



FINAL REPORT

Test Facility Study No. [REDACTED]

Sponsor Reference No. [REDACTED]

Electronic Reference No. [REDACTED]

**An Intramuscular Repeated Dose Combined Toxicity and Local
Tolerance Study [REDACTED]
Vaccine in New Zealand White Rabbits with a 3 Week Recovery
Period**

SPONSOR:

[REDACTED]

TEST FACILITY:

Charles River Laboratories [REDACTED]

[REDACTED]

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1. SUMMARY

The test item under investigation in this study was [REDACTED]

[REDACTED] The vaccine is being developed for [REDACTED]
 [REDACTED] objectives of this study were to determine the potential toxicity and local tolerance of [REDACTED]
 [REDACTED] when given by intramuscular injection on 3 occasions (Days 1, 15 and 29) to rabbits, and to evaluate the potential reversibility of any findings during a 3-week recovery period.

Ten males and 10 females were each assigned to 2 groups, and were treated as follows:

Text Table 1
 Experimental Design

Group No.	Treatment	Dosage	Dose Volume
1	Control	0	1 mL
2	[REDACTED]	[REDACTED]	1 mL

Control item = [REDACTED]

VP = Virus particles

The administrations were given to the hind limbs and a separate injection site was used on each injection occasion.

The following parameters and end points were evaluated in this study: clinical observations including assessment of the injection sites/dermal scoring, body weights, body weight gains, food consumption (males only), ophthalmology, body temperature, clinical pathology parameters (haematology, coagulation, clinical chemistry including C-reactive protein) and immunogenicity. On Day 31 (main) and Day 52 (recovery), 5 males and 5 females were euthanised from each group and gross necropsy findings and organ weights were recorded, with subsequent histopathologic examination.

1.1. In-Life

There were no unscheduled deaths and no adverse clinical signs recorded during the study period. There were no local reactions at the administration sites, no changes in the eye, no effects on body weights, body weight gains or body temperature that were considered to be related to treatment with [REDACTED]

There was slightly lower (10-20%) food consumption the day after the first and second injection in males that received [REDACTED] when compared with controls.

On Day 3, the number of monocytes was slightly higher (approximately 3x fold) in males and females that received [REDACTED] and on Day 31, the number of monocytes was slightly higher (approximately 2x fold) in females that received [REDACTED] when compared with controls.

On Days 3 and 31, there were slight disturbances in protein levels with higher fibrinogen (up to 2x fold) and higher globulin (up to 1.3x fold) in animals that received [REDACTED] when compared with controls. The higher globulin was associated with lower albumin/globulin ratios. One day after injection as measured on Days 2 and 30, there were substantially higher levels of C-reactive protein, approximately 34-66x fold in males and 8-12x fold in females, in animals that received [REDACTED] when compared with

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controls. These higher values had returned to similar values to those recorded during pretreatment at the next sample timepoint, either on Day 7 or on Day 52.

[REDACTED] was immunogenic in rabbits (data for which no claim of compliance with GLP is made), and induced [REDACTED] antibody responses, as measured on Days 14, 31 and 52.

1.2. Terminal

At necropsy on Day 31, there was a gross enlargement of the iliac lymph nodes in one female that received [REDACTED]. Microscopic findings associated with the test item were limited to local inflammatory effects of inflammation and/or inflammatory cell infiltration, necrosis or haemorrhage in the striated muscle or fascia/subcutaneous tissue at the administration sites, and increased lymphoid cellularity of the germinal centre in the draining iliac lymph node and the spleen, and increased generalised lymphoid cellularity in the iliac lymph node. The inflammatory effects in the last administration site (Day 29) were more pronounced than the effects in the administration sites used on Day 1 and Day 15. The findings in the spleen and iliac lymph node correlated with slightly higher weights for these tissues.

At Day 52, findings at all administration sites were diminished, comprising only mononuclear cell infiltration in the striated muscle with occasional degeneration/regeneration. Increased lymphoid cellularity of the germinal centre in the iliac lymph node and spleen was still recorded but at lower severity and incidence compared with the end of the dosing period, and these findings correlated with slightly higher spleen weights in males and females and lymph node weights in males.

1.3. Conclusion

The intramuscular injection on 3 occasions over a 29 day period of [REDACTED] at [REDACTED] to New Zealand White rabbits resulted in a transient acute phase inflammatory response, slightly higher numbers of monocytes, local inflammatory effects at the administration sites, and increased diffuse and/or germinal centre lymphoid cellularity in the draining iliac lymph node and spleen, which correlated with slightly higher organ weights for these tissues. After a 3-week recovery period, the microscopic findings were still evident, but at a lower frequency and/or grade, and this correlated with slightly higher spleen weights in males and females and lymph node weights in males. The observed findings indicated on-going recovery, were related to the immunologic response to [REDACTED] and were considered not to be adverse.

