charles river

FINAL REPORT

Test Facility Study No. 5002045

ZIKA: A 1-Month (3 Doses) Intramuscular Injection Toxicity Study of mRNA-1706 in Sprague-Dawley Rats with a 2-Week Recovery Period

SPONSOR:
Moderna Therapeutics, Inc.
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TEST FACILITY:
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QUALITY ASSURANCE STATEMENT

Study Number: 5002045

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

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
04-Oct-2016 - 05-Oct-2016	Final Study Plan	05-Oct-2016	05-Oct-2016
18-Oct-2016	Study Plan Amendment 1	19-Oct-2016	19-Oct-2016
20-Oct-2016	Addition of Study Plan to Provantis	20-Oct-2016	20-Oct-2016
21-Oct-2016	Dose Preparation	21-Oct-2016	21-Oct-2016
16-Nov-2016	Study Plan Amendment 2	16-Nov-2016	16-Nov-2016
18-Nov-2016	Necropsy	18-Nov-2016	18-Nov-2016
21-Nov-2016	Coagulation Analysis	21-Nov-2016	21-Nov-2016
08-Dec-2016	Sample Transfer	08-Dec-2016	08-Dec-2016
13-Dec-2016	Study Plan Amendment 3	13-Dec-2016	13-Dec-2016
16-Jan-2017 - 18-Jan-2017	Data Review - Animal Care	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Shipping/Receiving	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Veterinary Services	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Clinical Pathology	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Formulations	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Data Review - Technical Operations	19-Jan-2017	19-Jan-2017
16-Jan-2017 - 18-Jan-2017	Report Preparation	19-Jan-2017	19-Jan-2017
18-Jan-2017	Draft Phase Report - Ophthalmology	19-Jan-2017	19-Jan-2017
18-Jan-2017	Draft Report - Materials and Methods	20-Jan-2017	20-Jan-2017
25-Jan-2017	Study Plan Amendment 4	25-Jan-2017	25-Jan-2017
27-Jan-2017 - 30-Jan-2017	Data Review - Analytical Chemistry	31-Jan-2017	31-Jan-2017
27-Jan-2017 - 30-Jan-2017	Draft Phase Report - Dose Formulation Analysis	31-Jan-2017	31-Jan-2017
14-Feb-2017	Data Review - Bioanalysis & Immunology	15-Feb-2017	15-Feb-2017
14-Feb-2017	Draft Phase Report - Immunology	15-Feb-2017	15-Feb-2017
15-Feb-2017 - 16-Feb-2017	Data Review - Shipping/Receiving	17-Feb-2017	17-Feb-2017
15-Feb-2017 - 16-Feb-2017	Data Review - Histology	17-Feb-2017	17-Feb-2017
15-Feb-2017 - 16-Feb-2017	Data Review - Necropsy	17-Feb-2017	17-Feb-2017
15-Feb-2017 - 16-Feb-2017	Report Preparation	17-Feb-2017	17-Feb-2017
16-Feb-2017	Study Plan Amendment 5	16-Feb-2017	16-Feb-2017
22-Feb-2017 - 23-Feb-2017	Draft Report - Results	23-Feb-2017	23-Feb-2017
12-May-2017	Study Plan Amendment 6	15-May-2017	15-May-2017

QUALITY ASSURANCE STATEMENT - Study Number: 5002045

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
24-May-2017	Report Preparation	25-May-2017	25-May-2017
24-May-2017	Final Report	25-May-2017	25-May-2017
02-Jun-2017	Revised Draft Phase Report - Immunology	02-Jun-2017	02-Jun-2017
05-Jun-2017	Final Phase Report - Dose Formulation Analysis	05-Jun-2017	05-Jun-2017
24-Oct-2017	Final Report	25-Oct-2017	25-Oct-2017

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

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

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

[redacted]

[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 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 GLP or GMP regulations.
- Analysis of cytokines and anti-therapeutic antibody were conducted using scientifically-qualified methods and in accordance with all applicable analytical procedures.
- Pathology peer review.

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

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

[redacted] Date: [redacted]

1. RESPONSIBLE PERSONNEL

1.1. Test Facility

Study Director [redacted]

Test Facility Management [redacted]

1.2. Individual Scientists (IS) at Test Facility

Ophthalmology [redacted]
Consultant Ophthalmologist
Senneville, QC, Canada

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

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

Immunology
(Cytokine Analysis) [redacted]
Charles River Laboratories Montreal ULC
Sherbrooke, QC, Canada

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

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

1.4. PIs at Sponsor-designated Test Site

Anti-Therapeutic
Antibody Analysis [redacted]
Integrated BioTherapeutics, Inc.
Rockville, MD, USA

2. SUMMARY

The objectives of this study were to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 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,b] (µg/dose)	Dose Volume (µL/dose)	Dose Concentration[b] (mg/mL)	Number of Animal			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	10	10	5	5
2	mRNA-1706	10 / 13	200	0.05 / 0.07	10	10	-	-
3	mRNA-1706	50 / 65	200	0.25 / 0.33	10	10	-	-
4	mRNA-1706	100 / 129	200	0.5 / 0.65	10	10	5	5

- = Not applicable

[a] The End-of-use bulk Test Item purity analysis indicated RNA degradation while the concentration and particle size analysis were within specification. Study animals showed a significant average antibody response against the ZIKV lysate and increased average antibody titers following the final dose indicating that the potential decrease in purity did not affect activity. As the original doses were not adjusted for purity of the drug product, but based on total mRNA concentration, the nominal dose levels were maintained in the report, tables and appendices.

[b] Values based on Summary of Analysis (SoA) issued on 11 Oct 2016 / Values based on SoA issued on 03 May 2017 (Refer to memorandum in Appendix 2).

The following parameters and end points were evaluated in this study: mortality, clinical signs, local irritation, body weights, food consumption, ophthalmology, clinical pathology parameters (hematology, coagulation, and clinical chemistry), cytokines, anti-therapeutic antibody (ATA), gross necropsy findings, organ weights, and histopathologic examination.

All animals given mRNA-1706 showed detectable antibody responses against ZIKV lysate at the end of the dosing period, and higher antibody titers following the two-week recovery period.

There were no mortalities during the course of the study.

There were no mRNA-1706 related changes in ophthalmology and organ weights.

Edema and, less frequent, erythema, were noted at the injection site following the first dose for males and females given ≥ 13 µg/dose. The incidence and severity of the findings were dose-dependent with increased incidence and severity noted at higher doses of mRNA-1706. Injection site observations consisted of slight to moderate edema with occasional severe edema noted at the highest dose tested and slight to mild erythema. The apex of severity was generally 24 hours post dose and was decreased 72 hours post dose. Between Days 2 and 4 only, the severity of the edema in females given 129 µg/dose was increased and correlated with warmness of the skin observed clinically. Increased severity reaction was noted following the third (last) dose in both genders. Minimal decreases in body weight gain and food consumption were observed during dosing weeks for males and females given 129 µg/dose. During the off-dose

weeks and recovery period, higher body weight gains were noted for both sexes while food consumption returned to control values.

Macroscopic and microscopic changes correlative with the injection site reaction were noted, such as swelling, abnormal firm consistency, lymph nodes enlargement, minimal to moderate inflammation at the injection site and minimal to mild mixed cells infiltration in and around the popliteal and inguinal lymph nodes. Clinical pathology changes suggestive of inflammation were observed in all males and females treated with mRNA-1706 and include: minimal to moderate increases in neutrophil, eosinophil (males and females ≥ 13 µg/dose) and large unstained cell counts with concomitant increases in white blood cells (males ≥ 13 µg/dose), minimal decreases in lymphocyte counts (females ≥ 13 µg/dose), minimal decreases in reticulocyte counts (males ≥ 13 µg/dose) and/or platelet counts (males 129 µg/dose, females ≥ 65 µg/dose), mild increases in fibrinogen and/or minimal increases in globulin with concomitant decreases in A/G ratio (males ≥ 13 µg/dose). Increases in IP-10, MCP-1, MIP-1α (female only) and/or TNF-α (male only) were noted at ≥ 129 µg/dose. The highest cytokine levels were generally reached on Day 29 and correlated with the severity of edema/erythema noted at the injection site. At the end of the recovery period, all mRNA-1706-related changes return to control values or were partially (lymph nodes enlargement without microscopic correlates) or fully recovered.

In the spleen, minimal to mild depletion of lymphocytes in the periarteriolar sheath was present in a dose-related trend for both male and female rats given ≥ 13 µg/dose. These changes were fully resolved at the end of the recovery period.

In the liver of males given ≥ 13 µg/dose, the incidence of minimal hepatocytic vacuolation showed a dose-related trend. No macroscopic changes correlated with this finding and changes were fully recovered at the end of the recovery period.

In conclusion, administration of mRNA-1706 by intramuscular injection for 1 month (3 doses) was clinically well tolerated in rats up to 129 µg/dose. A positive antibody response against ZIKV was determined at the end of the dosing period which persisted, as determined by a higher antibody titers noted following a two-week recovery period. At ≥ 13 µg/dose, dose-dependent changes in clinical signs, clinical pathology parameters and cytokines levels were consistent with an inflammatory response at the injection site. Dose-dependent target organ effects were limited to the injection site, tissues surrounding lymph nodes regional to the injection site, spleen, and liver of animals given mRNA-1706. At the end of the recovery period, all changes were partially or fully recovered.

