Chemistry Changes

Dose (µg/dose)	8.9		27		89	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
ALB						
Day 44	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**	**0.9**
Day 57					1.0	**0.9**
GLOB						
Day 44	**1.2**	**1.2**	**1.2**	**1.2**	**1.3**	**1.2**
Day 57					**0.9**	1.0
A/G						
Day 44	**0.8**	**0.8**	**0.8**	**0.8**	**0.7**	**0.7**
Day 57					**1.1**	0.9

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

Minimal decreases in ALB and minimal increases in GLOB were noted for males and females given ≥ 8.9 µg/dose (0.9X controls and up to 1.3X controls respectively) and affected the A/G ratio (down to 0.7X controls, for both genders). At the end of the 2-week recovery period, changes 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-1647-related.

9.13. Alpha-1-Acid Glycoprotein

(Table 9, Appendix 13 and Appendix 18)

When compared to controls, statistically-significant dose-related increases in Alpha-1-Glycoprotein were noted in males and females, following the dosing period.

Following the 2-week recovery period, the concentrations of Alpha-1-Glycoprotein were comparable in both the controls and the males and females that were previously given 89 µg/dose, suggesting a full recovery.

9.14. Alpha-2-Macroglobulin

(Table 9, Appendix 13 and Appendix 18)

When compared to controls, dose-related increases in Alpha-2-Macroglobulin was noted in males and females, following the dosing period.

Following the 2-week recovery period, the concentrations of Alpha-2-Macroglobulin were still slightly higher than controls, suggesting only a partial recovery.

9.15. Cytokines

(Table 10, Appendix 14 and Appendix 18)

When compared to controls, statistically-significant higher concentrations of IP-10 were observed in both genders given 89 µg/dose at all timepoints, except on Day 57 (end of recovery) where the IP-10 concentrations were comparable to control levels. The highest IP-10 concentrations were generally observed 6 hours post Day 1 dose.

Higher concentrations of MCP-1 were noted in Test Item-given females on Days 1, 15 and 29, 6 hours postdose; the increases were statistically significant. MCP-1 concentrations were comparable to control levels on Day 57.

No mRNA-1647-related changes were observed in IL-1β, IL-6, MIP-1α and TNF-α levels.

9.16. Anti-Therapeutic Antibody (ATA)

(Appendix 16)

The Day 43 samples from mRNA-1647-treated Main Study animals had detectable antibody responses against CMV gB protein and CMV gH pentamer complex. The Day 57 samples from Recovery Study animals previously given 89 µg/dose had similar antibody titers compared to Day 43 titers.

9.17. PBMC

(Appendix 17)

T-cell responses were evaluated by assessment of Interferon gamma (INFγ) producing T cells. The results are detailed in the following tables.

Summary of Pentamer Specific INF γ Response

	Group	Test material	N	Dose level (µg)	Pentamer specific CD4+ T Cells Range (%)*;	Mean (%);	SD	Pentamer specific CD8+ T Cells Range (%)*;	Mean (%);	SD
Males	1	Reference	9	0	0.00-0.46;	0.03;	0.30	0.00-0.32;	0.01;	0.23
	2	mRNA-1647	10	8.9	0.00-1.20;	0.04;	0.52	0.00-2.73;	0.43;	0.88
	3	mRNA-1647	10	27	0.00-0.46;	0.08;	0.25	0.00-0.74;	0.21;	0.33
	4	mRNA-1647	10	89	0.00-6.99;	0.90;	2.19	0.00-8.96;	1.29;	2.83
Females	1	Reference	10	0	0.00-1.13;	0.02;	0.70	0.00-0.33;	0.01;	0.24
	2	mRNA-1647	10	8.9	0.00-1.39;	0.09;	0.78	0.00-3.91;	1.10;	1.61
	3	mRNA-1647	10	27	0.00-2.16;	0.34;	1.01	0.00-2.70;	0.69;	1.30
	4	mRNA-1647	10	89	0.00-3.16;	0.31;	1.42	0.00-4.35;	0.95;	1.56

Summary of Glycoprotein B Specific INF γ Response

	Group	Test material	N	Dose level (µg)	Glycoprotein specific CD4+ T Cells Range (%)*;	Mean (%);	SD	Glycoprotein specific CD8+ T Cells Range (%)*;	Mean (%);	SD
Males	1	Reference	9	0	0.00-0.57;	0.00;	0.31	0.00-0.12;	0.00;	0.17
	2	mRNA-1647	10	8.9	0.00-0.79;	0.00;	0.38	0.00-0.26;	0.00;	0.13
	3	mRNA-1647	10	27	0.00-0.91;	0.15;	0.35	0.00-0.64;	0.13;	0.28
	4	mRNA-1647	10	89	0.00-3.17;	0.53;	0.99	0.00-4.52;	0.46;	1.46
Females	1	Reference	10	0	0.00-0.79;	0.04;	0.41	0.00-0.69;	0.13;	0.36
	2	mRNA-1647	10	8.9	0.00-1.30;	0.03;	0.92	0.00-0.00;	0.00;	0.37
	3	mRNA-1647	10	27	0.00-2.15;	0.08;	1.28	0.00-4.17;	0.71;	1.62
	4	mRNA-1647	10	89	0.00-3.00;	0.00;	1.62	0.00-4.76;	0.79;	1.96

* For purpose of Range and Mean calculation, value <0.00 following unstimulated Control subtration were set to 0.00 for reporting

Maximal antigen-specific response was observed at 89 µg/dose for both Pentamer and Glycoprotein B peptide libraries. The Pentamer library produced the stronger response of the two antigen libraries with an individual maximal response in males of up to 6.99 and 8.96% in CD4+ and CD8+ T cells, respectively. The largest response to Glycoprotein B stimulation was at 89 µg/dose in males for CD4+ T cells at 3.17%, and in females at 4.76% for CD8+ T cells.

9.18. Gross Pathology

(Appendix 19)

9.18.1. Terminal Necropsy (Day 44)

mRNA-1647-related gross pathology findings are summarized in Text Table 17.

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

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**8.9**	**27**	**89**	**0**	**8.9**	**27**	**89**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Site, Injection (No. Examined)	10	10	10	10	10	10	10	10
Abnormal consistency, firm	0	1	5	9	0	3	5	7
Swelling	0	5	6	9	0	5	5	7
Focus, dark	0	0	0	0	0	1	1	3
Lymph Node, Inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	1	1	0	5	0	0	0	1
Lymph Node, Popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	7	7	0	8	6	7

At the intramuscular injection sites, dose-dependent mRNA-1647-related gross pathology observations of abnormal firm consistency, dark focus, and/or swelling were noted in animals given ≥ 8.9 µg/dose. These gross observations correlated microscopically with mixed cell inflammation of the subcutaneous and/or muscular tissue and/or subcutaneous edema at the injection site.

In the draining inguinal and/or popliteal lymph nodes, mRNA-1647-related gross enlargement was noted in animals given ≥ 8.9 µg/dose, and correlated microscopically to mixed cell inflammation. Gross enlargement and microscopic mixed cell inflammation most commonly involved the popliteal lymph nodes. Gross enlargement of the inguinal lymph node was noted in one male given the Reference Item, without any correlating microscopic finding.

Other gross pathology findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1647-related.

9.18.2. Recovery Necropsy (Day 57)

(Appendix 19)

There were no mRNA-1647-related gross pathology findings observed at the end of the 2-week recovery period.

All gross pathology findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1647-related.

9.19. Organ Weights

(Appendix 19)

9.19.1. Terminal Necropsy (Day 44)

(Appendix 19)

mRNA-1647-related organ weight changes are summarized in Text Table 18.

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

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**8.9**	**27**	**89**	**8.9**	**27**	**89**
No. Animals per Group	**10**	**10**	**10**	**10**	**10**	**10**
Spleen (No. Weighed)	10	10	10	10	10	10
Absolute weight	1.0794	1.0824	**1.2070** [b]	0.7125	**0.7566** [a]	**0.7934** [b]
% of body weight	**0.21190** [a]	**0.21678** [a]	**0.23429** [c]	0.22732	**0.24041** [b]	**0.25394** [c]
% of brain weight	48.79592	49.81185	**55.10209** [b]	34.70430	**36.98272** [a]	**38.80259** [b]

[a] Significantly different from Group 1value p≤0.05 (Dunnett).
[b] Significantly different from Group 1 value p≤0.01 (Dunnett).
[c] Significantly different from Group 1 value p≤0.001 (Dunnett).
Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – P ≤ 0.05; refer to data tables for actual significance levels and tests used.