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

2. SUMMARY TABLE

Repeat-Dose Toxicity

Report Title: An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study
[REDACTED] Vaccine in New Zealand White Rabbits with a

3 Week Recovery Period

Species/Strain: Rabbit/New Zealand White

Duration of Dosing: 29 days, one dose every 2 weeks

Sponsor Reference No.: [REDACTED]

Age at First Dose: 12-14 weeks

Duration of Postdose: 21 days

Location in CTD:

Date of First Dose: 04 Oct 2017

Route: Intramuscular

Vehicle/Formulation: None, vaccine given as supplied

GLP Compliance: Yes

Special Features: None

No Observed Adverse Effect Level:

The intramuscular injection on 3 occasions over a 29 day period of [REDACTED] at [REDACTED] to New Zealand White rabbits resulted in a transient acute phase inflammatory response, slightly higher numbers of monocytes, local inflammatory effects at the administration sites, and increased diffuse and/or germinal centre lymphoid cellularity in the draining iliac lymph node and spleen, which correlated with slightly higher organ weights for these tissues. After a 3-week recovery period, the microscopic findings were still evident, but at a lower frequency and/or grade, and this correlated with slightly higher spleen weights in males and females and lymph node weights in males. The observed findings indicated on-going recovery, were related to the immunologic response to [REDACTED] and were considered not to be adverse.

Treatment Days 1, 15 and 29

Group 1 [REDACTED]

Group 2 [REDACTED] [REDACTED]

Statistical analysis method. The homogeneity of the group variances was evaluated using the Levene test. Datasets 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.

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Repeat-Dose Toxicity (Continued)

Report Title: An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study
 [REDACTED] Vaccine in New Zealand White Rabbits with a

3 Week Recovery Period

Test Article: [REDACTED] Vaccine

Group	1 (control)		2	
No. of Animals	M: 10	F: 10	M: 10	F: 10
<u>Noteworthy Findings</u>				
Died or Sacrificed Moribund	0	0	0	0
Body Weight and Body Weight Gain (g)	-	-	-	-
Food Consumption ^a males (g/animal/day) ^A				
Days 1/2	116.4	-	0.88	-
Days 15/16	130.3	-	0.80*	-
Clinical Observations	-	-	-	-
Dermal Reactions	-	-	-	-
Ophthalmoscopy	-	-	-	-
Body Temperature (°C)	-	-	-	-
Haematology	-	-	-	-
Day 3				
Monocytes	0.069	0.080	2.7*	3.0**
Day 31				
Monocytes	-	0.108	-	2.1***
Day 52	-	-	-	-
Clinical chemistry ^A				
Day 3				
Globulin	11.9	11.7	1.3***	1.2***
Albumin/globulin ratio	3.72	3.69	0.78***	0.82***
Day 31				
Globulin	12.6	12.6	1.3**	1.2**
Albumin/globulin ratio	3.66	3.52	0.78**	0.82***
Day 52	-	-	-	-

A For controls, group means are shown. For the treated group, multiples (fold change) of control are shown.

Statistical analysis of significance was based on actual data - * p<0.05, ** p<0.01 *** p<0.001 (T-Test or Wilcoxon)

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Repeat-Dose Toxicity (Continued)

Report Title: An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study
 [REDACTED] Vaccine in New Zealand White Rabbits with a

3 Week Recovery Period

Test Article: [REDACTED] Vaccine

Group	1 (control)		2	
No. of Animals	M: 10	F: 10	M: 10	F: 10
<u>Noteworthy Findings</u>				
Coagulation^A				
Day 3				
Fibrinogen (g/L)	2.28	2.09	1.97***	2.00***
Day 31				
Fibrinogen (g/L)	2.47	1.93	1.75**	1.65*
Day 52	-	-	-	-
C-reactive protein (mg/L)^A				
Day 2	1.31	8.38	65.5	11.7
Day 7	-	-	-	-
Day 30	2.54	9.15	33.5	8.1
Day 52	-	-	-	-

A For controls, group means are shown. For the treated group, multiples (fold change) of control are shown.

Statistical analysis of significance was based on actual data - * p<0.05, ** p<0.01 *** p<0.001 (T-Test)

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Repeat-Dose Toxicity (Continued)

Report Title: An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study
 [REDACTED] Vaccine in New Zealand White Rabbits with a

3 Week Recovery Period

Test Article: [REDACTED] Vaccine

Group	1 (control)		2	
No. of animals at each necropsy	M: 5	F: 5	M: 5	F: 5
<u>Noteworthy Findings</u>				
Organ weights^A Day 31				
Iliac lymph node				
Absolute (g)	0.0296	0.0378	7.8*	10.4*
Relative (% to body weight)	0.00098	0.00124	8.6*	10.4*
Relative (% to brain weight)	0.295	0.368	8.1*	10.7*
Spleen weight				
Absolute (g)	1.2210	1.6214	1.0	1.4
Relative (% to body weight)	0.0395	0.0534	1.2	1.4
Relative (% to brain weight)	12.085	15.734	1.1	1.4*
Organ weights^A Day 52				
Iliac lymph node				
Absolute (g)	0.0234	-	1.7	-
Relative (% to body weight)	0.00076	-	1.7	-
Relative (% to brain weight)	0.245	-	1.7	-
Spleen weight				
Absolute (g)	1.0392	1.3702	1.3	1.2
Relative (% to body weight)	0.0344	0.0434	1.3	1.1
Relative (% to brain weight)	10.791	13.337	1.3	1.3
Gross necropsy Day 31				
Iliac lymph node enlargement	-	-	-	1

B For controls, group means are shown. For the treated group, multiples (fold change) of control are shown.

Statistical analysis of significance was based on actual data, Spleen = * p<0.05 (T-Test) and Iliac lymph node = * p<0.05 (Wilcoxon).