3. INTRODUCTION

The objectives of this study were to determine the potential toxicity of mRNA-1706, when given by intramuscular injection for 1 month (3 doses) to rats and to evaluate the potential reversibility of any findings following a 2-week recovery period.

The design of this study was based on:

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

The Study Director signed the study plan on 04 Oct 2016, and dosing of males was initiated on 20 Oct 2016 for males and on 21 Oct 2016 for females. The in-life phase of the study was completed on 19 Nov 2016 (Main Study animals) and 02 Dec 2016 (Recovery animals). The experimental start date was 05 Oct 2016, the experimental completion date was on 09 Mar 2017. The study plan, study plan amendments, and deviations are presented in Appendix 1.

4. MATERIALS AND METHODS

4.1. Test and Reference Items

4.1.1. Test Item

Identification: mRNA-1706

Batch (Lot) No.:	MTDP16064
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.
Concentration:	1.7 / 2.2* mg/mL
Physical Description:	White to off-white lipid nanoparticle dispersion
Storage Conditions:	Kept in a refrigerator set to maintain 4°C
Supplier:	Moderna Therapeutics, Inc.

* Concentration based on SoA released on 11 Oct 2016 / Concentration based on SoA released on 03 May 2017 (refer to memorandum in Appendix 2)

4.2. Reference Item

Identification:	Phosphate-buffered Saline (PBS), pH 7.2
Batch (Lot) Nos.:	1809319, 1759866 and 1740269
Expiration Dates:	Jul 2018 (Lot No. 1809319), Feb 2018 (Lot No. 1759866) and Nov 2017 (Lot No. 1740269).
Physical Description:	Clear liquid
Storage Conditions:	Kept in a controlled temperature area set to maintain 21°C
Supplier:	Gibco

4.3. Test Item Characterization

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

4.4. Analysis of Test Item

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

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

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

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

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

4.5. Reserve Samples

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

4.6. Test and Reference Item Inventory and Disposition

Records of the receipt, distribution, and storage of Test and Reference Items were maintained. With the exception of reserve samples, all unused Sponsor-supplied bulk Test Item were discarded prior to report finalization.

4.7. Dose Formulation and Analysis

4.7.1. Preparation of Reference Item

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

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

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

Any residual volumes of formulated Test Item were stored in a refrigerator set at 4°C and were shipped to the Sponsor on ice packs for analysis. Residual volumes of formulated Test Item were analyzed for mRNA/lipid identity confirmation. Results were provided to the Test Facility and were not reported.

Details of the preparation and dispensing of the Test Item were retained in the study records.

4.7.3. Sample Collection and Analysis

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

Text Table 2
Dose Formulation Sample Collection Schedule

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

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

Samples to be analyzed were transferred on the date prepared or within 3 days of preparation to the Analytical Chemistry Department of the Test Facility for analysis.

4.7.3.1. Analytical Method

Analyses described below were performed by IEX-HPLC using a validated analytical procedure (CR MTL Study No. 1801737).

4.7.3.2. Concentration Analysis

Duplicate set of samples collected on Days 1 and 29 (0.5 mL each, collected from the middle stratum, except on Day 1 where samples were collected from the top, middle and bottom strata) were transferred (on ice pack) to the analytical laboratory for analysis. Triplicate set of samples

(duplicate for Group 1) were retained at the Test Facility as backup samples. Concentration results were considered acceptable when the mean sample concentration results were within or equal to ± 15% of the theoretical concentration. Each individual sample concentration result was considered acceptable if it was within or equal to ± 20%. After acceptance of the analytical results, backup samples were discarded.

4.7.3.3. Homogeneity Analysis

On Day 1, duplicate sets of samples (0.5 mL each, collected from the top, middle and bottom strata for Groups 2 to 4 and from the middle stratum for Group 1) were transferred (on ice pack) to the analytical laboratory for analysis; similarly, triplicate sets of samples (duplicate for Group 1) were retained at the Test Facility as backup samples. Homogeneity results were considered acceptable if the relative standard deviation of the mean values at each sampling stratum was ≤ 5%. After acceptance of the analytical results, backup samples were discarded.

4.7.3.4. Stability Analysis

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

4.8. Test System

4.8.1. Receipt

On October 5, 2016, one hundred and twenty (60 males and 60 females) Crl:CD(SD) Sprague-Dawley rats were received from Charles River Canada, Inc., St. Constant, QC, Canada. At dosing onset, the animals were approximately 8 weeks old and the males weighed between 240 and 298 grams and the females, between 200 and 246 grams.

4.8.2. Justification for Test System and Number of Animals

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

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

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

4.8.3. Animal Identification

At study assignment, each animal was identified using a subcutaneously implanted electronic identification chip. Animals were also identified using a non-toxic pen, as needed.

4.8.4. Environmental Acclimation

A minimum acclimation period of at least 15 days was allowed between animal receipt and the start of dosing in order to accustom the animals to the laboratory environment.

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

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

Before the initiation of dosing, any assigned animals 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 disposition of all animals was documented in the study records.

4.8.6. Husbandry

4.8.6.1. Housing

Animals were group-housed (up to 3 animals of the same sex and same dosing group together) in polycarbonate cages containing appropriate bedding equipped with an automatic watering valve. These housing conditions were maintained unless deemed inappropriate by the Study Director and/or Clinical Veterinarian. The rooms in which the animals were kept were 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 numbers, and sex. Cages were arranged on the racks in group order. Control group animals were housed on a separate rack from the Test Item-treated 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. Wet pellets were provided as judged necessary.

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

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

4.8.6.4. Water

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

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

It was considered that there were no known contaminants in the water that could have interfered 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 and recommended therapeutic treatments were documented in the study records.

4.9. Experimental Design

Text Table 3
Experimental Design

Group No.	Test Material	Dose Level (µg/dose)[a]	Dose Volume (µL/dose)	Dose Concentration (mg/mL)[a]	Animals Nos.			
					Main Study		Recovery Study	
					Males	Females	Males	Females
1	Reference Item	0	200	0	1001-1003, 1104, 1005-1010	1501-1510	1011-1015	1511-1515
2	mRNA-1706	10 / 13	200	0.05 / 0.07	2001-2010	2501-2510	-	-
3	mRNA-1706	50 / 65	200	0.25 / 0.33	3001-3010	3501-3510	-	-
4	mRNA-1706	100 / 129	200	0.5 / 0.65	4001-4004, 4105, 4006-4010	4501-4510	4011-4015	4511-4515

- = Not applicable
[a] Values based on SoA issued on 11 Oct 2016 / Values based on SoA issued on 03 May 2017 (refer to memorandum in Appendix 2).

On Day -1, Animal No. 4005 was euthanized following complications from a skin lesion on the right hind limb, resulting from an accidental cut during shaving. This animal was replaced with a spare animal to become Animal No. 4105. On Day 1, prior to dosing initiation, due to compromising clinical signs (inguinal skin lesion), Animal No. 1004 was replaced with a spare animal to become Animal No. 1104. The final allocation of animals is listed under Text Table 3.

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 and 29, the injection site was alternated on each dosing occasion. The volume for each dose was administered using a syringe/needle within the demarcated area. The first day of dosing was designated as Day 1.

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

A low incidence of dosing reflux was observed for individual animals, mainly following Days 1 and 29 dosing. As reflux occurred only once per affected animal, was scattered in all dosing groups, including controls, it was considered to have no impact on overall exposure and on the study outcome.

4.9.2. Justification of Route and Dose Levels

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

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

4.10. In-life Procedures, Observations, and Measurements

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

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 (for exceptions, refer to Appendix 1). 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 their cage, and a detailed clinical observation was performed weekly, beginning 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 (for exceptions, refer to Appendix 1). Examinations were also performed weekly when there was no dosing and during the recovery period. On Day 29, no assessment was performed on Main Study animals at 72 hours postdose as these animals were sent to necropsy on Day 30.

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. A fasted weight was recorded on the day of necropsy (for exceptions, refer to Appendix 1).

4.10.5. Food Consumption

Food consumption was quantitatively measured weekly starting on Day -7 and continuing weekly throughout the dosing and recovery periods (refer to Appendix 1 for one exception).

4.10.6. Ophthalmic Examinations

All animals had funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations, once prior to dosing initiation and on Day 28 for males and Day 27 for females. The mydriatic used was Atropine 0.126%.

4.11. Laboratory Evaluations

4.11.1. Clinical Pathology

4.11.1.1. Sample Collection

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

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

Text Table 4
Samples for Clinical Pathology Evaluation

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

X = Sample collected
[a] Samples were only collected from Main Study Animals on Day 30.

4.11.1.2. Hematology

Blood samples (a target volume of 0.5 mL, collected in tubes 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.

4.11.1.3. Coagulation

Blood samples (target volume of 1.2 mL, collected in 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 Aspartate aminotransferase Alkaline phosphatase Gamma-glutamyltransferase Creatine Kinase Total bilirubin Urea nitrogen Creatinine Calcium Phosphorus	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride Sample Quality

4.11.2. Cytokine Analysis

Blood was collected from a jugular vein from all Recovery animals as specified in Text Table 8. After collection, blood samples for serum collection were transferred at ambient room

temperature and blood samples for plasma collection were transferred on wet ice to the appropriate laboratory for processing.