In the spleen, slight dose-dependent increases in absolute and/or relative organ weights were noted in males and females given ≥ 8.9 µg/dose. These changes were consistently statistically significant for increases in absolute and/or relative (to body and/or to brain) weights in males given 89 µg/dose and females given ≥ 27 µg/dose. These splenic weight changes were not correlated with any specific histopathology finding.

No other mRNA-1647-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or related to difference of sexual maturity and not mRNA-1647-related.

9.19.2. Recovery Necropsy (Day 57)

(Appendix 19)

mRNA-1647-related increased spleen weights noted at the terminal necropsy were also observed at the end of the 2-week recovery period and are summarized in Text Table 19.

Text Table 19
Summary of Organ Weight Data – Recovery Necropsy (Day 57)

	Males			Females		
Group	**2**	**3**	**4**	**2**	**3**	**4**
Dose (µg/dose)	**8.9**	**27**	**89**	**8.9**	**27**	**89**
No. Animals per Group	**0**	**0**	**5**	**0**	**0**	**5**
Spleen (No. Weighed)	0	0	5	0	0	5
Absolute value	-	-	1.1022	-	-	0.6522
% Difference	-	-	+18.90	-	-	+9.65
% of body weight	-	-	**0.18856** [a]	-	-	0.20057
% Difference	-	-	+21.50	-	-	+11.74
% of brain weight	-	-	48.35552	-	-	31.90101
% Difference	-	-	+19.86	-	-	+11.58

[a] Significantly different from Group 1 value p≤0.05 (T-Test).
Based upon statistical analysis of group means, values highlighted in bold are significantly different from Group 1– P ≤ 0.05; refer to data tables for actual significance levels and tests used.

In the spleen, a slight increase in absolute and/or relative organ weights were noted in males and females given 89 µg/dose. These changes were not statistically significant, with the exception of mean spleen weight relative to final body weight in the males; and thus, were considered to have limited toxicological importance. These splenic weight changes were not correlated with any specific histopathology finding.

No other mRNA-1647-related organ weight changes were noted. There were other isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, other organ weight differences observed were considered incidental and/or related to difference of sexual maturity and not mRNA-1647-related.

9.20. Histopathology

(Appendix 19)

9.20.1. Terminal Necropsy (Day 44)

(Appendix 19)

mRNA-1647-related microscopic pathology findings were noted at the injection sites, the draining lymph nodes (popliteal and/or inguinal), sciatic nerve, bone marrow, and spleen and these findings are summarized in Text Table 20

Text Table 20
Summary of Microscopic Findings – Terminal Necropsy (Day 44)

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (µg/dose)	0	8.9	27	89	0	8.9	27	89
No. Animals Examined	10	10	10	10	10	10	10	10
Site, Injection (No. Examined)	10	10	10	10	10	10	10	10
Inflammation: mixed cell; subcutaneous	0	10	9	10	0	10	10	10
Minimal	-	1	0	0	0	1	1	1
Mild	-	6	3	4	0	7	8	2
Moderate	-	3	6	6	0	2	1	7
Edema; subcutaneous	0	5	8	9	0	6	8	10
Minimal	-	2	0	2	-	2	2	0
Mild	-	3	2	3	-	3	4	3
Moderate	-	0	6	4	-	1	2	7
Degeneration; myofiber	5	7	9	6	5	5	8	6
Minimal	5	7	8	5	4	4	6	6
Mild	0	0	1	1	1	1	2	0
Lymph Node, Popliteal (No. Examined)	10	10	10	10	10	10	10	10
Inflammation; mixed cell	0	2	10	9	0	10	10	10
Minimal	-	0	2	1	-	4	2	0
Mild	-	2	4	3	-	6	7	5
Moderate	-	0	4	4	-	0	1	5
Marked	-	0	0	1	-	0	0	0
Lymph Node, Inguinal (No. Examined)	10	10	10	10	10	10	10	10
Inflammation; mixed cell	0	0	1	3	0	0	0	0
Minimal	-	-	1	1	-	-	-	-
Mild	-	-	0	2	-	-	-	-
Sciatic Nerve (No. Examined)	10	10	10	10	10	10	10	10
Inflammation; mixed; perineurial	0	10	10	10	0	10	10	10
Minimal	-	0	2	1	-	4	3	1
Mild	-	2	4	1	-	2	4	1
Moderate	-	3	4	8	-	4	3	7
Marked	-	5	0	0	-	0	0	1
Bone Marrow (No. Examined)	10	10	10	10	10	10	10	10
Increased hematopoiesis; myeloid	0	0	4	9	0	0	2	9
Minimal	-	-	4	9	-	-	2	9
Spleen (No. Examined)	10	10	10	10	10	10	10	10
Decreased cellularity; periarteriolar lymphoid sheath	0	5	9	10	0	7	10	10
Minimal	-	1	5	3	-	5	6	1
Mild	-	4	4	7	-	2	4	9

Localized tissue reactions involved the intramuscular injection sites, the draining popliteal and/or inguinal lymph nodes, and the sciatic nerves. Systemic tissue reactions involved the bone marrow and spleen.

At the intramuscular injection sites, there was a dose-related inflammatory reaction characterized by minimal to moderate mixed cell inflammation involving the subcutaneous tissues, skeletal muscle, and to a lesser extent the dermis, as well as associated minimal to moderate subcutaneous edema and minimal to mild myofiber degeneration in animals given ≥ 8.9 µg/dose. The inflammatory reaction, which increased in severity with increasing dose, often extended along and expanded endomysial and perimysial tissue layers, encircling individual muscle fibers

and/or bundles. This reaction was characterized by varying numbers of intact and degenerating neutrophils, mononuclear cells, and macrophages (mixed cell inflammation); accumulations of protein-rich fluid (edema); and varying degrees of myofiber degeneration.

In the draining popliteal and/or inguinal lymph nodes, an increased incidence and/or severity of minimal to marked mixed cell inflammation were noted in animals given ≥ 8.9 µg/dose. The inflammation often involved the adventitia surrounding the lymph nodes, and most commonly involved the popliteal lymph nodes.

Minimal to marked mixed cell inflammation was frequently observed in the perineurial tissue surrounding the sciatic nerve of animals given ≥ 8.9 µg/dose. This finding was considered to be an extension of the inflammatory reaction at the intramuscular injection sites to this region.

In the bone marrow, minimal increased myeloid hematopoiesis was noted in animals given ≥ 27 µg/dose. This finding was characterized by increased numbers of myeloid precursors in the marrow, and was secondary or compensatory inflammatory reaction noted at the intramuscular injection sites.

In the spleen, a dose-dependent minimal to mild decreased cellularity of the periarteriolar lymphoid sheath was noted in animals given ≥ 8.9 µg/dose.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1647-related.

9.20.2. Recovery Necropsy (Day 57)

(Appendix 19)

Following the 2-week recovery period, microscopic pathology findings seen at the terminal necropsy were no longer present in the draining lymph nodes (popliteal and/or inguinal), consistent with a complete recovery of these findings.

Microscopic findings noted at the terminal necropsy were also observed at the recovery necropsy at the injection sites (however, a shift to mononuclear cell infiltration rather than mixed cell inflammation was observed), sciatic nerve, bone marrow, and spleen and these findings are summarized in Text Table 21.

Text Table 21
Summary of Microscopic Findings – Recovery Necropsy (Day 57)

	Males		Females	
Group	1	4	1	4
Dose (µg/dose)	0	89	0	89
No. Animals Examined	4	5	4	5
Site, Injection (No. Examined)	4	5	5	5
Infiltration, mononuclear cell; myofiber	0	2	0	5
Minimal	-	1	-	4
Mild	-	1	-	1
Nerve, Sciatic	4	5	5	5
Inflammation, mixed cell; perineurial	0	0	0	2
Minimal	-	-	-	2
Bone Marrow (No. Examined)	4	5	5	5
Increased hematopoiesis; myeloid	0	2	0	1
Minimal	-	2	-	1
Spleen (No. Examined)	4	5	5	5
Decreased cellularity; periarteriolar lymphoid sheath	0	2	0	0
Minimal	-	2	-	-

At the intramuscular injection sites, there was a residual inflammatory reaction characterized by minimal to mild mononuclear cell infiltration involving the subcutaneous tissues and skeletal muscle at 89 µg/dose. Minimal to mild myofiber degeneration did not differ in incidence or severity from the Reference Item-treated group.