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Repeat-Dose Toxicity (Continued)

Report Title: An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study
 [REDACTED] Vaccine in New Zealand White Rabbits with a
 3 Week Recovery Period

Test Article: [REDACTED] Vaccine

Group	1 (control)		2	
No. of animals at each necropsy	M: 5	F: 5	M: 5	F: 5
<u>Noteworthy Findings</u>				
Histopathology Day 31				
Administration sites ^B				
Infiltration, mononuclear cell, striated muscle/fascia	(0)	(1)	(3)	(4)
Minimal	0	1	3	2
Mild	0	0	0	2
Infiltration, mixed cell, fascia/subcutaneous tissue	(0)	(0)	(3)	(3)
Minimal	0	0	3	1
Mild	0	0	0	2
Degeneration/regeneration, striated muscle, Minimal	(0)	(0)	(0)	(1)
Necrosis, striated muscle	(0)	(0)	(3)	(1)
Mild	0	0	1	0
Moderate	0	0	2	1
Inflammation, mixed cell, striated muscle/fascia	(0)	(0)	(3)	(2)
Mild	0	0	1	1
Moderate	0	0	2	1
Haemorrhage, striated muscle/fascia	(0)	(0)	(2)	(1)
Mild/Moderate	0	0	2	1
Spleen				
Increased cellularity, lymphoid germinal centre	(0)	(0)	(5)	(5)
Minimal	0	0	1	1
Mild	0	0	4	4

B There were 3 injection sites collected from each animal. The total number of sites available for evaluation from each group/sex was 15. The value reported reflects the number of sites with the individual finding.

() Total number of incidences for the finding detailed.

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Repeat-Dose Toxicity (Continued)

Report Title: An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study
 [REDACTED] Vaccine in New Zealand White Rabbits with a
 3 Week Recovery Period

Test Article: [REDACTED] Vaccine

Group	1 (control)		2	
No. of animals at each necropsy	M: 5	F: 5	M: 5	F: 5
<u>Noteworthy Findings</u>				
Histopathology Day 31				
Iliac lymph node				
Increased cellularity, lymphoid, generalised	(0)	(0)	(4)	(3)
Mild	0	0	2	1
Moderate	0	0	2	2
Increased cellularity, lymphoid, germinal centre	(0)	(0)	(5)	(5)
Mild	0	0	5	5
Histopathology Day 52				
Administration sites^B				
Infiltration, mononuclear cell, striated muscle	(0)	(0)	(3)	(1)
Minimal/Mild	0	0	3	1
Degeneration/regeneration, striated muscle,	(0)	(0)	(0)	(1)
Minimal				
Spleen				
Increased cellularity, lymphoid germinal centre	(0)	(0)	(4)	(4)
Minimal	0	0	3	3
Mild	0	0	1	1
Iliac lymph node				
Increased cellularity, lymphoid, germinal centre	(0)	(0)	(4)	(2)
Minimal	0	0	2	0
Mild	0	0	2	2

B There were 3 injection sites collected from each animal. The total number of sites available for evaluation from each group/sex was 15. The value reported reflects the number of sites with the individual finding.

() Total number of incidences for the finding detailed.

3. INTRODUCTION

The objectives of this study were to determine the potential toxicity and local tolerance of [REDACTED] when given by intramuscular injection on 3 occasions (Days 1, 15 and 29) to rabbits, and to evaluate the potential reversibility of any findings during a 3-week recovery period.

The design of this study was based on the study objectives, the overall product development strategy for the test item, and the following study design guidelines:

- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity. CPMP/SWP/1042/99rev1.*
- WHO Guideline on nonclinical evaluation of vaccines, Nov 2005 and WHO Guideline on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines Oct 2013.

The study protocol, the last amended study protocol, deviations and other events are presented in [Appendix 1](#).

Study Initiation Date:	26 Sep 2017
Initiation of Dosing:	04 Oct 2017
Completion of In-life:	03 Nov 2017 (Main Study) 24 Nov 2017 (Recovery Study)
Experimental Start Date:	27 Sep 2017
Experimental Completion Date:	19 Mar 2018

4. MATERIALS AND METHODS

4.1. Test Item

4.1.1. [REDACTED]

Batch (Lot) Number:	[REDACTED]
Assigned shelf life:	12 months from manufacture*
Physical Description:	Neutral colourless frozen liquid
Concentration:	[REDACTED] mL
Storage Conditions:	Kept in a freezer set to maintain -70°C (see protocol deviations and other events in Appendix 1), protected from light.

* The test item was manufactured on 12 Jul 2017. A retest date of 12 Jan 2018 was previously indicated, but stability data were supplied that supported an assigned shelf-life of period of 12 months from the date of manufacture. These data covered the dosing phase of this preclinical study.

4.1.2. Control Item

Identification:

This was provided by the Test Facility, details of the batches used have been retained within the study records.

4.2. Test and Control Item Characterisation

The Sponsor supplied test item was provided with documentation that confirmed the identity and composition, and where appropriate, also confirmed strength. A certificate of analysis was provided to the Test Facility and is presented in [Appendix 2](#).

Information on the control item has been retained in the study records at the Test Facility.

4.3. Reserve Samples

For each batch (lot) of test item, a reserve sample (one vial) was collected and maintained under the appropriate storage conditions by the Test Facility.

4.4. Test and Control Item Inventory and Disposition

Records of the receipt, distribution, and storage of test and control items were maintained. With the exception of reserve samples, all unused Sponsor-supplied test item will be returned to the Sponsor after completion of the scheduled programme of work.