Text Table 8
Sample Collection Schedule and Information

Target Blood Volume (mL)			0.5	0.5
Anticoagulant			**None (SST)**	**EDTA**
Centrifugation setting			2400x g, 10 minutes, set at 4°C	1200x g, 10 minutes, set at 4°C
Timepoints			**Sample Type**	
Day	**Hrs**	**No. of Males/ Females**	IFN-α	IL-1ß, IL-6, TNF-α, IP-10, MIP-1-α, MCP-1
1	6	5/5	X	X
15	6	5/5	X	X
29	6	5/5	X	X
43	N/A	5/5	X	X
Matrix			Serum	Plasma
Volume per aliquot (µL)			all volume	all volume
Number of aliquot(s)			1	1
Storage condition (set to maintain)			-80°C	-80°C
Responsible Lab			CR SHB	CR SHB

X = Sample collected; N/A = not applicable

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

Note that the IFN-α results were considered invalid since samples were analyzed with an ELISA kit which detects anti-IFN-α antibodies instead of the cytokine IFN-α. As the wrong assay reagents were used and as there is no remaining samples to repeat the analysis; results were maintained in the raw data but were not reported (Refer to Appendix 1).

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

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

Before the initiation of dosing and at study termination (i.e. Day 30 for Main Study animals and Day 43 for Recovery animals), a target volume of 0.5 mL of blood was collected in serum separator tubes by jugular venipuncture and via abdominal aorta, while under isoflurane anesthesia (terminal).

Samples were mixed gently and allowed to clot at room temperature until centrifugation which was carried out as soon as practical (not exceeding 60 minutes after collection; for exceptions, refer to Appendix 1). 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.

Samples were shipped on dry ice to Integrated BioTherapeutics, Inc., Rockville, MD, USA, and were analyzed for rat anti-ZIKA antibodies using a qualified ELISA method.

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

4.12. Terminal Procedures

Terminal procedures are summarized in Text Table 9.

Text Table 9
Terminal Procedures

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

X = Procedure conducted; - = Not applicable.
[a] See Section 4.12.5 for listing of tissues.
[b] Animals euthanized before the initiation of dosing.

4.12.1. Unscheduled Deaths

Before the initiation of dosing, one male was euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia and was subjected to complete necropsy examination and limited tissue retention (standard diagnostic tissue list).

4.12.2. Scheduled Euthanasia

Main Study and Recovery animals surviving until scheduled euthanasia had a terminal body weight recorded, samples for clinical pathology and antibody analysis were collected (as appropriate), and were euthanized by exsanguination by incision from the abdominal aorta following isoflurane anesthesia. The animals were euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, were necropsied throughout the day. Animals were fasted overnight before their scheduled necropsy.

4.12.3. Necropsy

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

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

4.12.4. Organ Weights

The organs identified in Text Table 10 were weighed at necropsy. 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 weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight were calculated.

Text Table 10
Organs Weighed at Necropsy

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

[a] Paired organ weight.

4.12.5. Tissue Collection and Preservation

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

Text Table 11
Tissue Collection and Preservation

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

[a] Preserved in Davidson's fixative.
[b] Preserved in Modified Davidson's fixative.
[C] Lymph node draining the administration site used on Day 29 (unilateral examination).
[d] Gross lesions were collected and examined only on animals presenting gross abnormalities.

4.12.6. Histology

Tissues identified in Text Table 11 (except animal identification and bone marrow smears) were embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin (refer to Appendix 1 for exceptions).

4.12.7. Histopathology

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

Target tissues identified by the pathologist (i.e. site, injection; lymph node, inguinal; lymph node, popliteal; liver; spleen) were evaluated and reported.

4.12.8. Peer Review

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

The peer review statement is included in Appendix 18.

4.12.9. Bone Marrow Smear Analysis

Two bone marrow smears were prepared from each euthanized animal, air dried and stained with Wright's Giemsa stain.

5. CONSTRUCTED VARIABLES

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

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

6. STATISTICAL ANALYSIS

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

Numerical data collected on scheduled occasions for the listed variables were analyzed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation (or %CV or SE when deemed appropriate) were reported whenever possible. Values may also 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
Cytokine Analysis	X
Organ Weights	X
Body Weight Gains	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparisons were made:

Group 2 vs. Group 1

Group 3 vs. Group 1

Group 4 vs. Group 1

6.1. Parametric/Non-parametric

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

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

7. COMPUTERIZED SYSTEMS

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

Text Table 13
Critical Computerized Systems

System Name	Version No.	Description of Data Collected and/or Analyzed
Provantis	8	In-life; clinical pathology; postmortem
Dispense	8	Test Material receipt, accountability and/or formulation activities
In-house reporting software Nevis (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 5.4 (M5) 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
BioPlex Manager	4.1	Biomarker data collection
Softmax Pro GxP	5.0.1	IFN-α data collection
Watson LIMS	7.2.0.02	Biomarker data analysis

8. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, documentation, study plan, study plan amendments, samples, specimens, and final reports from this study will be transferred to CR MTL archive by no later than the date of final report issue. One year after issue of the audited draft report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Electronic data generated by the Test Facility will be archived as noted above, except that the data collected using Provantis 8 and reporting files stored on SDMS, which will be 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).

All records, retained samples and specimens, and reports generated from phases or segments performed by Sponsor-designated subcontractors were maintained at Integrated BioTherapeutics, Inc. Rockville, MD, USA for archiving. The materials will be retained for at least three years.

9. RESULTS

9.1. Dose Formulation Analyses

(Appendix 3)

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

9.2. End of Use Bulk Test Item Analysis

(Appendix 3 and Appendix 15)

Concentration and particle size results obtained were consistent with the Certificate of Analysis.

The End of Use bulk Test Item analysis demonstrated a purity of 53.1%, which is lower than the original purity results of 75%, provided by the Sponsor per the Certificate of Analysis.

Although the purity analysis indicated RNA degradation, the concentration and particle size were within specification. Study animals showed a significant average antibody response against the ZIKV lysate and increased average antibody titers following the final dose indicating that the potential decrease in purity did not affect activity. As the original doses were not adjusted for purity of the drug product, but based on total mRNA concentration, the nominal dose levels were maintained in the report, tables and appendices.

9.3. Mortality

(Appendix 4)

There were no mortalities during the course of the study.

9.4. Clinical Observations

(Table 1 and Appendix 5)

mRNA-1706-related clinical signs were limited to warm to the touch noted on Day 2, for females given 129 µg/dose.

9.5. Local Irritation Assessment

(Appendix 6)

Edema and, less frequent, erythema, were noted at the injection site following the first dose for males and females given ≥ 13 µg/dose. The incidence and severity of the findings were dose-dependent with increased incidence and severity noted at higher doses of mRNA-1706. Injection site observations consisted of slight to moderate edema with occasional severe edema noted at the highest dose tested and slight to mild erythema. The apex of severity was generally 24 hours post dose and was decreased 72 hours post dose. Between Days 2 and 4 only, the severity of the edema in females given 129 µg/dose was increased and correlated with warmness of the skin observed clinically. Increased severity reaction was noted following the third (last) dose in both genders.

9.6. Body Weights and Body Weight Gains

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

During the weeks of dosing, males and females given 129 µg/dose tend to gain less weight (0.68X and 0.64X controls, respectively) while the body weight gain was higher during the off-dose weeks (1.1X and 1.3X controls, respectively) and Week 2 of the recovery period (1.4X and 3.9X controls, respectively).

9.7. Food Consumption

(Table 4 and Appendix 9)

Slight decreases in food consumption were noted for males and females given 129 µg/dose during dosing weeks and return close to control values during the off-dose weeks and the recovery period.

9.8. Ophthalmic Examinations

(Appendix 13)

There were no mRNA-1706-related ocular changes observed during the course of the study. The findings noted were age-related or incidental in origin and expected in this population of animals.

9.9. Hematology

(Table 5 and Appendix 10)

mRNA-1706-related hematology changes were noted for males and females at ≥ 13 µg/dose. Decreases in reticulocyte (RETIC) and/or platelet (PLT) counts, 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 counts (LYM). These changes are illustrated in Text Table 14.

Text Table 14
Hematology Changes in Rats Administered mRNA-1706

Dose (µg/dose)	13		65		129	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
WBC						
Day 30	**1.6**	–	**2.3**	–	**1.8**	–
Day 43					–	–
NEUT						
Day 30	8.2	**5.5**	**14.1**	**7.2**	**11.7**	**7.0**
Day 43					–	–
LYM						
Day 30	–	0.82	–	**0.47**	–	**0.39**
Day 43						–
EOS						
Day 30	2.1	**4.0**	**2.7**	**3.1**	2.1	**3.6**
Day 43					–	–
LUC						
Day 30	**6.0**	–	**4.1**	–	2.4	–
Day 43					–	–
RETIC						
Day 30	**0.77**	–	**0.68**	–	**0.69**	–
Day 43					–	–
PLT						
Day 30	0.92	0.97	0.92	**0.87**	0.85	**0.76**
Day 43					–	–

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

Mild increases in WBC counts (up to 2.3X controls) were noted in males given ≥ 13 µg/dose, mainly due to minimal to moderate increases in NEUT, EOS and LUC (up to 14.1X, 2.7X and 6.0X controls, respectively). Minimal to mild increases in NEUT and EOS (up to 7.2X and 4.0X controls, respectively) with minimal decreases in LYM (down to 0.39X compared to control) were noted for females at ≥ 13 µg/dose.

Minimal decreases in RETIC was noted for males at ≥ 13 µg/dose (down to 0.68X controls).