Mixed cell inflammation involving the draining lymph nodes (popliteal and/or inguinal) and sciatic nerves, as noted as the terminal euthanasia, was not noted at the recovery necropsy, consistent with complete recovery.

Minimal mixed cell inflammation was observed in the perineurial tissue surrounding the sciatic nerve of females given 89 µg/dose. The incidence and severity of this finding was reduced compared to the terminal necropsy.

In the bone marrow, minimal increased myeloid hematopoiesis was noted in animals given 89 µg/dose. The incidence of this finding was reduced compared to the terminal necropsy.

In the spleen, a minimal decreased cellularity of the periarteriolar lymphoid sheath was noted in males given 89 µg/dose. The incidence and severity of this finding was reduced compared to the terminal necropsy.

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of rats, and/or were of similar incidence and severity in Reference and Test Item-treated animals and, therefore, were considered not mRNA-1647-related.

10. CONCLUSION

In conclusion, administration of mRNA-1647 by intramuscular injection for 6 weeks (4 doses) was clinically well tolerated (no mortality, major decreases in body weight and no changes in food consumption or deleterious changes in hematology, coagulation or clinical chemistry parameters) in rats up to 89 µg/dose. Starting at 8.9 µg/dose, generally dose-dependent changes in clinical signs at the injection site, clinical pathology parameters, cytokines and acute protein levels were consistent with an inflammatory response at the injection site. Dose-related target organ effects were limited to the injection site, the bone marrow, the inguinal and popliteal lymph nodes, the connective tissue surrounding the sciatic nerve and the spleen of animals given mRNA-1647. At the end of the 2-week recovery period, all changes were partially or fully recovered.