4.5. Dose Formulation and Analysis

4.5.1. Preparation of Control Item

The control item was administered as received. On each day of dosing, an adequate volume was dispensed and transferred to the animal unit for administration to group 1 control animals.

Any residual volumes were discarded.

4.5.2. Preparation of Test Item

On each day of dosing, [REDACTED] vaccine vials were removed from frozen storage and allowed to thaw. Each vial of test item was mixed by ‘swirling’ and the contents of one vial was extracted and added to a second vial of [REDACTED]. The vials were dispensed protected from light to the animal unit for administration to the animals in group 2. The injection of the pooled vials occurred within 4 hours of removal of the test item from the freezer.

Any residual volumes were discarded.

4.5.3. Sample Collection and Analysis

The test item was used as received from the Sponsor, that is no dilution or addition of another substance occurred, therefore samples for dose formulation analysis were not collected by the Test Facility.

4.6. Test System

New Zealand White rabbits; supplier designation HsdIf:NZW.

4.6.1. Receipt

On 20 Sep 2017, 20 male and 20 female rabbits were received from [REDACTED]. At the initiation of dosing the animals were approximately 12 to 14 weeks old and the males weighed between 2.1 to 2.8 kg and the females between 2.3 to 2.6 kg (see protocol deviations and other events in [Appendix 1](#)).

4.6.2. Justification for Test System and Number of Animals

The rabbit was chosen as the animal model for this study as it is a species accepted by regulatory agencies for toxicity testing.

The New Zealand White (NZW) rabbit was selected for this study because it is a widely used species to assess preclinical toxicity and local tolerance of vaccine candidates, for which sufficient historical control data exist. Rabbits have sufficient muscle mass to receive a full human dose (of up to 1.0 mL) *via* the intramuscular route. In addition, NZW rabbits have been used in the past to assess preclinical safety of [REDACTED] vaccine candidates. Such studies showed that this vaccine induced an immune response following intramuscular injection in NZW rabbits.

The total number of animals used in this study was considered to be the minimum required to properly characterise 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.

4.6.3. Animal Identification

At study assignment, each animal was identified using a subcutaneously implanted electronic cylindrical, ‘glass-sealed’ microchip.

4.6.4. Environmental Acclimation

The animals were allowed to acclimate to the Test Facility rabbit toxicology accommodation for a period of 2 weeks before the commencement of dosing.

4.6.5. Selection, Assignment, Replacement and Disposition of Animals

Animals were removed in random order from their transport boxes and allocated to dose group on arrival by placing them in cages (males)/pens (females). Cages/pens were labelled with the study number, animal number and group number.

Control animals were housed on a separate rack or in a separate pen.

Before the commencement of dosing, the animals were approved for entry into the experiment on the basis of satisfactory clinical observation records and body weight profile (see protocol deviations and other events in [Appendix 1](#)).

There was no replacement of any animal.

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

4.6.6. Husbandry

Husbandry practices and environmental enrichment were carried out as per Test Facility SOPs and protocol. Each batch of diet, bedding, and all environmental enrichment items were supplied with a Certificate of Analysis. Hay was not analysed. Water from the public supply is routinely analysed for quality (including microbiological burden). Copies of the certificates for all materials and the water analysis are retained centrally at the Test Facility. It was considered that there were no contaminants in any of these materials that influenced the outcome of this study.

4.6.6.1. Housing

Males were individually housed in appropriately sized stainless steel cages with a 'Noryl' dual level interior and perforated floor. Beneath each cage was a suspended tray containing absorbent paper.

Females were socially housed in groups of 10 animals (5 animals during recovery) in pens with adequate floor space. Bedding material (sterilised wood shavings) was placed on each pen floor.

4.6.6.2. Environmental Conditions

Temperatures of 17°C to 19°C (target 16°C to 20°C) with a relative humidity of 29% to 66% (target 40% to 70%) were maintained, see protocol deviations and other events in [Appendix 1](#). A 12-hour light/12-hour dark cycle was also maintained.

Ten or greater air changes per hour were maintained in the animal rooms.

4.6.6.3. Food

Envigo Diet was available to the animals *ad libitum*. Each animal was also offered a supplement of hay daily.

4.6.6.4. Water

The animals had access to water *ad libitum* from the public supply.

4.6.6.5. Animal Enrichment

Both males and females were provided with a device for hiding in, an object for chewing and bunny blocks, except when interrupted by study procedures/activities. Males were allowed a period of exercise (at least once per week) in a separate pen. Females were housed socially for psychological/environmental enrichment.

4.6.6.6. 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 treatments were completed and have been documented/retained in the study records and reviewed by the Study Director.

During the pretreatment period, one control male (Animal 1006M) had a wound on an ear. The animal was given approximately 2.5 mg of a non-steroidal anti-inflammatory drug (meloxicam) by subcutaneous injection on a single occasion, and the ear was bathed for 3 consecutive days with the antiseptic chlorhexidine gluconate. This minor treatment for a few days had no impact on the study objectives.

4.7. Experimental Design

Text Table 2
Experimental Design

Group No.	Treatment	Dosage	Dose Volume	Animal Numbers			
				Main Study		Recovery Study	
				Males	Females	Males	Females
1	Control	0	1 mL	1001-1005	1501-1505	1006-1010	1506-1510
2	[REDACTED]	[REDACTED] [REDACTED]	1 mL	2001-2005	2501-2505	2006-2010	2506-2510

VP = Virus particles

The injection site locations and days of administration are presented in [Text Table 3](#).