Minimal decreases in PLT were noted in males given 129 µg/dose (down to 0.85X controls) and females given ≥ 65 µg/dose (down to 0.76X controls).

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-1706-related.

9.10. Coagulation

(Table 6 and Appendix 11)

mRNA-1706-related increases in fibrinogen (FIB) were noted at ≥ 13 µg/dose. The changes are illustrated in Text Table 15.

Text Table 15
Coagulation Changes in Rats Administered mRNA-1706

Dose (µg/dose)	13		65		129	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
FIB						
Day 30	**2.2**	**2.0**	**2.5**	**2.2**	**2.4**	**1.9**
Day 43					–	–

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

Mild increases in FIB were noted for males and females given ≥ 13 µg/dose (up to 2.5X and 2.2X controls, respectively).

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-1706-related.

9.11. Clinical Chemistry

(Table 7 and Appendix 12)

mRNA-1706-related clinical chemistry changes in globulin (GLOB) and A/G ratio were noted for males given ≥ 13 µg/dose. These changes are illustrated in Text Table 16.

Text Table 16
Clinical Chemistry Changes in Rats Administered mRNA-1706

Dose (µg/dose)	13		65		129	
Parameter	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
GLOB						
Day 30	**1.3**	–	**1.3**	–	**1.3**	–
Day 43					–	–
A/G						
Day 30	**0.70**	–	**0.71**	–	**0.71**	–
Day 43					–	–

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

Minimal increases in GLOB were noted for males at ≥ 13 µg/dose (up to 1.3X controls) and affected the A/G ratio in that gender (down to 0.70Xto controls).

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-1706-related.

9.12. Cytokines

(Appendix 14)

Increases in IP-10 and MCP-1 concentrations were observed in males and females. Higher IP-10 concentrations were observed on Day 29, 6 hours post-dose in males and on Day 1, 6 hours post-dose in females while higher MCP-1 concentrations were observed on Day 29, 6 hours post-dose for both genders. These changes were statistically significant when compared to controls. At the end of the recovery period, IP-10 and MCP-1 levels were back to the control range.

No changes in MIP-1α were noted in males. In females, increases in MIP-1α concentrations were observed on Day 15 and Day 29, 6 hours post-dose. Peak concentrations were generally reached on Day 29, 6 hours post-dose. The changes observed were statistically significant. MIP-1α concentrations were back to the control range at the end of the recovery period.

No changes in TNF-α were noted in females given mRNA-1706. Statistically significant increases were however observed in treated males on Day 15, 6 hours post-dose.

No mRNA-1706-related changes were observed in IL-1β and IL-6.

Note that the IFN-α results are considered invalid since samples were analyzed with a rat interferon alpha antibody ELISA kit which detect anti-IFN-α antibodies instead of the cytokine IFN-α.

9.13. Anti-therapeutic Antibody (ATA) Analysis

(Appendix 16)

On Day 30, sera from animals given mRNA-1706 at 13 µg/dose, 65 µg/dose, 129 µg/dose on Days 1, 15, and 29 intramuscularly showed detectable antibody responses against the ZIKV lysate. On Day 43, the antibody titers were higher than those on Day 30.

9.14. Gross Pathology

(Appendix 17)

9.14.1. Terminal Euthanasia(Day 30)

mRNA-1706-related gross pathology findings were limited to the injection site (firm consistency, swelling) and to the inguinal, popliteal, and iliac lymph nodes (enlargement), and are summarized in Text Table 17.

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

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**13**	**65**	**129**	**0**	**13**	**65**	**129**
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	10	10	10	0	10	10	10
Swelling	0	4	7	7	0	6	8	9
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	2	5	6	0	1	1	4
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Enlargement	0	3	8	7	0	4	5	4
Lymph node[a,b] (No. Examined)	0	1	7	4	0	2	4	6
Enlargement	0	1	7	4	0	2	4	6

[a] The tissue, Lymph node, included iliac and mediastinal lymph nodes at collection. Here, only iliac lymph nodes are presented.
[b] Tissues presented are considered as gross lesions.

Other gross findings observed were considered incidental, of the nature commonly observed in this strain and age of Sprague-Dawley rats, and/or were of similar incidence in control and Test Item-treated animals and, therefore, were considered not mRNA-1706-related.

9.14.2. Recovery Euthanasia(Day 43)

(Appendix 17)

mRNA-1706-related enlargement of the lymph nodes noted at the terminal euthanasia was still observed, but at a lower incidence, in males at the end of the recovery period (Day 43) and is summarized in Text Table 18, however no microscopic correlate was noted at this time point. Injection sites were grossly unremarkable at the end of the recovery period.

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

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**13**	**65**	**129**	**0**	**13**	**65**	**129**
No. Animals Examined	**5**	**-**	**-**	**5**	**5**	**-**	**-**	**5**
Lymph node, inguinal (No. Examined)	5	-	-	5	5	-	-	5
Enlargement	0	-	-	2	0	-	-	0
Lymph node, popliteal (No. Examined)	5	-	-	5	5	-	-	5
Enlargement	0	-	-	2	0	-	-	0

9.15. Organ Weights

(Appendix 17)

There were no mRNA-1706-related organ weight changes noted at the terminal and recovery necropsies.

There were isolated organ weight values that were statistically different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. Thus, the organ weight differences observed were considered incidental and/or related to difference of sexual maturity and not mRNA-1706-related.

9.16. Histopathology

(Appendix 17)

9.16.1. Terminal Euthanasia (Day 30)

mRNA-1706-related microscopic findings were noted in the liver of males, and in both genders in the spleen, the injection site, and in tissues surrounding lymph nodes regional to the injection site, and are summarized in Text Table 19.

Text Table 19
Summary of Microscopic Findings – Terminal Euthanasia (Day 30)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (µg/dose)	**0**	**13**	**65**	**129**	**0**	**13**	**65**	**129**
No. Animals Examined	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Liver (No. Examined)	10	10	10	10	10	10	10	10
Vacuolation	(1)	(3)	(4)	(5)	(7)	(8)	(8)	(5)
Minimal	1	3	4	5	7	8	8	5
Spleen (No. Examined)	10	10	10	10	10	10	10	10
Decreased cellularity; lymphoid, periarteriolar lymphoid sheath	(0)	(4)	(7)	(10)	(0)	(5)	(9)	(10)
Minimal	0	4	7	7	0	5	9	5
Mild	0	0	0	3	0	0	0	5
Site, injection (No. Examined)	10	10	10	10	10	10	10	10
Inflammation	(0)[a]	(10)	(10)	(10)	(0)	(10)	(10)	(10)
Minimal	0	0	0	0	0	1	0	0
Mild	0	0	0	0	0	6	2	4
Moderate	0	10	10	10	0	3	8	6
Lymph node, inguinal (No. Examined)	10	10	10	10	10	10	10	10
Infiltration, mixed cell	(0)	(0)	(0)	(2)	(0)	(0)	(1)	(3)
Minimal	0	0	0	1	0	0	0	0
Mild	0	0	0	1	0	0	1	3
Lymph node, popliteal (No. Examined)	10	10	10	10	10	10	10	10
Infiltration, mixed cell	(0)	(6)	(7)	(8)	(0)	(9)	(10)	(9)
Minimal	0	0	2	6	0	7	4	2
Mild	0	6	5	2	0	2	6	7

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

Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of Sprague-Dawley rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered not mRNA-1706-related.

9.16.2. Recovery Euthanasia (Day 43)

Findings noted at the terminal euthanasia were not observed at the end of the recovery period (Day 43). Other microscopic findings observed were considered incidental, of the nature commonly observed in this strain and age of Sprague-Dawley rats, and/or were of similar incidence and severity in control and treated animals and, therefore, were considered not mRNA-1706-related.

10. CONCLUSION

In conclusion, administration of mRNA-1706 by intramuscular injection for 1 month (3 doses) was clinically well tolerated in rats up to 129 µg/dose. A positive antibody response against ZIKV was determined at the end of the dosing period which persisted, as determined by a higher antibody titers noted following a two-week recovery period. At ≥ 13 µg/dose, dose-dependent changes in clinical signs, clinical pathology parameters and cytokines levels were consistent with an inflammatory response at the injection site. Dose-dependent target organ effects were limited to the injection site, tissues surrounding lymph nodes regional to the injection site, spleen, and liver of animals given mRNA-1706. At the end of the recovery period, all changes were partially or fully recovered.