Figure 1

Summary of Body Weights - Males

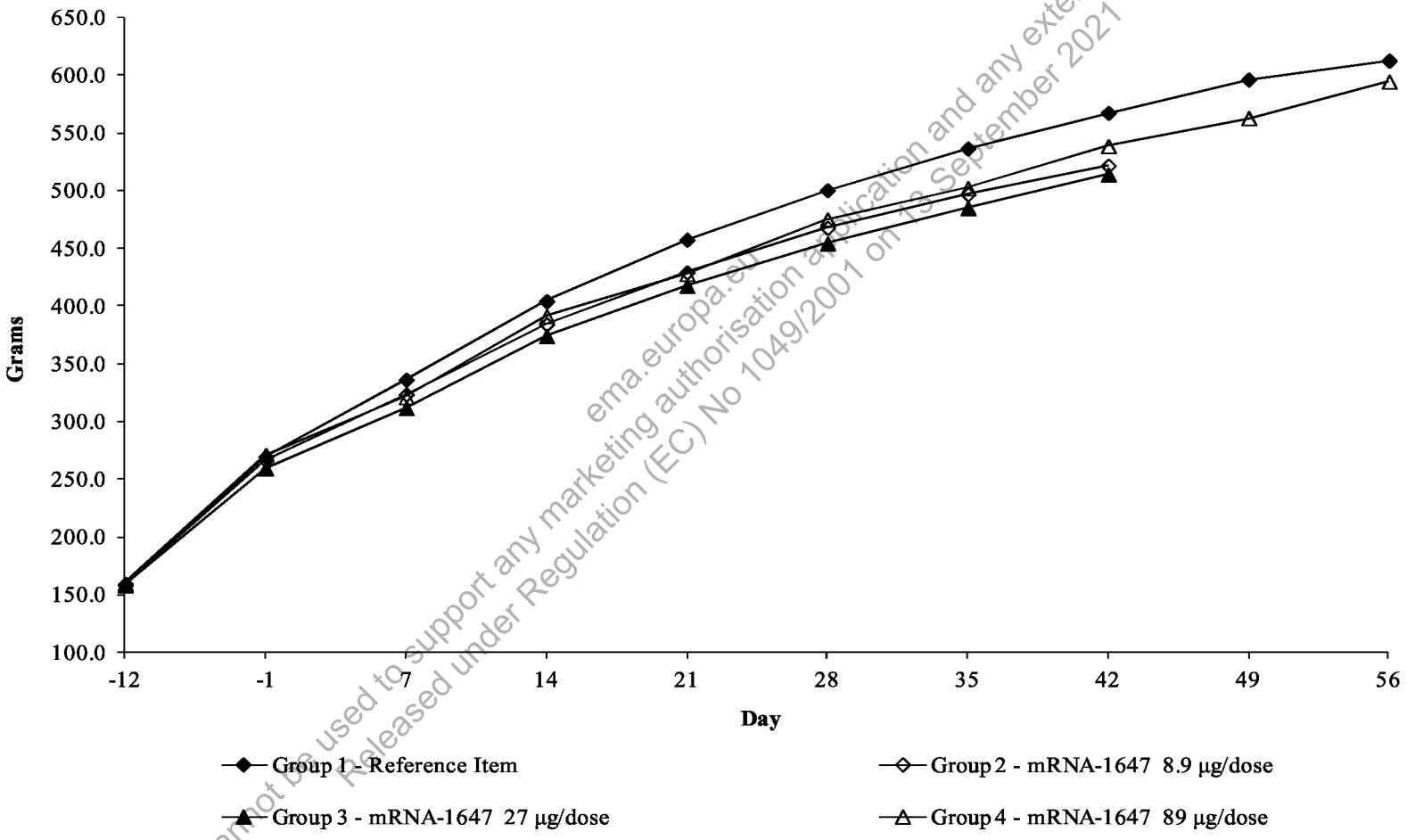

Figure 2

Summary of Body Weights - Females

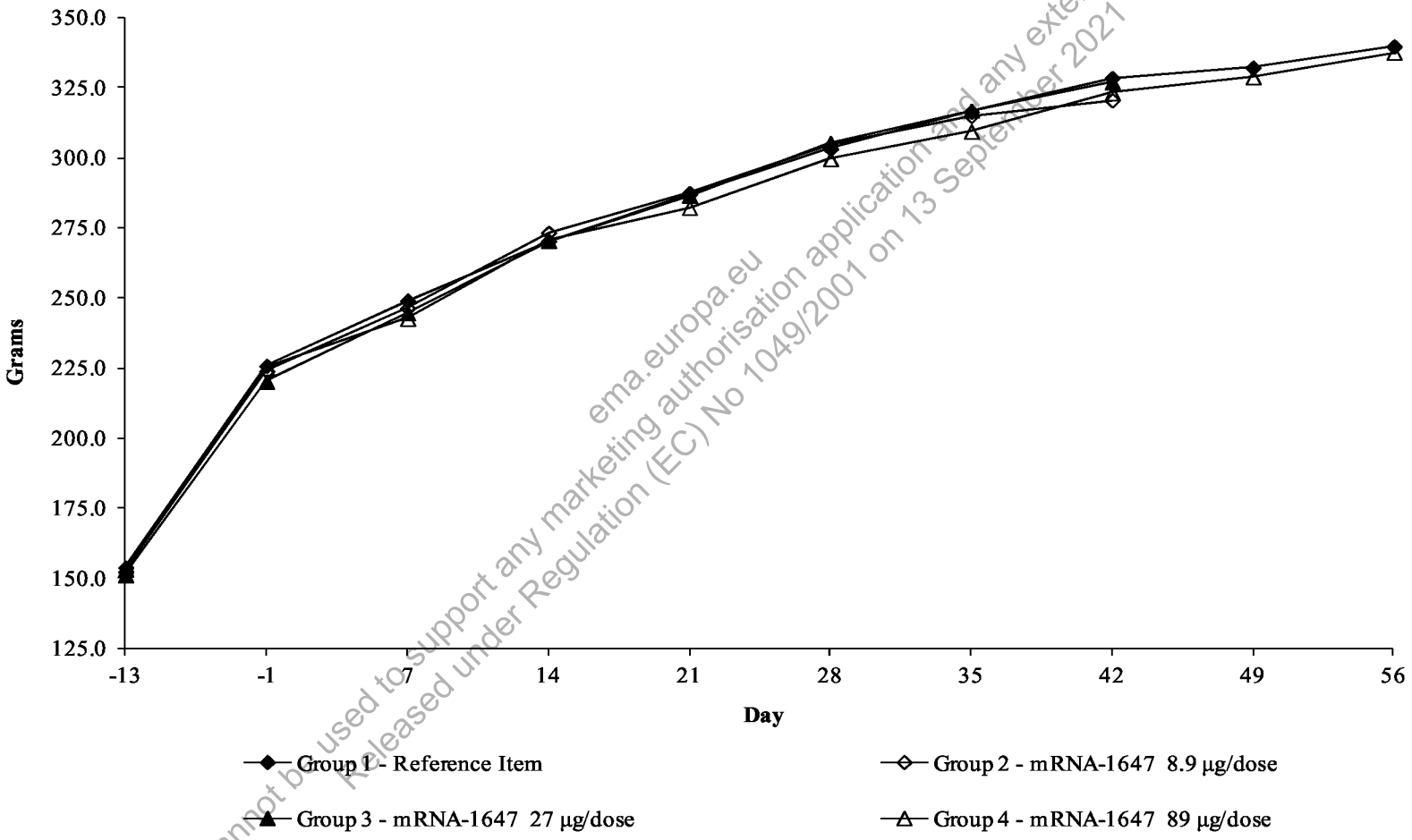

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Swollen Soft				
Number of Observations	.	10	13	13
Number of Animals	.	10	10	12
Days from - to	.	44 44	28 44	31 45
Swollen Firm				
Number of Observations	.	.	.	4
Number of Animals	.	.	.	3
Days from - to	.	.	.	31 44
Skin, Red				
Number of Observations	2	7	1	7
Number of Animals	2	2	1	6
Days from - to	7 44	14 44	14 14	31 45
Skin, Lesion w/ Discharge				
Number of Observations	.	1	.	.
Number of Animals	.	1	.	.
Days from - to	.	-1 -1	.	.
Skin, Scab				
Number of Observations	3	11	1	4
Number of Animals	3	4	1	2
Days from - to	7 44	-1 44	14 14	28 35
Fur, Erected				
Number of Observations	.	2	2	1
Number of Animals	.	2	2	1
Days from - to	.	44 44	44 44	44 44
Fur, Staining, Red				
Number of Observations	.	5	.	9
Number of Animals	.	2	.	3
Days from - to	.	28 44	.	14 57

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Fur, Thin Cover				
Number of Observations	3	1	.	1
Number of Animals	1	1	.	1
Days from - to	28 42	44 44	.	44 44
Malocclusion				
Number of Observations	.	.	7	.
Number of Animals	.	.	1	.
Days from - to	.	.	7 44	.
Testis, Enlarged				
Number of Observations	.	1	.	.
Number of Animals	.	1	.	.
Days from - to	.	28 28	.	.
Digit Bent				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	44 44	.

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Hyperreactive				
Number of Observations	.	3	.	.
Number of Animals	.	1	.	.
Days from - to	.	35 44	.	.
Hypersensitive				
Number of Observations	.	.	.	8
Number of Animals	.	.	.	1
Days from - to	.	.	.	7 44
Vocalization Increased				
Number of Observations	.	.	.	8
Number of Animals	.	.	.	1
Days from - to	.	.	.	7 44
Caught in Cage				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	28 28	.
Swollen Soft				
Number of Observations	.	10	11	14
Number of Animals	.	10	10	13
Days from - to	.	44 44	7 44	31 45
Swollen Firm				
Number of Observations	.	.	.	10
Number of Animals	.	.	.	10
Days from - to	.	.	.	31 31
Warm to Touch				
Number of Observations	.	.	.	2
Number of Animals	.	.	.	2
Days from - to	.	.	.	44 44

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Skin, Red				
Number of Observations	4	.	3	35
Number of Animals	2	.	2	15
Days from - to	21 38	.	7 35	17 56
Skin, Dry				
Number of Observations	7	.	.	9
Number of Animals	2	.	.	5
Days from - to	21 49	.	.	21 57
Skin, Lesion				
Number of Observations	1	.	1	.
Number of Animals	1	.	1	.
Days from - to	-1 -1	.	35 35	.
Skin, Lesion w/ Discharge				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	28 28	.
Skin, Scab				
Number of Observations	11	.	8	14
Number of Animals	4	.	5	7
Days from - to	-1 49	.	7 44	28 57
Fur, Staining, Red				
Number of Observations	11	6	5	9
Number of Animals	6	1	1	4
Days from - to	35 57	14 44	21 44	21 57
Fur, Thin Cover				
Number of Observations	16	.	9	1
Number of Animals	4	.	2	1
Days from - to	28 57	.	-14 44	57 57

Table 1

Summary of Clinical Observations

5002034

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	8.9 ug/dose	27 ug/dose	89 ug/dose
Teeth, Broken				
Number of Observations	.	.	.	8
Number of Animals	.	.	.	1
Days from - to	.	.	.	-1 44
Skin Staining				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	44 44	.

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day -12	-1	7	14	21	28	35
1M	Mean	159.5	269.5	336.4	404.4	457.7	500.5	536.7
	SD	5.0	13.5	19.3	27.8	31.4	36.3	40.5
	N	15	15	15	15	15	15	15
2M	Mean	158.3	266.7	323.6	384.4	429.3a	467.9	497.0a
	SD	5.2	12.1	17.6	23.3	30.0	42.9	48.7
	N	10	10	10	10	10	10	10
	%Diff G1	-0.7	-1.0	-3.8	-4.9	-6.2	-6.5	-7.4
3M	Mean	158.3	259.3	312.0b	374.1b	417.6b	454.3b	484.9b
	SD	6.1	7.6	10.7	15.1	20.2	25.3	28.9
	N	10	10	10	10	10	10	10
	%Diff G1	-0.7	-3.8	-7.3	-7.5	-8.8	-9.2	-9.7
4M	Mean	159.5	271.2	321.2a	391.5	428.1a	475.3	502.3a
	SD	4.8	14.9	16.2	20.1	22.6	26.0	27.2
	N	15	15	15	15	15	15	15
	%Diff G1	0.0	0.6	-4.5	-3.2	-6.5	-5.0	-6.4

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

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day 42	Day 49	Day 56
1M	Mean	567.5	596.3	612.8
	SD	46.3	44.3	45.5
	N	15	4	4
2M	Mean	521.8a	--	--
	SD	52.1	--	--
	N	10	--	--
	%Diff G1	-8.0	--	--
3M	Mean	514.1b	--	--
	SD	34.1	--	--
	N	10	--	--
	%Diff G1	-9.4	--	--
4M	Mean	538.7	563.0	594.6
	SD	29.2	27.1	25.9
	N	15	5	5
	%Diff G1	-5.1	-5.6	-3.0

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

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day -13	-1	7	14	21	28	35
1F	Mean	153.9	225.9	249.1	270.4	287.0	303.3	316.5
	SD	7.0	15.5	17.2	22.3	22.5	26.9	29.3
	N	15	15	15	15	15	15	15
2F	Mean	152.4	223.9	246.5	273.3	287.4	304.4	315.0
	SD	5.1	13.6	19.6	27.0	31.3	33.5	35.2
	N	10	10	10	10	10	10	10
	%Diff G1	-1.0	-0.9	-1.1	1.1	0.1	0.4	-0.5
3F	Mean	151.2	220.2	244.7	270.4	286.6	305.3	316.9
	SD	6.0	12.2	18.0	26.6	25.6	31.2	33.1
	N	10	10	10	10	10	10	10
	%Diff G1	-1.8	-2.5	-1.8	0.0	-0.1	0.7	0.1
4F	Mean	153.1	225.1	242.7	270.6	282.3	299.5	309.4
	SD	6.5	9.2	13.6	18.7	20.9	20.4	26.1
	N	15	15	15	15	15	15	15
	%Diff G1	-0.6	-0.4	-2.6	0.1	-1.6	-1.3	-2.2

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day 42	Day 49	Day 56
1F	Mean	328.5	332.2	339.8
	SD	31.4	31.9	31.3
	N	15	5	5
2F	Mean	320.6	--	--
	SD	36.5	--	--
	N	10	--	--
	%Diff G1	-2.4	--	--
3F	Mean	327.0	--	--
	SD	32.7	--	--
	N	10	--	--
	%Diff G1	-0.5	--	--
4F	Mean	323.1	328.8	337.6
	SD	26.1	36.6	33.5
	N	15	5	5
	%Diff G1	-1.7	-1.0	-0.6