Text Table 3
Injection Site Location and Days of Dosing

Group No.	Treatment	Dosing days (dosing site)		
		1	15	29
1	Control	Site 1	Site 2	Site 3
2	[REDACTED]	Site 1	Site 2	Site 3

Site 1: Day 1 = right thigh (posterior)

Site 2: Day 15 = left thigh

Site 3: Day 29 = right thigh (anterior)

4.7.1. Administration of Test and Control Items

The first day of dosing for each individual animal was designated as Day 1. The dose was 1 mL per injection.

The test and control items were administered to the appropriate animals by intramuscular injection on Days 1, 15 and 29 where appropriate. The doses were given using a graduated polycarbonate syringe (BD Syringe) and needle (BD 25G Microlance). The injection of the test item occurred within 4 hours of removal of the test item from the freezer. The injection site was marked at each administration, and this marking remained throughout the study. The last injection site (site 3) was marked by an X to ease collection at necropsy. Further clipping and marking occurred as necessary to maintain visibility of each site.

4.7.2. Justification of Route and Dosage Levels

The intramuscular route is the intended route of administration of the [REDACTED] vaccine in humans.

The dose for [REDACTED] [REDACTED] viral particles was selected on the basis of available data from previous animal studies and was equivalent to the maximum anticipated dosage that will be used in human clinical studies, that is, a full human dose was administered to the animals.

4.8. In-life Procedures, Observations, and Measurements

4.8.1. Mortality/Moribundity Checks

Animals were observed for general health/mortality and moribundity twice daily, once at the start and once towards the end of the working day throughout the study. Animals were not removed from the cage/pens during observation, unless necessary for identification or confirmation of possible findings.

4.8.2. Clinical Observations

4.8.2.1. Detailed Clinical Observations

Animals were removed from the cage/pen for detailed examination weekly, beginning Week -1 including each dosing day (Days 1, 15 and 29).

The animals were examined for general appearance including movement and behaviour pattern. Other examinations included the eyes, ears and external genitalia for discharge, redness or other abnormalities, the skin, coat and feet for the presence or abnormalities or injuries, and an observation for any abnormalities of respiration.

4.8.2.2. Postdose Observations

All animals were examined for reaction to treatment at least twice on each day of dosing (Days 1, 15 and 29) including before dose administrations and approximately 1 and 6 hours after injection. Particular attention was paid to the animals during and for the first hour after dosing (see protocol deviations and other events in [Appendix 1](#)).

On non-dosing days, signs were recorded at least once. The onset, intensity and duration of these signs were recorded (if appropriate).

4.8.3. Dermal Scoring

The skin at the injection sites was evaluated before each dose, 6 hours (+/- 30 min) after injection, daily for 3 days postdose and weekly thereafter (see protocol deviations and other events in [Appendix 1](#)).

Skin was assessed for erythema and eschar formations, oedema formation and any other reaction to treatment.

4.8.4. Body Weights

Animals were individually weighed once during pretreatment, before each dose, daily for 3 days post each dose then twice weekly thereafter and before each necropsy. All weights were recorded in grams (see protocol deviations and other events in [Appendix 1](#)).

4.8.5. Food Consumption

Food consumption was quantitatively measured for males once during pretreatment, daily for 3 days post each dose, then twice weekly and on each day of necropsy.

The female food consumption was assessed by visual inspection of the food bowls. These assessments were recorded and retained in the study records.

4.8.6. Ophthalmic Examinations

All animals were examined once during pretreatment and once after the last administration, that is, during Week 5. Recovery animals were also examined during Week 8 towards the end of the recovery period. The anterior, lenticular and fundic areas of both eyes were examined using an indirect ophthalmoscope after the application of mydriatic agent (1% Tropicamide, Mydriacyl®).

The anterior and medium segments of the eyes, including the conjunctiva, cornea, anterior chamber, iris, lens and vitreous body were also examined with a slit lamp ophthalmoscope after the application of fluorescein to the eyes for epithelial staining.

4.8.7. Body Temperature

The body temperature of each animal was recorded using a digital thermometer in the rectum. Temperatures were recorded once during pretreatment, before each dose, and 6 hours (± 0.5 hours) and 24 hours (± 1 hour) after each dose, as well as on each day of necropsy (see protocol deviations and other events in [Appendix 1](#)). There were no additional body temperatures recorded as all values during the treatment period were $\geq \pm 1^\circ\text{C}$ from the mean pretreatment value (mean of pretreatment value and measurement recorded on Day 1 before the first dose).

4.9. Laboratory Evaluations

4.9.1. Clinical Pathology

4.9.1.1. Sample Collection

Blood was collected from an auricular artery. Additional blood samples were obtained, for example, due to clotting of non-serum samples, when necessary.

Animals were not fasted. Samples were collected according to [Text Table 4](#).

Text Table 4
Samples for Clinical Pathology Evaluation

Animals	Time Point	Haematology	Coagulation	Clinical Chemistry	C-Reactive Protein
All	Pretreatment	X	X	X	X
All	Day 2 ^a	-	-	-	X
All	Day 3	X	X	X	-
All	Day 7	-	-	-	X
All	Day 30	-	-	-	X
Main	Day 31 (necropsy)	X	X	X	-
Recovery	Day 52 (necropsy)	X	X	X	X

X = sample collected; - = not applicable; ^a = 24 h (± 2 h) postdose

Day 1 = first dose administered

After collection, samples were transferred to the appropriate laboratory for processing.