Figure 1

Summary of Body Weights - Males

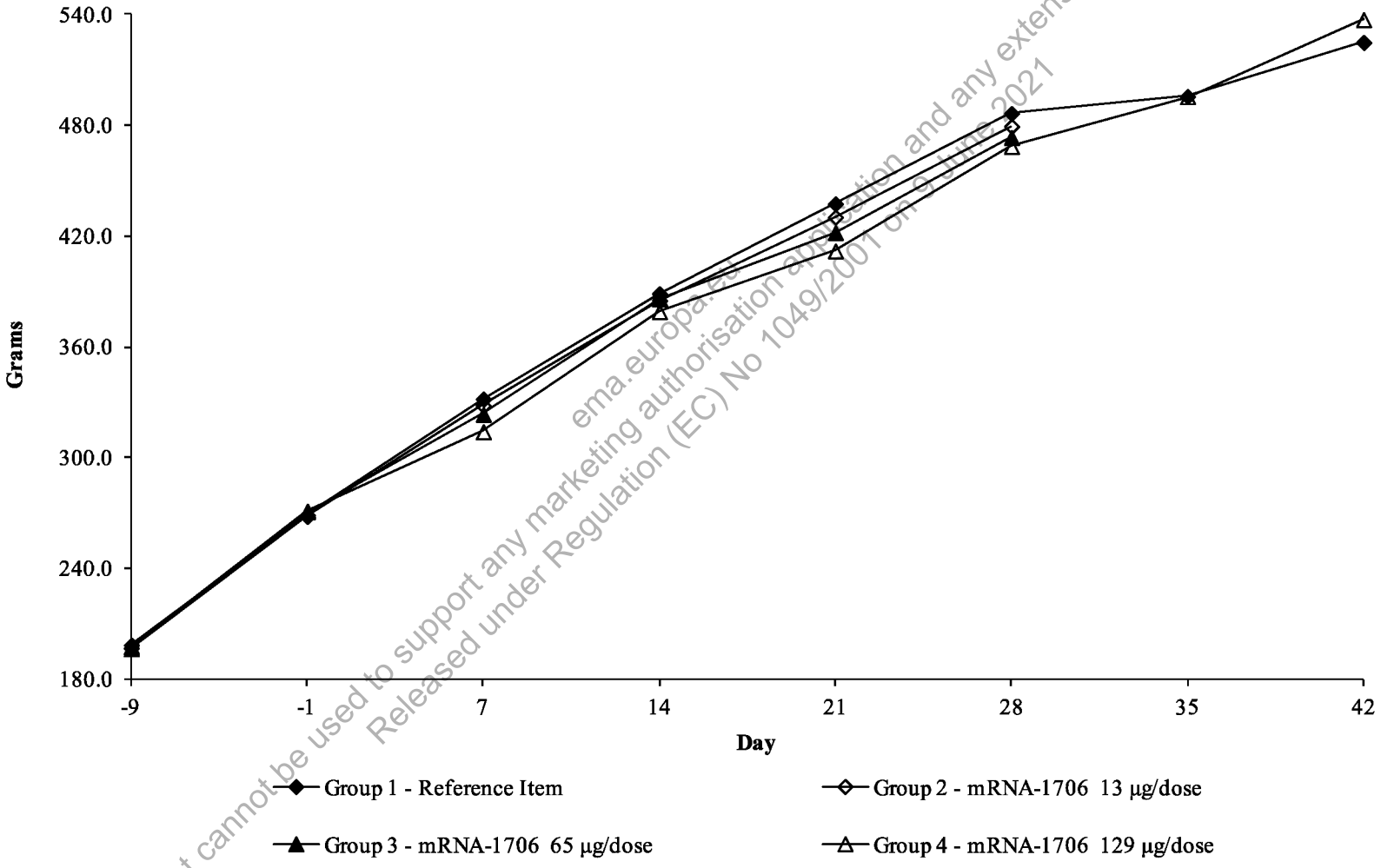

Figure 2

Summary of Body Weights - Females

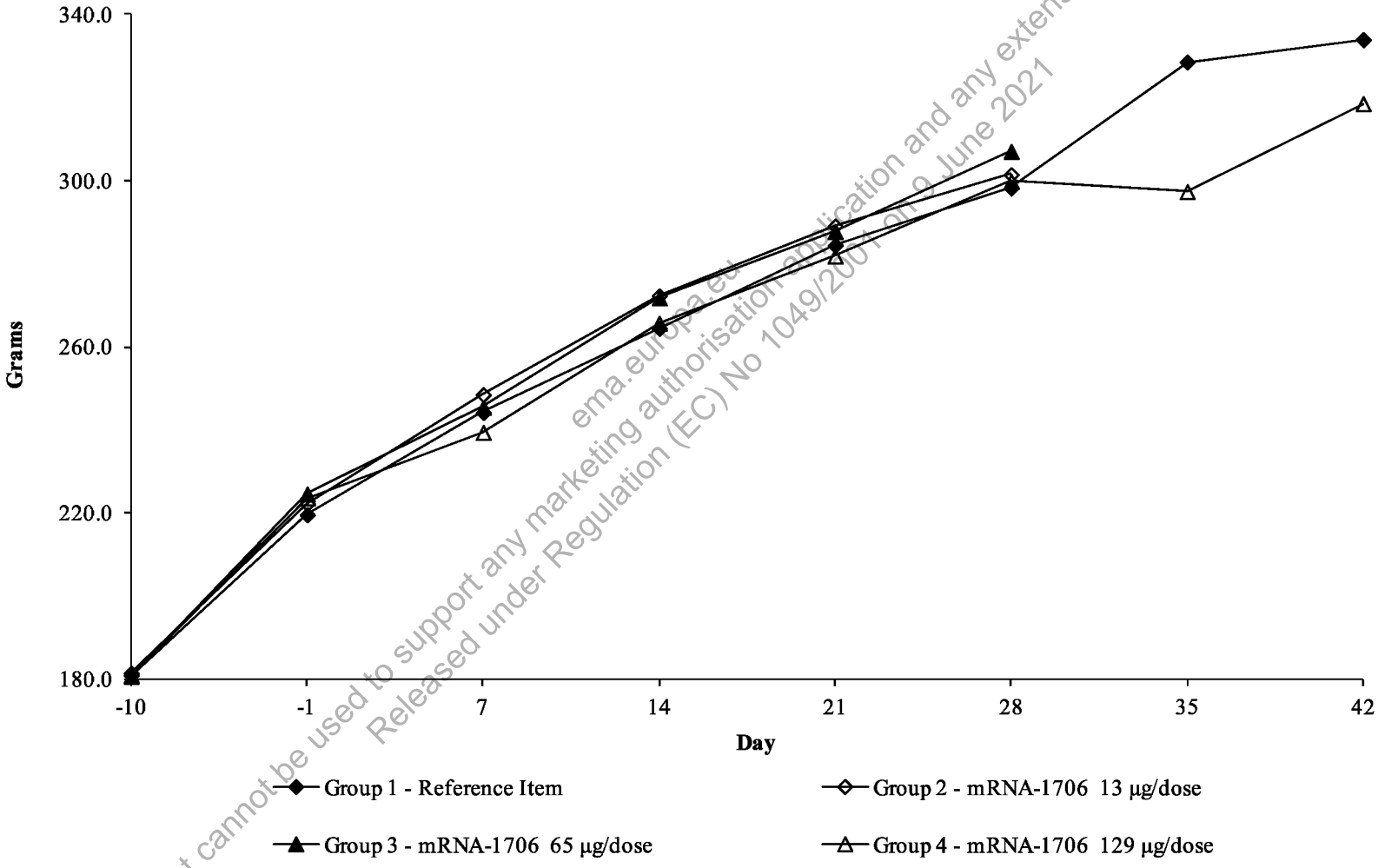

Table 1

Summary of Clinical Observations

5002045

Day numbers relative to Start Date

Sex: Male

	0 ug/dose	13 ug/dose	65 ug/dose	129 ug/dose
Skin, Red				
Number of Observations	.	1	.	.
Number of Animals	.	1	.	.
Days from - to	.	21 21	.	.
Skin, Scab				
Number of Observations	14	3	2	14
Number of Animals	6	3	1	6
Days from - to	14 43	-1 30	-1 7	-1 43
Fur, Erected				
Number of Observations	.	.	1	.
Number of Animals	.	.	1	.
Days from - to	.	.	-14 -14	.
Fur, Staining, Brown				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	43 43
Fur, Staining, Red				
Number of Observations	1	.	.	2
Number of Animals	1	.	.	1
Days from - to	28 28	.	.	21 28
Fur, Thin Cover				
Number of Observations	.	1	2	11
Number of Animals	.	1	2	6
Days from - to	.	28 28	-1 -1	-1 30
Nictitating MembraneProtruding				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	-14 -14

Table 1

Summary of Clinical Observations

5002045

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	13 ug/dose	65 ug/dose	129 ug/dose
Vocalization Increased				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	-1 -1
Caught in Cage				
Number of Observations	1	.	.	.
Number of Animals	1	.	.	.
Days from - to	7 7	.	.	.
Dehydrated Suspected				
Number of Observations	.	.	.	1
Number of Animals	.	.	.	1
Days from - to	.	.	.	2 2
Warm to Touch				
Number of Observations	.	.	.	15
Number of Animals	.	.	.	15
Days from - to	.	.	.	2 2
Skin, Red				
Number of Observations	2	.	.	1
Number of Animals	1	.	.	1
Days from - to	42 43	.	.	30 30
Skin, Dry				
Number of Observations	2	.	.	.
Number of Animals	1	.	.	.
Days from - to	42 43	.	.	.
Skin, Lesion				
Number of Observations	2	.	1	.
Number of Animals	2	.	1	.
Days from - to	3 7	.	-1 -1	.

Table 1

Summary of Clinical Observations

5002045

Day numbers relative to Start Date

Sex: Female

	0 ug/dose	13 ug/dose	65 ug/dose	129 ug/dose
Skin, Scab				
Number of Observations	15	3	4	9
Number of Animals	8	1	3	5
Days from - to	-1 30	-1 14	7 30	7 43
Fur, Staining, Red				
Number of Observations	1	.	.	7
Number of Animals	1	.	.	4
Days from - to	43 43	.	.	28 43
Fur, Thin Cover				
Number of Observations	5	3	.	1
Number of Animals	1	1	.	1
Days from - to	-1 30	-1 14	.	21 21
Tail, Sloughing				
Number of Observations	2	.	.	.
Number of Animals	1	.	.	.
Days from - to	28 30	.	.	.
Pinna Partly Missing				
Number of Observations	7	.	4	5
Number of Animals	1	.	1	1
Days from - to	7 43	.	14 30	7 30
Nail Missing				
Number of Observations	3	.	.	.
Number of Animals	1	.	.	.
Days from - to	14 28	.	.	.