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day Change -12 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1M	Mean	110.0	66.9	68.0	53.3	42.9	36.2	30.7
	SD	11.9	6.7	10.1	7.1	7.5	6.0	6.7
	N	15	15	15	15	15	15	15
2M	Mean	108.4	56.9b	60.8	44.9b	38.6	29.1a	24.8
	SD	9.4	8.4	9.5	7.9	13.6	7.0	8.0
	N	10	10	10	10	10	10	10
3M	Mean	101.0	52.7c	62.1	43.5b	36.7	30.6	29.2
	SD	7.4	8.2	5.6	6.7	7.6	4.8	7.4
	N	10	10	10	10	10	10	10
4M	Mean	111.7	50.0c	70.3	36.6c	47.2	26.9c	36.4
	SD	12.7	6.8	7.3	5.0	6.8	5.4	5.9
	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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day			
		Change -1 - 42	Change 42 - 49	Change 49 - 56	Change 42 - 56
1M	Mean	298.0	28.8	16.5	45.3
	SD	36.1	6.7	4.0	9.2
	N	15	4	4	4
2M	Mean	255.1a	--	--	--
	SD	47.3	--	--	--
	N	10	--	--	--
3M	Mean	254.8a	--	--	--
	SD	34.9	--	--	--
	N	10	--	--	--
4M	Mean	267.5	20.8	31.6e	52.4
	SD	23.9	3.6	7.6	7.0
	N	15	5	5	5

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

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day Change -13 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change 28 - 35	Change 35 - 42
1F	Mean	72.0	23.2	21.3	16.6	16.3	13.2	12.1
	SD	14.6	6.8	8.9	7.6	7.6	6.5	6.1
	N	15	15	15	15	15	15	15
2F	Mean	71.5	22.6	26.8	14.1	17.0	10.6	5.6b
	SD	11.9	8.8	8.9	7.9	8.7	5.9	5.3
	N	10	10	10	10	10	10	10
3F	Mean	69.0	24.5	25.7	16.2	18.7	11.6	10.1
	SD	13.9	9.1	11.3	10.4	9.0	5.9	3.9
	N	10	10	10	10	10	10	10
4F	Mean	72.0	17.6	27.9	11.7	17.2	9.9	13.7
	SD	9.5	6.9	7.1	7.9	4.1	7.8	4.0
	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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day Change -1 - 42	Change 42 - 49	Change 49 - 56	Change 42 - 56
1F	Mean	102.6	7.2	7.6	14.8
	SD	20.0	9.7	7.5	12.8
	N	15	5	5	5
2F	Mean	96.7	--	--	--
	SD	25.8	--	--	--
	N	10	--	--	--
3F	Mean	106.8	--	--	--
	SD	25.4	--	--	--
	N	10	--	--	--
4F	Mean	98.0	10.6	8.8	19.4
	SD	19.1	6.7	10.0	6.3
	N	15	5	5	5

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day (From/To)							
		-9/1	1/8	8/15	15/22	22/29	29/36	36/43	43/50
1M	Mean	29.79	32.44	33.35	34.38	35.31	35.08	35.83	34.50
	SD	2.04	2.32	2.78	2.09	1.99	1.90	1.89	0.60
	N	15	15	15	15	15	15	15	4
2M	Mean	30.26	31.32	33.02	33.52	34.60	33.55	33.85	--
	SD	0.71	0.57	1.67	1.61	1.11	1.67	1.63	--
	N	7	10	10	10	10	10	10	--
	%Diff G1	1.58	-3.45	-0.98	-2.50	-2.02	-4.36	-5.52	--
3M	Mean	27.69	28.56	31.18	31.72	32.89	31.89	33.51	--
	SD	0.76	1.51	1.13	0.94	1.04	1.40	1.62	--
	N	7	10	10	10	10	10	10	--
	%Diff G1	-7.05	-11.96	-6.50	-7.74	-6.86	-9.09	-6.47	--
4M	Mean	30.79	30.11	35.05	33.24	36.78	33.65	36.55	34.88
	SD	0.91	1.13	1.28	1.14	1.16	0.80	1.52	0.44
	N	15	15	15	15	15	15	15	5
	%Diff G1	3.36	-7.19	5.10	-3.32	4.15	-4.09	2.03	1.10

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day (From/To) 50/56
1M	Mean	34.23
	SD	1.35
	N	4
2M	Mean	--
	SD	--
	N	--
	%Diff G1	--
3M	Mean	--
	SD	--
	N	--
	%Diff G1	--
4M	Mean	37.18
	SD	0.66
	N	5
	%Diff G1	8.63

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day (From/To)							
		-9/1	1/8	8/15	15/22	22/29	29/36	36/43	43/50
1F	Mean	22.94	23.02	23.17	23.99	23.81	23.97	23.18	23.28
	SD	1.47	1.47	1.43	1.66	1.40	1.13	1.49	1.20
	N	12	15	15	15	15	15	15	5
2F	Mean	22.25	23.38	24.17	24.37	24.28	24.50	23.83	--
	SD	1.14	0.61	0.88	1.65	2.03	1.12	1.44	--
	N	10	10	10	10	10	10	10	--
	%Diff G1	-3.01	1.56	4.33	1.60	1.96	2.20	2.80	--
3F	Mean	22.13	23.37	24.13	24.19	24.72	24.45	24.64	--
	SD	0.23	0.60	0.91	1.12	1.31	1.57	1.04	--
	N	7	10	10	10	10	10	10	--
	%Diff G1	-3.54	1.52	4.16	0.85	3.81	1.99	6.30	--
4F	Mean	21.65	21.89	23.57	24.00	23.84	23.63	24.17	23.08
	SD	1.44	1.81	2.29	1.91	2.10	2.15	2.45	0.71
	N	15	15	15	15	15	15	15	5
	%Diff G1	-5.62	-4.92	1.76	0.06	0.11	-1.45	4.29	-0.86

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		Day (From/To) 50/56
1F	Mean	25.18
	SD	0.66
	N	5
2F	Mean	--
	SD	--
	N	--
	%Diff G1	--
3F	Mean	--
	SD	--
	N	--
	%Diff G1	--
4F	Mean	24.84
	SD	0.77
	N	5
	%Diff G1	-1.35

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1		Day 2	Day 43		Day 44
		pr	p		pr	p	
1M	Mean	36.24	35.26	37.45	36.23	36.79	36.91
	SD	0.44	0.88	0.50	0.41	0.56	0.65
	N	15	15	15	15	15	14
2M	Mean	36.82b	35.99	36.92d	36.89d	36.66	36.47
	SD	0.25	0.52	0.24	0.84	0.49	0.41
	N	10	10	10	10	10	10
	%Diff G1	1.60	2.07	-1.42	1.81	-0.36	-1.20
3M	Mean	36.64	36.66e	37.13	37.97f	37.60e	36.99
	SD	0.26	1.06	0.41	0.60	0.66	0.28
	N	10	10	10	10	10	10
	%Diff G1	1.10	3.97	-0.86	4.79	2.19	0.21
4M	Mean	36.61	38.05f	37.47	36.81d	37.53e	37.29
	SD	0.52	1.08	0.55	0.56	0.52	0.73
	N	15	15	15	15	15	15
	%Diff G1	1.01	7.90	0.05	1.60	2.01	1.01

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

Table 5

Summary of Body Temperature Values

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Parameter: Body Temp
°C

Group / Sex		Day 1		Day 2	Day 3	Day 43		Day 44
		pr	p			pr	p	
1F	Mean	37.32	36.25	37.62	--	38.01	37.04	37.39
	SD	0.41	0.50	0.33	--	0.61	0.58	0.71
	N	15	15	15	--	15	15	15
2F	Mean	37.59	36.79a	37.37	--	37.98	37.31	37.58
	SD	0.42	0.41	0.32	--	0.59	0.60	0.57
	N	10	10	10	--	10	10	10
	%Diff G1	0.72	1.48	-0.66	--	-0.07	0.73	0.52
3F	Mean	37.50	36.87b	37.67	--	38.43	37.78b	37.88
	SD	0.47	0.54	0.35	--	0.57	0.46	0.74
	N	10	10	10	--	10	10	10
	%Diff G1	0.48	1.70	0.13	--	1.11	2.00	1.32
4F	Mean	37.64	37.55c	38.56c	37.55	37.77	38.59c	38.12b
	SD	0.51	0.44	0.53	0.48	0.74	0.34	0.57
	N	15	15	15	15	15	15	15
	%Diff G1	0.86	3.59	2.50	--	-0.63	4.18	1.96