4.9.1.2. Haematology

Blood samples (0.5 mL) were collected, transferred into tubes containing K₂EDTA and analysed for the parameters specified in [Text Table 5](#).

Text Table 5
Haematology Parameters

Red blood cell count	Platelet count
Haemoglobin concentration	White blood cell count
Haematocrit	Neutrophil count (absolute)
Mean corpuscular volume	Lymphocyte count (absolute)
Red blood cell distribution width	Monocyte count (absolute)
Mean corpuscular haemoglobin concentration	Eosinophil count (absolute)
Mean corpuscular haemoglobin	Basophil count (absolute)
Reticulocyte count (absolute)	Large unstained cells (absolute)

A blood smear was prepared from each haematology sample. Blood smears were labelled, stained, and stored. Blood smears were evaluated as required to confirm analyser results as per Test Facility SOPs.

4.9.1.3. Coagulation

Blood samples (0.9 mL) were collected, transferred into tubes containing 3.8% (w/v) trisodium citrate and processed for plasma, which was analysed for the parameters listed in [Text Table 6](#).

Text Table 6
Coagulation Parameters

Activated partial thromboplastin time Fibrinogen	Prothrombin time Sample Quality
---	------------------------------------

4.9.1.4. Clinical Chemistry

Blood samples (1.5 mL) were collected, transferred into tubes containing lithium heparin and processed for plasma, which was analysed 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 ^a Urea Creatinine Calcium Phosphate	Total protein Albumin Globulin Albumin/globulin ratio Glucose Cholesterol Triglycerides Sodium Potassium Chloride
--	--

^a Total bilirubin from all samples was below the reportable range. Indirect and direct bilirubin were not measured.

4.9.1.5. C-Reactive Protein

Blood samples of 0.6 mL (2 x 0.6 mL at pretreatment) were collected and transferred into plain tubes with a gel separator. One pretreatment sample was for method re-establishment. The blood was processed to serum which was analysed at the Test Facility using ELISA methodology established under [REDACTED] [REDACTED].

4.9.2. Immunogenicity Sample Collection, Processing and Analysis

Blood samples (2 mL) were collected from an auricular artery from all animals once during pretreatment, and on Days 14 and 31, and from recovery animals on Day 52. Samples were transferred into plain tubes with a gel separator and allowed to stand for at least one hour before centrifugation to serum (1500 g at 4°C for 10 minutes). Resultant serum was split into 2 aliquots of approximately 0.5 mL and stored in a freezer set to maintain -20°C.

Samples were shipped to the Responsible Scientist on dry ice.

The presence of [REDACTED] specific antibodies was determined in serum obtained before first dosing, at Day 14 postdose and at termination (at main and recovery), using an ELISA analytical method. This work was not conducted in compliance with GLP.

The antibody data were generated to confirm responsiveness of the animals to the vaccine. There is no regulatory requirement for these data to be generated under a claim of compliance with GLP, as they are not generally considered a toxicology safety assessment endpoint.

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Details of the procedure and analysis can be found in the phase report (document number DS-TEC-122286) in [Appendix 16](#) (see protocol deviations and other events in [Appendix 1](#)).

Residual samples were retained by the Test Site and may be used for research purposes with results from any analysis being outside the scope of this present study. Results will have no influence on the study objectives or conclusions drawn from this current preclinical study.

4.10. Terminal Procedures

Terminal procedures are summarised in [Text Table 8](#).

Text Table 8
Terminal Procedures

Group No.	Number of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology^a	Histopathology^a
	M	F		Necropsy	Tissue Collection^a	Organ Weights^a		
1	5	5	31 (main) and 52 (recovery)	X	X	X	Full Tissue Gross lesions	Full Tissue Gross lesions
2	5	5					Full Tissue Gross lesions	Full Tissue Gross lesions

X = procedure conducted

^aSee [Text Table 9](#) for listing of organs weighed at necropsy and [Text Table 10](#) for listing of tissues.

4.10.1. Scheduled Euthanasia

Animals were euthanised by an intravenous overdose of a barbiturate and weighed. Major blood vessels were severed to exsanguinate. The animals were euthanised in a rotating order such that similar numbers of animals from the control and vaccine treated groups were necropsied at similar times throughout the day. Animals were not fasted before their scheduled necropsy.

4.10.2. Necropsy

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.

4.10.3. Organ Weights

The organs identified in [Text Table 9](#) were weighed at necropsy for all animals. Paired organs were weighed together. Organs were weighed before fixation. Organ to body weight percentage (using the terminal body weight) and organ to brain weight percentages were calculated.

Text Table 9
Organs Weighed at Necropsy

Brain Epididymis ^a Gland, adrenal ^a Gland, pituitary Gland, prostate Gland, thyroid ^a Heart	Kidney ^a Liver Lymph node, medial iliac ^a Ovary ^a Spleen Testis ^a Thymus
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^a Paired organ weight

4.10.4. Tissue Collection and Preservation

Representative samples of the tissues identified in [Text Table 10](#) were collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated (see protocol deviations and other events in [Appendix 1](#)).