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day -9	-1	7	14	21	28	35	42
1M	Mean	198.5	268.9	331.7	388.9	437.6	486.5	495.8	525.0
	SD	10.4	17.6	24.2	30.0	34.5	38.0	36.0	33.6
	N	15	15	15	15	15	15	5	5
2M	Mean	196.9	268.2	328.1	385.2	430.4	479.5	--	--
	SD	5.7	10.2	13.2	14.1	18.8	22.1	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	-0.8	-0.2	-1.1	-1.0	-1.6	-1.4	--	--
3M	Mean	196.4	270.6	323.5	386.2	422.0	473.5	--	--
	SD	5.8	7.9	9.5	12.9	16.3	19.8	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	-1.1	0.6	-2.5	-0.7	-3.6	-2.7	--	--
4M	Mean	197.7	271.1	314.1	379.2	412.1	468.7	495.6	537.4
	SD	9.1	14.2	18.9	24.4	30.4	37.2	58.3	57.2
	N	15	15	15	15	15	15	5	5
	%Diff G1	-0.4	0.8	-5.3	-2.5	-5.8	-3.6	0.0	2.4

Table 2

Summary of Body Weights (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day -10	-1	7	14	21	28	35	42
1F	Mean	180.9	219.6	244.2	264.5	284.5	298.3	328.6	334.0
	SD	7.0	10.2	13.2	16.2	20.6	21.8	30.9	30.6
	N	15	15	15	15	15	15	5	5
2F	Mean	181.4	222.3	248.5	272.3	289.1	301.5	--	--
	SD	4.2	7.9	9.1	14.1	16.5	18.8	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	0.3	1.2	1.8	2.9	1.6	1.1	--	--
3F	Mean	180.9	224.6	245.4	271.8	287.8	307.1	--	--
	SD	4.0	8.6	12.6	20.5	22.7	25.9	--	--
	N	10	10	10	10	10	10	--	--
	%Diff G1	0.0	2.3	0.5	2.7	1.2	3.0	--	--
4F	Mean	180.7	223.6	239.4	265.7	281.9	299.9	297.4	318.6
	SD	7.0	13.9	16.6	23.5	21.5	22.0	12.6	11.5
	N	15	15	15	15	15	15	5	5
	%Diff G1	-0.1	1.8	-2.0	0.5	-0.9	0.5	-9.5	-4.6

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day Change -9 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change -1 - 28	Change 28 - 35
1M	Mean	70.3	62.9	57.2	48.7	48.9	217.6	20.8
	SD	8.6	10.2	8.4	6.0	6.8	26.2	8.8
	N	15	15	15	15	15	15	5
2M	Mean	71.3	59.9	57.1	45.2	49.1	211.3	--
	SD	7.5	5.8	4.4	7.3	7.0	19.2	--
	N	10	10	10	10	10	10	--
3M	Mean	74.2	52.9a	62.7	35.8f	51.5	202.9	--
	SD	4.3	3.8	6.9	4.6	8.1	16.5	--
	N	10	10	10	10	10	10	--
4M	Mean	73.5	43.0c	65.1e	32.9f	56.7d	197.6	16.2
	SD	7.4	8.1	6.4	9.1	9.4	27.1	7.5
	N	15	15	15	15	15	15	5

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

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day Change 35 - 42	Day Change 28 - 42
1M	Mean	29.2	50.0
	SD	5.2	7.0
	N	5	5
2M	Mean	--	--
	SD	--	--
	N	--	--
3M	Mean	--	--
	SD	--	--
	N	--	--
4M	Mean	41.8b	58.0
	SD	4.0	7.1
	N	5	5

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

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day						
		Change -10 - -1	Change -1 - 7	Change 7 - 14	Change 14 - 21	Change 21 - 28	Change -1 - 28	Change 28 - 35
1F	Mean	38.7	24.6	20.3	19.9	13.8	78.7	26.0
	SD	7.5	6.7	5.0	6.7	5.7	16.0	19.0
	N	15	15	15	15	15	15	5
2F	Mean	40.9	26.2	23.8	16.8	12.4	79.2	--
	SD	6.9	4.1	6.5	4.9	5.8	13.1	--
	N	10	10	10	10	10	10	--
3F	Mean	43.7	20.8	26.4	16.0	19.3a	82.5	--
	SD	6.0	6.1	10.5	8.1	5.1	20.3	--
	N	10	10	10	10	10	10	--
4F	Mean	42.9	15.8b	26.3	16.2	17.9	76.3	9.4
	SD	9.2	9.0	7.9	9.8	4.6	11.8	5.5
	N	15	15	15	15	15	15	5

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

Table 3

Summary of Body Weight Gains (g)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day Change 35 - 42	Day Change 28 - 42
1F	Mean	5.4	31.4
	SD	21.7	11.7
	N	5	5
2F	Mean	--	--
	SD	--	--
	N	--	--
3F	Mean	--	--
	SD	--	--
	N	--	--
4F	Mean	21.2	30.6
	SD	1.9	4.4
	N	5	5

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day (From/To) -7/1	1/8	8/15	15/22	22/29	29/36	36/42
1M	Mean	29.27	31.01	32.30	32.97	33.59	31.60	32.86
	SD	2.32	2.37	2.36	2.44	2.24	1.10	1.15
	N	15	15	15	15	15	5	5
2M	Mean	27.90	29.69	32.55	32.17	33.86	--	--
	SD	1.25	0.87	1.14	1.53	1.50	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	-4.67	-4.25	0.77	-2.44	0.79	--	--
3M	Mean	28.19	27.84	32.36	29.21	32.76	--	--
	SD	0.67	0.25	0.97	1.26	1.27	--	--
	N	10	10	7	10	10	--	--
	%Diff G1	-3.68	-10.21	0.18	-11.41	-2.48	--	--
4M	Mean	28.92	27.21	33.90	30.17	35.55	33.48	38.16
	SD	1.85	2.36	2.63	3.08	2.94	4.22	3.78
	N	12	15	15	15	15	5	5
	%Diff G1	-1.20	-12.23	4.95	-8.51	5.81	5.95	16.13

Table 4

Summary of Food Consumption (g/animal/day)

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		Day (From/To)						
		-7/1	1/8	8/15	15/22	22/29	29/36	36/42
1F	Mean	20.55	21.72	23.35	23.59	24.48	26.84	25.84
	SD	1.16	1.20	1.67	1.38	1.14	0.77	1.04
	N	15	15	15	15	15	5	5
2F	Mean	20.63	21.54	23.15	22.50	23.60	--	--
	SD	0.68	1.02	0.98	1.05	0.92	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	0.41	-0.83	-0.87	-4.61	-3.59	--	--
3F	Mean	21.69	21.64	24.20	23.27	25.85	--	--
	SD	0.65	1.53	2.72	2.45	1.85	--	--
	N	10	10	10	10	10	--	--
	%Diff G1	5.56	-0.37	3.63	-1.34	5.60	--	--
4F	Mean	21.23	20.06	22.85	22.07	24.32	21.58	24.84
	SD	1.23	0.59	1.22	0.96	1.23	0.44	0.05
	N	15	15	15	15	15	5	5
	%Diff G1	3.34	-7.64	-2.17	-6.44	-0.65	-19.60	-3.87

Table 5

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	7.999	0.794	6.906	0.158	0.070	0.014	0.057
	SD	1.232	0.192	1.143	0.034	0.033	0.007	0.013
	N	10	10	10	10	10	10	10
2M	Mean	13.136f	6.501	5.892	0.264b	0.147	0.019	0.341c
	SD	2.148	1.405	1.233	0.128	0.052	0.011	0.113
	N	10	10	10	10	10	10	9
	%Diff G1	64.221	718.766	-14.683	67.089	110.000	35.714	498.441
3M	Mean	18.125f	11.215c	6.231	0.253	0.189b	0.028d	0.234c
	SD	2.435	1.958	1.774	0.148	0.095	0.015	0.079
	N	10	10	10	10	10	10	9
	%Diff G1	126.591	1312.469	-9.774	60.127	170.000	100.000	311.306
4M	Mean	14.212f	9.256c	4.487d	0.211	0.149	0.010	0.137
	SD	3.111	1.479	2.703	0.070	0.124	0.009	0.063
	N	10	10	10	10	10	10	7
	%Diff G1	77.672	1065.743	-35.028	33.544	112.857	-28.571	140.602