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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 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	10.570	1.595	8.402	0.303	0.108	0.020	0.138
	SD	3.788	0.794	3.157	0.067	0.043	0.013	0.063
	N	10	10	10	10	10	10	10
2M	Mean	10.776	2.920	7.017	0.236	0.277b	0.020	0.304e
	SD	1.208	0.957	1.092	0.070	0.072	0.007	0.142
	N	10	10	10	10	10	10	10
	%Diff G1	1.949	83.072	-16.484	-22.112	156.481	0.000	120.290
3M	Mean	14.091	6.990f	6.259	0.216	0.301b	0.023	0.304e
	SD	2.499	1.908	1.840	0.114	0.068	0.009	0.104
	N	10	10	10	10	10	10	10
	%Diff G1	33.311	338.245	-25.506	-28.713	178.704	15.000	120.290
4M	Mean	18.827c	11.493f	6.487	0.188d	0.413c	0.023	0.251
	SD	3.862	2.497	1.959	0.098	0.147	0.013	0.092
	N	10	10	10	10	10	10	9
	%Diff G1	78.117	620.564	-22.792	-37.954	282.407	15.000	81.965

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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.682	13.69	41.38	53.87	17.84	33.10	12.70
	SD	0.252	0.35	1.29	1.50	0.60	0.49	0.66
	N	10	10	10	10	10	10	10
2M	Mean	7.817	13.59	41.54	53.16	17.41	32.73	13.05
	SD	0.290	0.36	1.05	1.76	0.67	0.39	0.43
	N	10	10	10	10	10	10	10
	%Diff G1	1.757	-0.73	0.39	-1.32	-2.41	-1.12	2.76
3M	Mean	7.590	13.30	40.50	53.36	17.51	32.83	13.46b
	SD	0.228	0.41	1.32	0.98	0.31	0.27	0.52
	N	10	10	10	10	10	10	10
	%Diff G1	-1.198	-2.85	-2.13	-0.95	-1.85	-0.82	5.98
4M	Mean	7.900	13.93	42.58	53.88	17.66	32.74	13.82c
	SD	0.237	0.45	1.57	0.89	0.30	0.45	0.43
	N	10	10	10	10	10	10	10
	%Diff G1	2.838	1.75	2.90	0.02	-1.01	-1.09	8.82

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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1078.6	220.08
	SD	95.1	27.59
	N	10	10
2M	Mean	1043.8	223.42
	SD	132.4	31.08
	N	10	10
	%Diff G1	-3.2	1.52
3M	Mean	1059.2	213.30
	SD	117.1	25.80
	N	10	10
	%Diff G1	-1.8	-3.08
4M	Mean	1063.1	218.49
	SD	73.4	26.57
	N	10	10
	%Diff G1	-1.4	-0.72

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	Mean	6.541	0.724	5.498	0.151	0.069	0.010	0.087
	SD	1.905	0.338	1.893	0.058	0.022	0.005	0.039
	N	10	10	10	10	10	10	10
2F	Mean	7.919	3.320	4.026	0.126	0.275b	0.008	0.166
	SD	1.209	0.645	0.880	0.061	0.057	0.006	0.100
	N	10	10	10	10	10	10	10
	%Diff G1	21.067	358.564	-26.773	-16.556	298.551	-20.000	90.805
3F	Mean	9.060a	4.490c	3.996	0.110	0.272b	0.009	0.181
	SD	1.455	0.983	0.772	0.039	0.122	0.003	0.085
	N	10	10	10	10	10	10	10
	%Diff G1	38.511	520.166	-27.319	-27.152	294.203	-10.000	108.046
4F	Mean	11.735c	6.434c	4.555	0.102	0.451c	0.012	0.176
	SD	3.029	1.624	1.495	0.036	0.265	0.009	0.105
	N	10	10	10	10	10	10	10
	%Diff G1	79.407	788.674	-17.152	-32.450	553.623	20.000	102.299

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

Table 6

Summary of Hematology Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.102	12.75	38.01	53.50	17.98	33.56	11.51
	SD	0.224	0.44	1.31	0.89	0.34	0.21	0.44
	N	10	10	10	10	10	10	10
2F	Mean	6.916	12.51	37.43	54.11	18.12	33.47	11.89
	SD	0.302	0.63	1.86	0.91	0.38	0.60	0.55
	N	10	10	10	10	10	10	10
	%Diff G1	-2.619	-1.88	-1.53	1.14	0.78	-0.27	3.30
3F	Mean	6.960	12.69	37.90	54.53	18.26	33.47	12.19a
	SD	0.491	0.86	2.58	1.52	0.62	0.57	0.62
	N	10	10	10	10	10	10	10
	%Diff G1	-1.999	-0.47	-0.29	1.93	1.56	-0.27	5.91
4F	Mean	7.176	13.03	38.69	53.92	18.19	33.69	12.79c
	SD	0.274	0.37	1.25	0.99	0.31	0.50	0.49
	N	10	10	10	10	10	10	10
	%Diff G1	1.042	2.20	1.79	0.79	1.17	0.39	11.12

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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1060.4	185.68
	SD	172.2	23.56
	N	10	10
2F	Mean	1019.1	196.20
	SD	100.9	32.57
	N	10	10
	%Diff G1	-3.9	5.67
3F	Mean	971.1	218.11
	SD	95.1	36.36
	N	10	10
	%Diff G1	-8.4	17.47
4F	Mean	868.1b	198.61
	SD	102.0	36.03
	N	10	10
	%Diff G1	-18.1	6.96

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-1647 89 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	9.998	2.120	7.315	0.288	0.133	0.015	0.125
	SD	2.902	1.787	1.616	0.154	0.043	0.006	0.090
	N	4	4	4	4	4	4	4
4M	Mean	10.702	1.342	8.692	0.384	0.130	0.016	0.138
	SD	0.998	0.266	0.934	0.212	0.057	0.005	0.053
	N	5	5	5	5	5	5	5
	%Diff G1	7.047	-36.698	18.824	33.565	-1.887	6.667	10.400

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.843	13.63	40.90	52.18	17.38	33.33	12.73
	SD	0.207	0.17	0.89	0.67	0.41	0.63	0.57
	N	4	4	4	4	4	4	4
4M	Mean	7.656	13.36	41.00	53.54a	17.48	32.64	14.60b
	SD	0.250	0.33	1.16	0.68	0.40	0.40	0.61
	N	5	5	5	5	5	5	5
	%Diff G1	-2.378	-1.94	0.24	2.62	0.60	-2.06	14.73

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

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	999.0	214.63
	SD	135.9	18.22
	N	4	4
4M	Mean	1105.6	265.30a
	SD	119.7	32.68
	N	5	5
	%Diff G1	10.7	23.61

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-1647 89 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	4.132	0.892	2.970	0.152	0.066	0.000	0.052
	SD	1.035	0.265	0.905	0.063	0.011	0.000	0.029
	N	5	5	5	5	5	5	5
4F	Mean	4.590	0.844	3.530	0.090	0.080	0.002	0.042
	SD	1.866	0.606	1.391	0.056	0.027	0.004	0.022
	N	5	5	5	5	5	5	5
	%Diff G1	11.084	-5.381	18.855	-40.789	21.212	--	-19.231

Table 6

Summary of Hematology Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	6.938	12.60	37.38	53.92	18.14	33.64	11.48
	SD	0.245	0.58	1.41	1.19	0.61	0.63	0.41
	N	5	5	5	5	5	5	5
4F	Mean	6.846	12.46	36.76	53.68	18.20	33.88	12.66b
	SD	0.206	0.47	1.30	1.36	0.33	0.54	0.47
	N	5	5	5	5	5	5	5
	%Diff G1	-1.326	-1.11	-1.66	-0.45	0.33	0.71	10.28

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-1647 89 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1044.0	163.78
	SD	139.5	16.45
	N	5	5
4F	Mean	1105.2	169.54
	SD	80.9	21.05
	N	5	5
	%Diff G1	5.9	3.52