Text Table 10
Tissue Collection and Preservation

Administration sites (3 sites)	Lesions/masses
Artery, aorta	Liver
Bone marrow smear ^a	Lung
Bone marrow, femur	Lymph node, mandibular
Bone marrow, sternum	Lymph node, mesenteric
Bone, femur with articulating surface	Lymph node, medial iliac
Bone, sternum	Muscle, skeletal
Brain	Nasal cavity
Cervix	Nerve, optic ^b
Diaphragm	Nerve, sciatic
Epididymis	Oesophagus
Eye ^b	Ovary
Gallbladder	Oviduct
Gland, adrenal	Pancreas
Gland, lacrimal	Skin
Gland, mammary	Small intestine, duodenum
Gland, parathyroid	Small intestine, ileum
Gland, pituitary	Small intestine, jejunum
Gland, prostate	Small intestine, sacculus rotundus
Gland, salivary, mandibular	Spinal cord
Gland, seminal vesicle	Spleen
Gland, thyroid	Stomach
Gut-associated lymphoid tissue (Peyer's Patches)	Testis ^c
Heart	Thymus
Kidney	Tongue
Large intestine, appendix	Trachea
Large intestine, caecum	Ureter
Large intestine, colon	Urinary bladder
Large intestine, rectum	Uterus
Larynx	Vagina

^a Air dried, fixed in methanol.

^b Preserved in Davidson's fixative.

^c Preserved in Modified Davidson's fixative.

4.10.5. Histology

Tissues identified in [Text Table 10](#) (except animal identification and bone marrow smears) from animals identified in [Text Table 8](#) were embedded in paraffin, sectioned, mounted on glass slides, and stained with haematoxylin and eosin.

4.10.6. Histopathology

Histopathological evaluation was performed by a veterinary pathologist with training and experience in laboratory animal pathology.

4.10.7. Peer Review

A pathology peer review was conducted by the Sponsor according to the Sponsor's SOPs.

The peer review documentation is included in [Appendix 23](#).

4.10.8. Bone Marrow Smear Evaluation

Two bone marrow smears were taken from the femur. Both bone marrow smears were air dried, fixed in methanol, stained with May-Grunwald-Giemsa stain and coverslipped. Bone marrow smears were not evaluated.

5. COMPUTERISED SYSTEMS

Critical computerised systems used in the study are listed in [Text Table 11](#) or presented in the appropriate phase report. All computerised systems used in the conduct of this study have been validated.

Text Table 11
Critical Computerised Systems

System Name	Version No.	Description of Data Collected and/or Analysed
Dispense	8 (or higher)	Test item receipt and accountability.
Provantis	8 (or higher)	Applicable in-life, clinical pathology and postmortem.
In-house reporting software Nevis 2012 (using SAS)	Nevis 2012 2 (SAS 9.2)	Applicable in-life, clinical pathology and postmortem.

6. CONSTRUCTED VARIABLES

The following constructed variables were calculated and are reported.

- | | |
|--|---|
| Body weight gains: | calculated between Days 1 to 31 and 31 to 52. |
| Organ weight relative to body weight: | calculated against the terminal body weight. |
| Organ weight relative to brain weight: | calculated against the brain weight. |

7. STATISTICAL ANALYSIS

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.

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 analysed as indicated according to sex and occasion. Descriptive statistics number, mean and standard deviation were reported whenever possible. Inferential statistics were performed according to [Text Table 12](#) 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
Food Consumption (males only)	X
Body Temperature	X
Haematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	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

7.1. Parametric/Non-Parametric

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

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.

8. RETENTION OF RECORDS, SAMPLES, AND SPECIMENS

All study-specific raw data, documentation, protocol, protocol amendments, retained samples and specimens from this study were transferred to the Test Facility archive. Two years after issue of the final report, the Sponsor will be contacted to determine the disposition of materials associated with the study.

Electronic data generated by the Test Facility were archived as noted above, except Provantis and Dispense data and reporting files stored on the Test Facility internal document management system, SDMS, which were archived at the Charles River Laboratories facility location in [REDACTED]

Data generated at the Test Site ([REDACTED] [REDACTED]) were stored at that site indefinitely, as per local policy.

The original signed copy of the Final Report will be archived indefinitely at the Test Facility.

9. RESPONSIBLE PERSONNEL

9.1. Test Facility

Study Director [REDACTED]
[REDACTED]
[REDACTED]

9.2. Individual Scientists (IS) at Test Facility

Pathology [REDACTED]

9.3. Responsible Scientist (RS) at Sponsor or Sponsor-designated Test Site

Immunology (non-GLP) [REDACTED]
[REDACTED]
[REDACTED]

9.4. Other Contributors

Pathology Peer Review [REDACTED]
[REDACTED]
[REDACTED]

10. RESULTS

10.1. Mortality

([Appendix 3](#))

There were no unscheduled deaths during the study period.

10.2. Clinical Observations

([Table 1](#) and [Appendix 4](#))

There were no clinical signs recorded in any animal receiving [REDACTED]

The only clinical sign recorded was scabbing which was noted on the ear in one control male (Animal 1006M) up to Day 29, and on the eyelid of one control female (Animal 1507F) up to Day 15.

10.3. Dermal Scoring

([Appendix 5](#))

There was no erythema or oedema noted at any administration site at any timepoint.