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 Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.770	14.41	42.64	54.92	18.55	33.76	12.34
	SD	0.238	0.37	1.15	2.01	0.67	0.44	0.52
	N	10	10	10	10	10	10	10
2M	Mean	7.968	14.67	43.19	54.19	18.41	33.95	12.80
	SD	0.271	0.59	1.60	1.40	0.47	0.28	0.31
	N	10	10	10	10	10	10	10
	%Diff G1	2.548	1.80	1.29	-1.33	-0.75	0.56	3.73
3M	Mean	7.805	14.41	42.63	54.63	18.48	33.82	13.12c
	SD	0.338	0.78	2.21	1.70	0.79	0.65	0.38
	N	10	10	10	10	10	10	10
	%Diff G1	0.450	0.00	-0.02	-0.53	-0.38	0.18	6.32
4M	Mean	7.965	15.00	44.21	55.55	18.83	33.93	13.58c
	SD	0.312	0.53	1.31	1.70	0.73	0.54	0.50
	N	10	10	10	10	10	10	10
	%Diff G1	2.510	4.09	3.68	1.15	1.51	0.50	10.05

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

Table 5

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1117.7	257.59
	SD	172.9	35.75
	N	10	10
2M	Mean	1027.2	198.37c
	SD	255.8	18.00
	N	10	10
	%Diff G1	-8.1	-22.99
3M	Mean	1029.5	174.65c
	SD	158.7	22.90
	N	10	10
	%Diff G1	-7.9	-32.20
4M	Mean	949.6	176.42c
	SD	179.2	35.00
	N	10	10
	%Diff G1	-15.0	-31.51

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

Table 5

Summary of Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		WBC 10^3/uL	NEUT 10^3/uL	LYMPH 10^3/uL	MONO 10^3/uL	EOS 10^3/uL	BASO 10^3/uL	LUC 10^3/uL
1F	Mean	7.061	0.802	5.959	0.174	0.058	0.010	0.058
	SD	1.321	0.322	1.247	0.066	0.016	0.005	0.038
	N	9	9	9	9	9	9	9
2F	Mean	9.875	4.397a	4.903	0.147	0.232c	0.017	0.177a
	SD	2.542	1.101	1.711	0.064	0.080	0.009	0.125
	N	10	10	10	10	10	10	10
	%Diff G1	39.851	448.102	-17.720	-15.732	301.538	70.000	206.346
3F	Mean	8.931	5.757c	2.813f	0.114	0.178a	0.005	0.070
	SD	2.117	0.917	1.410	0.088	0.111	0.007	0.020
	N	10	10	10	10	10	10	9
	%Diff G1	26.482	617.632	-52.793	-34.650	208.077	-50.000	21.154
4F	Mean	8.316	5.576c	2.308f	0.116	0.206b	0.009	0.112
	SD	2.905	2.377	0.810	0.066	0.085	0.006	0.062
	N	10	10	10	10	10	10	9
	%Diff G1	17.772	595.069	-61.268	-33.503	256.538	-10.000	94.231

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 Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.783	14.24	40.39	51.89	18.31	35.30	10.83
	SD	0.329	0.46	1.27	1.29	0.70	0.52	0.27
	N	9	9	9	9	9	9	9
2F	Mean	7.866	14.49	41.13	52.33	18.43	35.23	11.10
	SD	0.592	0.93	2.90	0.98	0.56	0.55	0.26
	N	10	10	10	10	10	10	10
	%Diff G1	1.062	1.72	1.83	0.85	0.65	-0.20	2.46
3F	Mean	7.975	14.99	42.33	53.12	18.85	35.47	11.91f
	SD	0.392	0.54	1.52	1.73	0.73	0.53	0.36
	N	10	10	10	10	10	10	10
	%Diff G1	2.463	5.23	4.81	2.37	2.94	0.48	9.94
4F	Mean	8.120	15.16a	42.88a	52.84	18.68	35.34	12.22f
	SD	0.435	0.67	2.08	1.17	0.51	0.37	0.41
	N	10	10	10	10	10	10	10
	%Diff G1	4.325	6.43	6.17	1.83	2.01	0.11	12.80

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 Hematology Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1145.8	194.90
	SD	85.3	35.25
	N	9	9
2F	Mean	1115.8	150.91b
	SD	127.5	17.17
	N	10	10
	%Diff G1	-2.6	-22.57
3F	Mean	995.0a	176.97
	SD	109.0	33.10
	N	10	10
	%Diff G1	-13.2	-9.20
4F	Mean	866.2c	192.20
	SD	140.9	34.21
	N	10	10
	%Diff G1	-24.4	-1.39

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

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	9.914	1.204	8.326	0.212	0.100	0.016	0.050
	SD	2.212	0.350	2.049	0.073	0.043	0.009	0.025
	N	5	5	5	5	5	5	5
4M	Mean	8.226	1.456	6.430	0.238	0.066	0.016	0.024
	SD	1.949	0.531	1.704	0.144	0.032	0.005	0.009
	N	5	5	5	5	5	5	5
	%Diff G1	-17.026	20.930	-22.772	12.264	-34.000	0.000	-52.000

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1M	Mean	7.580	13.32	40.38	53.28	17.56	32.98	12.56
	SD	0.285	0.37	1.17	2.02	0.59	0.18	0.90
	N	5	5	5	5	5	5	5
4M	Mean	7.416	13.32	40.72	54.94	17.98	32.72	13.66
	SD	0.199	0.29	0.72	1.28	0.46	0.43	0.71
	N	5	5	5	5	5	5	5
	%Diff G1	-2.164	0.00	0.84	3.12	2.39	-0.79	8.76

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1M	Mean	1095.0	221.56
	SD	233.2	25.57
	N	5	5
4M	Mean	1114.6	245.88
	SD	155.1	33.19
	N	5	5
	%Diff G1	1.8	10.98

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	6.810	0.664	5.900	0.120	0.068	0.010	0.042
	SD	1.901	0.288	1.628	0.059	0.022	0.007	0.020
	N	5	5	5	5	5	5	5
4F	Mean	6.462	0.756	5.498	0.112	0.050	0.008	0.038
	SD	2.512	0.329	2.131	0.048	0.012	0.008	0.025
	N	5	5	5	5	5	5	5
	%Diff G1	-5.110	13.855	-6.814	-6.667	-26.471	-20.000	-9.524

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		RBC 10^6/uL	HGB g/dL	HCT %	MCV fL(um3)	MCH pg	MCHC g/dL	RDW %
1F	Mean	7.480	13.30	39.70	53.10	17.78	33.50	11.28
	SD	0.489	0.84	2.06	0.99	0.22	0.57	0.13
	N	5	5	5	5	5	5	5
4F	Mean	7.060	12.82	38.96	55.22a	18.14	32.86	13.16d
	SD	0.227	0.19	0.39	1.52	0.42	0.26	0.46
	N	5	5	5	5	5	5	5
	%Diff G1	-5.615	-3.61	-1.86	3.99	2.02	-1.91	16.67

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

Table 5

Summary of Hematology Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PLT 10^3/uL	RETIC 10^9/L
1F	Mean	1100.0	166.46
	SD	58.7	42.62
	N	5	5
4F	Mean	1231.0	225.46a
	SD	135.3	24.89
	N	5	5
	%Diff G1	11.9	35.44

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 Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	15.12	15.57	300.8
	SD	1.40	0.69	28.9
	N	10	10	10
2M	Mean	13.86	18.27f	662.0f
	SD	0.49	0.67	51.0
	N	10	10	10
	%Diff G1	-8.33	17.34	120.1
3M	Mean	12.79b	19.95f	742.3f
	SD	0.51	0.70	55.1
	N	10	10	10
	%Diff G1	-15.41	28.13	146.8
4M	Mean	19.78	12.37f	727.7f
	SD	2.14	0.53	56.5
	N	10	10	10
	%Diff G1	30.82	-20.55	141.9

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 Coagulation Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	15.04	15.64	236.3
	SD	0.60	0.74	21.2
	N	9	9	9
2F	Mean	15.33	18.76c	478.6c
	SD	0.90	1.14	24.4
	N	10	10	10
	%Diff G1	1.90	19.91	102.5
3F	Mean	15.29	19.17c	510.5c
	SD	0.48	0.93	29.8
	N	10	10	10
	%Diff G1	1.63	22.54	116.0
4F	Mean	16.45b	20.28c	457.5c
	SD	1.07	0.71	34.9
	N	10	10	10
	%Diff G1	9.34	29.63	93.6

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

Table 6

Summary of Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1M	Mean	17.02	15.96	271.2
	SD	0.84	0.66	15.7
	N	5	5	5
4M	Mean	17.43	15.88	254.8
	SD	0.97	0.49	18.1
	N	4	4	4
	%Diff G1	2.38	-0.53	-6.1

Table 6

Summary of Coagulation Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		PT sec	APTT sec	FIB mg/dL
1F	Mean	17.14	15.48	226.8
	SD	0.62	0.24	19.9
	N	5	5	5
4F	Mean	17.70	16.00a	206.4
	SD	0.53	0.37	19.7
	N	5	5	5
	%Diff G1	3.27	3.36	-9.0

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

Table 7

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	71.9	42.9	161.0	2.0	346.5	0.070	13.8
	SD	17.1	9.6	39.5	0.0	187.2	0.017	2.3
	N	10	10	10	10	10	10	10
2M	Mean	90.8	44.1	161.9	2.0	631.7	0.087	17.5a
	SD	23.4	7.7	30.2	0.0	382.2	0.025	2.8
	N	10	10	10	10	10	10	10
	%Diff G1	26.3	2.8	0.6	0.0	82.3	24.286	26.8
3M	Mean	78.8	38.9	164.7	2.0	410.9	0.097a	17.5a
	SD	15.6	4.8	23.6	0.0	197.7	0.025	2.8
	N	10	10	10	10	10	10	10
	%Diff G1	9.6	-9.3	2.3	0.0	18.6	38.571	26.8
4M	Mean	96.1a	42.5	212.2b	2.0	521.0	0.102a	16.9a
	SD	18.2	10.5	42.0	0.0	285.9	0.029	3.0
	N	10	10	10	10	10	10	10
	%Diff G1	33.7	-0.9	31.8	0.0	50.4	45.714	22.5