Table 7

Summary of Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	17.61	15.50	302.6
	SD	0.86	0.75	26.0
	N	10	10	10
2M	Mean	17.55	16.21	514.2c
	SD	0.54	0.77	36.4
	N	10	10	10
	%Diff G1	-0.34	4.58	69.9
3M	Mean	17.51	17.62c	576.2c
	SD	0.74	0.69	53.6
	N	10	10	10
	%Diff G1	-0.57	13.68	90.4
4M	Mean	17.09	18.79c	645.7c
	SD	1.15	1.07	56.6
	N	10	10	10
	%Diff G1	-2.95	21.23	113.4

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

Table 7

Summary of Coagulation Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.13	14.97	252.0
	SD	0.76	1.58	33.1
	N	10	10	10
2F	Mean	17.44	17.99c	416.3c
	SD	0.78	1.24	50.2
	N	10	10	10
	%Diff G1	1.81	20.17	65.2
3F	Mean	16.70	17.80b	473.7c
	SD	0.95	2.09	59.3
	N	10	10	10
	%Diff G1	-2.51	18.90	88.0
4F	Mean	16.72	18.35c	526.3c
	SD	0.63	1.41	73.5
	N	10	10	10
	%Diff G1	-2.39	22.58	108.8

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 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	18.10	16.08	288.5
	SD	0.77	0.22	22.5
	N	4	4	4
4M	Mean	18.38	15.96	274.4
	SD	0.81	0.69	11.5
	N	5	5	5
	%Diff G1	1.55	-0.72	-4.9

Table 7

Summary of Coagulation Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.74	15.64	195.4
	SD	0.64	0.96	19.9
	N	5	5	5
4F	Mean	17.98	15.00	218.8
	SD	1.00	1.08	38.5
	N	5	5	5
	%Diff G1	1.35	-4.09	12.0

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 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	99.8	40.0	113.1	2.0	560.1	0.069	13.2
	SD	21.7	5.3	21.4	0.0	424.7	0.021	2.6
	N	10	10	10	10	10	10	10
2M	Mean	98.7	40.8	114.7	2.0	500.5	0.073	15.0
	SD	15.0	6.2	14.2	0.0	181.9	0.023	2.5
	N	10	10	10	10	10	10	10
	%Diff G1	-1.1	2.0	1.4	0.0	-10.6	5.797	13.6
3M	Mean	97.2	44.3	119.9	2.0	447.2	0.082	16.2a
	SD	34.3	12.6	30.2	0.0	256.7	0.023	1.9
	N	10	10	10	10	10	10	10
	%Diff G1	-2.6	10.8	6.0	0.0	-20.2	18.841	22.7
4M	Mean	102.7	38.7	121.2	2.0	495.6	0.082	13.8
	SD	18.5	3.7	16.6	0.0	265.4	0.021	1.7
	N	10	10	10	10	10	10	10
	%Diff G1	2.9	-3.3	7.2	0.0	-11.5	18.841	4.5

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

Table 8

Summary of Clinical Chemistry Values: Day 44

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 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	0.34	188.2	68.1	88.8	5.77	3.64	2.13
	SD	0.05	29.0	16.2	38.8	0.21	0.13	0.19
	N	10	10	10	10	10	10	10
2M	Mean	0.37	194.6	74.9	70.6	5.88	3.38c	2.50c
	SD	0.05	44.0	17.1	38.1	0.21	0.18	0.12
	N	10	10	10	10	10	10	10
	%Diff G1	8.82	3.4	10.0	-20.5	1.91	-7.14	17.37
3M	Mean	0.39	197.6	75.5	63.1	5.85	3.29c	2.56c
	SD	0.06	30.7	8.8	15.8	0.26	0.09	0.22
	N	10	10	10	10	10	10	10
	%Diff G1	14.71	5.0	10.9	-28.9	1.39	-9.62	20.19
4M	Mean	0.39	178.8	71.8	68.7	5.94	3.27c	2.67c
	SD	0.03	31.4	15.1	24.2	0.26	0.15	0.20
	N	10	10	10	10	10	10	10
	%Diff G1	14.71	-5.0	5.4	-22.6	2.95	-10.16	25.35

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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.72	10.23	8.02	140.2	5.19	100.7
	SD	0.18	0.30	0.81	1.3	0.46	1.2
	N	10	10	10	10	10	10
2M	Mean	1.37c	10.20	7.80	139.8	5.49	100.1
	SD	0.11	0.29	0.45	1.2	0.36	1.7
	N	10	10	10	10	10	10
	%Diff G1	-20.35	-0.29	-2.74	-0.3	5.78	-0.6
3M	Mean	1.29c	10.42	7.96	139.4	5.67a	100.1
	SD	0.11	0.24	0.68	1.2	0.39	1.6
	N	10	10	10	10	10	10
	%Diff G1	-25.00	1.86	-0.75	-0.6	9.25	-0.6
4M	Mean	1.22c	10.42	8.36	140.3	5.76b	100.4
	SD	0.11	0.40	0.71	1.3	0.21	1.4
	N	10	10	10	10	10	10
	%Diff G1	-29.07	1.86	4.24	0.1	10.98	-0.3

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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 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	89.7	36.7	62.8	2.0	365.5	0.064	14.2
	SD	23.0	7.6	16.7	0.0	208.8	0.019	2.0
	N	10	10	10	10	10	10	10
2F	Mean	100.1	38.6	68.1	2.0	427.6	0.077	15.5
	SD	25.8	8.6	11.6	0.0	243.6	0.018	3.0
	N	10	10	10	10	10	10	10
	%Diff G1	11.6	5.2	8.4	0.0	17.0	20.313	9.2
3F	Mean	105.0	40.1	64.6	2.0	477.4	0.085	15.7
	SD	40.5	16.0	18.8	0.0	317.6	0.025	1.8
	N	10	10	10	10	10	10	10
	%Diff G1	17.1	9.3	2.9	0.0	30.6	32.813	10.6
4F	Mean	106.6	38.3	74.4	2.0	500.5	0.087	17.5a
	SD	25.0	10.8	12.1	0.0	282.0	0.025	2.7
	N	10	10	10	10	10	10	10
	%Diff G1	18.8	4.4	18.5	0.0	36.9	35.938	23.2

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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 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	209.9	82.2	79.8	6.51	4.54	1.97
	SD	0.04	37.4	13.1	62.9	0.41	0.27	0.18
	N	10	10	10	10	10	10	10
2F	Mean	0.40	192.0	88.1	47.3	6.32	4.02c	2.30c
	SD	0.05	24.9	17.3	7.7	0.39	0.35	0.15
	N	10	10	10	10	10	10	10
	%Diff G1	-4.76	-8.5	7.2	-40.7	-2.92	-11.45	16.75
3F	Mean	0.42	181.3	85.5	57.7	6.40	4.07b	2.33c
	SD	0.06	23.2	13.9	14.9	0.16	0.21	0.12
	N	10	10	10	10	10	10	10
	%Diff G1	0.00	-13.6	4.0	-27.7	-1.69	-10.35	18.27
4F	Mean	0.45	182.3	76.5	56.4	6.35	3.93c	2.42c
	SD	0.05	20.2	15.2	17.2	0.22	0.24	0.15
	N	10	10	10	10	10	10	10
	%Diff G1	7.14	-13.1	-6.9	-29.3	-2.46	-13.44	22.84

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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.32	10.82	6.59	139.6	4.76	101.2
	SD	0.17	0.24	0.82	1.4	0.21	1.6
	N	10	10	10	10	10	10
2F	Mean	1.75c	10.65	6.90	140.2	4.99	101.8
	SD	0.18	0.39	0.71	1.1	0.34	1.5
	N	10	10	10	10	10	10
	%Diff G1	-24.57	-1.57	4.70	0.4	4.83	0.6
3F	Mean	1.76c	10.78	7.05	140.5	4.96	101.5
	SD	0.16	0.30	0.64	1.3	0.32	2.7
	N	10	10	10	10	10	10
	%Diff G1	-24.14	-0.37	6.98	0.6	4.20	0.3
4F	Mean	1.64c	10.62	7.12	139.8	5.09	101.1
	SD	0.16	0.28	0.71	0.8	0.18	2.0
	N	10	10	10	10	10	10
	%Diff G1	-29.31	-1.85	8.04	0.1	6.93	-0.1