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

Table 7

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	0.30	211.0	78.4	83.8	5.63	3.86	1.77
	SD	0.00	48.6	20.1	45.9	0.21	0.11	0.22
	N	10	10	10	10	10	10	10
2M	Mean	0.36	177.6	65.5	55.6	5.78	3.49f	2.29f
	SD	0.05	35.1	11.1	21.0	0.23	0.12	0.15
	N	10	10	10	10	10	10	10
	%Diff G1	20.00	-15.8	-16.5	-33.7	2.66	-9.59	29.38
3M	Mean	0.42c	173.8	73.2	60.8	5.85	3.55f	2.30f
	SD	0.06	20.1	16.6	17.3	0.20	0.13	0.17
	N	10	10	10	10	10	10	10
	%Diff G1	40.00	-17.6	-6.6	-27.4	3.91	-8.03	29.94
4M	Mean	0.40c	163.3	77.3	69.6	5.83	3.55f	2.28f
	SD	0.05	31.9	17.4	27.8	0.26	0.13	0.21
	N	10	10	10	10	10	10	10
	%Diff G1	33.33	-22.6	-1.4	-16.9	3.55	-8.03	28.81

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

Table 7

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	2.21	10.49	8.66	140.4	5.04	101.2
	SD	0.30	0.17	0.74	1.6	0.27	1.6
	N	10	10	10	10	10	10
2M	Mean	1.54c	10.87e	8.47	139.4	5.59e	100.0
	SD	0.11	0.26	0.49	1.2	0.41	1.2
	N	10	10	10	10	10	10
	%Diff G1	-30.32	3.62	-2.19	-0.7	10.91	-1.2
3M	Mean	1.56c	10.88e	8.82	139.5	5.65e	100.4
	SD	0.13	0.35	0.70	1.0	0.36	0.7
	N	10	10	10	10	10	10
	%Diff G1	-29.41	3.72	1.85	-0.6	12.10	-0.8
4M	Mean	1.57c	10.66	9.31	140.1	5.78f	100.5
	SD	0.16	0.24	0.67	1.0	0.42	1.2
	N	10	10	10	10	10	10
	%Diff G1	-28.96	1.62	7.51	-0.2	14.68	-0.7

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

Table 7

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	97.5	32.9	95.4	2.0	525.5	0.075	15.1
	SD	26.3	6.1	22.0	0.0	274.0	0.022	1.4
	N	10	10	10	10	10	10	10
2F	Mean	104.9	53.9a	86.9	2.0	457.0	0.092	16.8
	SD	36.6	25.0	19.9	0.0	328.0	0.023	2.8
	N	10	10	10	10	10	10	10
	%Diff G1	7.6	63.8	-8.9	0.0	-13.0	22.667	11.3
3F	Mean	112.1	51.3	109.5	2.0	459.7	0.098	17.3
	SD	27.6	29.5	16.3	0.0	400.6	0.020	2.7
	N	10	10	10	10	10	10	10
	%Diff G1	15.0	55.9	14.8	0.0	-12.5	30.667	14.6
4F	Mean	132.6	41.7	126.4e	2.0	446.2	0.115e	14.8
	SD	63.4	14.3	20.4	0.0	384.2	0.025	2.3
	N	10	10	10	10	10	10	10
	%Diff G1	36.0	26.7	32.5	0.0	-15.1	53.333	-2.0

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

Table 7

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 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	129.2	76.5	50.1	6.31	4.54	1.77
	SD	0.06	16.5	12.0	22.0	0.36	0.30	0.22
	N	10	10	10	10	10	10	10
2F	Mean	0.39	149.8	85.6	49.4	6.33	4.36	1.97
	SD	0.03	39.8	15.0	15.1	0.26	0.16	0.16
	N	10	10	10	10	10	10	10
	%Diff G1	-7.14	15.9	11.9	-1.4	0.32	-3.96	11.30
3F	Mean	0.44	144.9	92.3	61.1	6.22	4.26a	1.96
	SD	0.07	20.3	26.8	25.8	0.31	0.23	0.12
	N	10	10	10	10	10	10	10
	%Diff G1	4.76	12.2	20.7	22.0	-1.43	-6.17	10.73
4F	Mean	0.43	143.2	69.3	50.4	5.87b	4.16b	1.71
	SD	0.05	14.3	16.5	11.5	0.30	0.21	0.24
	N	10	10	10	10	10	10	10
	%Diff G1	2.38	10.8	-9.4	0.6	-6.97	-8.37	-3.39

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

Table 7

Summary of Clinical Chemistry Values: Day 30

Group 1 - Reference Item
Group 2 - mRNA-1706 13 µg/dose
Group 3 - mRNA-1706 65 µg/dose
Group 4 - mRNA-1706 129 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.61	10.89	7.17	141.2	4.57	102.2
	SD	0.40	0.38	0.39	1.5	0.27	1.5
	N	10	10	10	10	10	10
2F	Mean	2.22	11.09	7.19	140.4	4.67	101.0
	SD	0.18	0.25	0.35	1.2	0.39	1.3
	N	10	10	10	10	10	10
	%Diff G1	-14.94	1.84	0.28	-0.6	2.19	-1.2
3F	Mean	2.17a	10.89	7.71d	140.6	4.65	100.3
	SD	0.12	0.29	0.45	1.2	0.35	1.5
	N	10	10	10	10	10	10
	%Diff G1	-16.86	0.00	7.53	-0.4	1.75	-1.9
4F	Mean	2.50	10.51d	7.33	140.5	4.72	101.6
	SD	0.46	0.33	0.63	1.5	0.33	3.0
	N	10	10	10	10	10	10
	%Diff G1	-4.21	-3.49	2.23	-0.5	3.28	-0.6

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

Table 7

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 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	103.2	43.0	133.6	2.0	623.6	0.044	17.2
	SD	14.8	6.4	40.0	0.0	206.8	0.030	1.3
	N	5	5	5	5	5	5	5
4M	Mean	116.6	47.6	146.4	2.0	802.0	0.050	17.8
	SD	28.8	6.7	39.5	0.0	359.0	0.012	2.8
	N	5	5	5	5	5	5	5
	%Diff G1	13.0	10.7	9.6	0.0	28.6	13.636	3.5

Table 7

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1M	Mean	0.36	224.8	71.4	90.6	5.54	3.82	1.72
	SD	0.05	23.1	17.8	20.3	0.18	0.25	0.19
	N	5	5	5	5	5	5	5
4M	Mean	0.32	189.8	69.4	71.2	5.54	3.86	1.68
	SD	0.04	31.2	9.2	22.6	0.18	0.11	0.15
	N	5	5	5	5	5	5	5
	%Diff G1	-11.11	-15.6	-2.8	-21.4	0.00	1.05	-2.33

Table 7

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	2.26	10.78	7.86	138.6	5.00	100.0
	SD	0.35	0.24	0.76	0.9	0.07	1.2
	N	5	5	5	5	5	5
4M	Mean	2.32	10.82	8.56	140.0a	5.34	100.4
	SD	0.22	0.26	0.78	1.0	0.47	1.7
	N	5	5	5	5	5	5
	%Diff G1	2.65	0.37	8.91	1.0	6.80	0.4

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

Table 7

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL mg/dL	UREAN mg/dL
1F	Mean	86.0	41.0	93.0	2.0	446.6	0.022	16.4
	SD	32.3	9.1	36.8	0.0	355.5	0.030	3.0
	N	5	5	5	5	5	5	5
4F	Mean	96.2	43.8	119.8	2.0	509.4	0.036	14.4
	SD	17.9	7.2	28.6	0.0	318.5	0.023	1.7
	N	5	5	5	5	5	5	5
	%Diff G1	11.9	6.8	28.8	0.0	14.1	63.636	-12.2

Table 7

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		CREAT mg/dL	GLUC mg/dL	CHOL mg/dL	TRIG mg/dL	TPROT g/dL	ALB g/dL	GLOB g/dL
1F	Mean	0.38	227.0	87.6	76.0	6.24	4.58	1.66
	SD	0.08	41.3	13.4	17.1	0.51	0.44	0.19
	N	5	5	5	5	5	5	5
4F	Mean	0.40	228.6	64.6a	56.2	5.86	4.38	1.48
	SD	0.00	30.4	10.2	14.9	0.40	0.34	0.11
	N	5	5	5	5	5	5	5
	%Diff G1	5.26	0.7	-26.3	-26.1	-6.09	-4.37	-10.84

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

Table 7

Summary of Clinical Chemistry Values: Day 43

Group 1 - Reference Item

Group 4 - mRNA-1706 129 µg/dose

Group / Sex		A/G ratio	CA mg/dL	PHOS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	2.76	10.66	6.18	137.6	4.64	99.8
	SD	0.39	0.47	0.90	1.7	0.63	2.2
	N	5	5	5	5	5	5
4F	Mean	2.98	10.94	6.96	138.2	4.68	101.0
	SD	0.24	0.29	0.50	1.3	0.28	1.4
	N	5	5	5	5	5	5
	%Diff G1	7.97	2.63	12.62	0.4	0.86	1.2