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 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 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	97.8	40.5	120.0	2.0	661.5	0.073	17.0
	SD	11.5	11.5	11.0	0.0	195.7	0.021	3.2
	N	4	4	4	4	4	4	4
4M	Mean	77.2	40.8	104.6	2.0	323.4a	0.064	15.0
	SD	14.7	4.3	18.0	0.0	119.2	0.009	2.9
	N	5	5	5	5	5	5	5
	%Diff G1	-21.0	0.7	-12.8	0.0	-51.1	-11.724	-11.8

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-1647 89 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	0.33	188.8	81.0	107.8	5.93	3.65	2.28
	SD	0.05	23.2	16.1	34.2	0.15	0.10	0.10
	N	4	4	4	4	4	4	4
4M	Mean	0.34	260.2	65.8	98.2	5.62a	3.60	2.02b
	SD	0.05	62.8	7.9	33.1	0.13	0.10	0.08
	N	5	5	5	5	5	5	5
	%Diff G1	4.62	37.9	-18.8	-8.9	-5.15	-1.37	-11.21

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-1647 89 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	1.60	10.45	7.05	140.3	5.20	99.8
	SD	0.08	0.26	0.41	1.3	0.16	2.2
	N	4	4	4	4	4	4
4M	Mean	1.80a	10.50	7.60	137.4a	5.24	98.8
	SD	0.10	0.56	0.42	1.5	0.29	2.3
	N	5	5	5	5	5	5
	%Diff G1	12.50	0.48	7.80	-2.0	0.77	-1.0

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-1647 89 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	104.0	44.0	58.8	2.0	644.2	0.068	19.6
	SD	14.5	7.5	10.9	0.0	186.1	0.016	3.4
	N	5	5	5	5	5	5	5
4F	Mean	78.4b	36.4	74.2	2.0	213.0b	0.052	19.0
	SD	5.0	4.4	21.1	0.0	64.2	0.013	2.7
	N	5	5	5	5	5	5	5
	%Diff G1	-24.6	-17.3	26.2	0.0	-66.9	-23.529	-3.1

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-1647 89 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	0.44	195.2	82.4	135.2	6.52	4.68	1.84
	SD	0.05	27.5	21.8	45.7	0.15	0.11	0.13
	N	5	5	5	5	5	5	5
4F	Mean	0.42	182.2	65.6	59.4a	6.12	4.30a	1.82
	SD	0.04	38.5	8.7	3.0	0.41	0.30	0.15
	N	5	5	5	5	5	5	5
	%Diff G1	-4.55	-6.7	-20.4	-56.1	-6.13	-8.12	-1.09

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

Table 8

Summary of Clinical Chemistry Values: Day 57

Group 1 - Reference Item

Group 4 - mRNA-1647 89 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	10.90	5.82	138.8	4.64	100.4
	SD	0.21	0.29	0.83	1.3	0.23	1.5
	N	5	5	5	5	5	5
4F	Mean	2.36	10.56	6.56	138.0	4.58	100.2
	SD	0.15	0.42	1.10	1.0	0.31	1.6
	N	5	5	5	5	5	5
	%Diff G1	-7.09	-3.12	12.71	-0.6	-1.29	-0.2

Table 9

Summary of α1-acid Glycoprotein and α2-macroglobulin Values

Day 44
Males

Group 1 - Reference Item
Group 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	94.060	23.506
	SD	29.429	12.169
	N	10	10
2	Mean	257.432 C	115.194
	SD	43.395	68.816
	N	10	10
	% Diff (G1)	174	390
3	Mean	390.988 C	293.504 F
	SD	56.379	237.643
	N	10	10
	% Diff (G1)	316	1149
4	Mean	551.569 C	382.531 F
	SD	151.980	211.063
	N	10	10
	% Diff (G1)	486	1527

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-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	72.220	42.357
	SD	24.521	20.773
	N	10	10
2	Mean	235.634 C	55.994
	SD	52.630	15.029
	N	10	10
	% Diff (G1)	226	32
3	Mean	339.454 C	123.631 E
	SD	50.928	113.492
	N	10	10
	% Diff (G1)	370	192
4	Mean	505.421 C	186.357 E
	SD	137.000	249.663
	N	10	10
	% Diff (G1)	600	340

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 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	88.440	20.773
	SD	8.092	4.717
	N	4	4
4	Mean	87.166	37.996 a
	SD	12.415	12.667
	N	5	5
	% Diff (G1)	-1	83

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 2 - mRNA-1647 8.9 µg/dose
Group 3 - mRNA-1647 27 µg/dose
Group 4 - mRNA-1647 89 µg/dose

Group	Summary Information	α1-acid Glycoprotein µg/mL	α2-macroglobulin µg/mL
1	Mean	68.932	35.152
	SD	4.834	13.723
	N	5	5
4	Mean	75.622	54.802
	SD	10.977	38.529
	N	5	5
	% Diff (G1)	10	56

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-1647 89 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	81.768	21.700	59.374	124.482	51.913
	SD	151.835	24.183	88.301	265.269	92.125
	N	4	5	5	5	4
4	Mean	58.354	44.110	58.726	39.250	15.068
	SD	52.019	36.995	80.621	48.320	20.612
	N	5	5	5	5	5
	% Diff (G1)	-29	103	-1	-68	-71

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-1647 89 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	4
4	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
	% 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

TNF-α (pg/mL)
Males

Group 1 - Reference Item

Group 4 - mRNA-1647 89 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	2.534	1.470	2.450	3.098
	SD	0.000	2.379	0.000	2.191	3.255
	N	4	5	5	5	4
4	Mean	1.470	3.648	1.470	3.746	1.470
	SD	0.000	3.010	0.000	3.170	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	44	0	53	-53

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-1647 89 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	119.183	81.600	108.196	114.608	111.973
	SD	55.636	18.170	42.739	70.494	79.736
	N	4	5	5	5	4
4	Mean	1215.712 b	882.356 d	993.816 b	667.464 c	70.600
	SD	481.589	311.841	523.188	176.698	19.924
	N	5	5	5	5	5
	% Diff (G1)	920	981	819	482	-37

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-1647 89 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	4
4	Mean	5.850	9.986	5.850	5.850	5.850
	SD	0.000	9.248	0.000	0.000	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	71	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-1647 89 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	385.368	407.454	387.200	352.102	209.503
	SD	84.450	64.383	87.399	29.006	161.154
	N	4	5	5	5	4
4	Mean	531.784	649.598	563.292	484.526	166.148
	SD	127.495	337.498	151.572	283.312	130.973
	N	5	5	5	5	5
	% Diff (G1)	38	59	45	38	-21

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-1647 89 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	81.260	81.770	24.666	51.744	14.792
	SD	67.051	93.939	29.166	52.373	12.313
	N	4	5	5	5	5
4	Mean	25.924	25.974	15.594	23.160	9.680
	SD	44.887	44.999	21.788	38.706	8.564
	N	5	5	5	5	5
	% Diff (G1)	-68	-68	-37	-55	-35

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-1647 89 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	176.000	176.000
	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

TNF-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1647 89 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	2.790	1.470	1.470	3.682
	SD	0.000	2.952	0.000	0.000	3.031
	N	4	5	5	5	5
4	Mean	1.470	4.792	3.996	2.544	1.470
	SD	0.000	4.765	3.459	2.402	0.000
	N	5	5	5	5	5
	% Diff (G1)	0	72	172	73	-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

IP-10 (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1647 89 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	101.380	78.686	75.830	105.752	52.852
	SD	45.097	30.456	30.099	35.779	18.137
	N	4	5	5	5	5
4	Mean	1484.720 d	1254.524 c	1374.798 d	947.402 d	47.134
	SD	308.884	241.636	414.653	333.750	13.418
	N	5	5	5	5	5
	% Diff (G1)	1365	1494	1713	796	-11

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

Table 10

Summary of Cytokine Values

MIP-1-α (pg/mL)
Females

Group 1 - Reference Item

Group 4 - mRNA-1647 89 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	20.474	25.098	24.632	10.984	5.850
	SD	13.535	18.462	17.515	11.480	0.000
	N	5	5	5	5	5
	% Diff (G1)	250	329	321	88	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-1647 89 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	128.680	158.156	174.606	169.772	113.614
	SD	116.360	120.028	143.082	136.358	96.406
	N	4	5	5	5	5
4	Mean	525.168 a	1032.490 a	1032.040 b	397.324	132.256
	SD	272.356	668.447	408.110	461.595	138.091
	N	5	5	5	5	5
	% Diff (G1)	308	553	491	134	16

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)