10.4. Body Weights and Body Weight Gains

([Figure 1](#), [Figure 2](#), [Table 2](#) and [Appendix 6](#))

Body weights and body weight gains were unaffected by treatment with [REDACTED]

The group mean data indicated that the day after each injection there was a minimal body weight loss in males receiving [REDACTED] when the group mean body weight recorded on Days 2, 16 and 30 was compared with the values recorded on Days 1, 15 and 29, respectively. This effect was also noted in females at the first injection. The minimal body weight loss was considered not to be adverse because the group mean differences were in all cases no more than 1%, the body weight loss was not noted in every individual animal, and body weights had recovered 2 days after injection. These transient effects did not cause any difference in body weight gain over the treatment period (Days 1-31) in animals receiving [REDACTED] when compared with controls.

There were statistically significant differences noted in the females, when body weights for animals receiving [REDACTED] were compared with controls, with body weights of [REDACTED] treated animals generally being higher than controls. These differences were minor, were noted intermittently, were consistent during the treatment and recovery periods, and were recorded during the pretreatment period. There were no statistically significant differences in the overall body weight change at the end of the dosing or recovery periods between controls and animals receiving, or had received, [REDACTED]. The differences were therefore considered not related to treatment with [REDACTED]

10.5. Food Consumption

([Table 3](#) and [Appendix 7](#))

Food consumption was quantitatively recorded in only males.

There was slightly lower (10-20%) food consumption the day after the first and second injection in males receiving [REDACTED] when compared with controls. This achieved statistical significance on Days 15/16 at the second injection.

Although at Day 29/30, the day after the third injection, there was also slightly lower food

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consumed in animals receiving [REDACTED] when compared with controls, the amount of food consumed by the vaccine treated animals was similar to that consumed during the pretreatment period. This finding was considered not to be related to treatment.

During the recovery period there was slightly higher food consumption (5-22%) in animals that had received [REDACTED] when compared with controls. The data showed that one control male (Animal 1010M) had lower food consumption than other animals in the recovery phase, and that if this animal was excluded the individual values are broadly similar in the control and vaccine-treated group. This effect was considered unrelated to previous treatment with [REDACTED]

10.6. Ophthalmic Examinations

([Appendix 8](#))

There were no changes in the eye that were considered to be related to treatment with [REDACTED] The findings recorded were either noted in the controls or had been recorded during pretreatment.

10.7. Body Temperature

([Table 4](#) and [Appendix 9](#))

Body temperature was unaffected by treatment with [REDACTED]

There were statistically significant differences noted when the temperatures recorded for animals receiving [REDACTED] were compared with controls. These differences were slight, there was no pattern or trend, and, with one exception, all group mean and individual values were within the expected range for rabbits of 38.6-40.1°C (101.5-104.2°F). These differences were considered to be unrelated to treatment.

10.8. Haematology

([Table 5](#), [Appendix 10](#), [Appendix 11](#) and [Appendix 12](#))

On Day 3, the number of monocytes was slightly higher (approximately 3x fold) in males and females receiving [REDACTED] and on Day 31, the number of monocytes was slightly higher (approximately 2x fold) in females receiving [REDACTED] when compared with controls. On Day 52, haematology was unaffected by previous treatment with [REDACTED]

The number of reticulocytes was noted to be higher on Day 3 (males and females) and Day 31 (females) in both the animals receiving [REDACTED] and controls, when values were compared with those measured during pretreatment. This effect was considered to be due to the blood draw.

There were miscellaneous differences, in some instances statistically significantly different from controls, which were not considered to be related to treatment with [REDACTED] The differences were considered minor, had no correlation with other related parameters, or were also noted during pretreatment.

10.8.1. Overall Haematology Summary

The only haematology difference noted that was considered related to [REDACTED] was the number of monocytes noted on Day 3 (males and females) and on Day 31 (females), where the group mean numbers of these cells were slightly higher in animals receiving [REDACTED] when compared with controls.

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Although there was individual variation within the data, all individual values with the exception of one recorded for a male on Day 3 (Animal 2002M) were within recent historical control data, the effect was only evident in a few animals within the group receiving [REDACTED]

[REDACTED] and this difference was also noted in males during the pretreatment period, the numbers of monocytes was higher in the animals receiving [REDACTED] when compared with controls. There was no effect on the total number of white blood cells. These differences were considered minor. Data are presented graphically in [Text Table 13](#).

Text Table 13
Group Mean Values: Monocytes ($10^9/L$)

10.9. Coagulation

([Table 5](#), [Appendix 10](#) and [Appendix 11](#))

Fibrinogen was slightly higher, approximately 2x fold on Day 3 and 1.8x fold on Day 31, in animals receiving [REDACTED] when compared with controls.

There were statistically significant differences in prothrombin times with a shorter prothrombin time in females on Day 3 and males on Day 31, when values in controls were compared with animals receiving [REDACTED]. Activated partial thromboplastin times were unaffected. These difference were considered minor, there was individual variation within the data, and broadly values between the controls and animals receiving [REDACTED]

were similar. Overall, these limited minor differences, being only noted in one sex each at one timepoint, were considered unrelated to treatment with [REDACTED]. Group mean values and the range for the sex/timepoint indicated in brackets are presented in [Text Table 14](#).

Text Table 14
Group Mean Values (and range): Prothrombin Time in Seconds

		PT	Day 3	Day 31	Day 52
Males	Control	12.2	12.1	10.7	10.8
		(11.1-13.5)	(10.5-14.9)	(10.4-11.4)	(10.1-11.6)
	[REDACTED]	12.9	11.3	10.1	11.4
		(11.6-16.8)	(10.6-12.4)	(9.8-10.3)	(10.4-12.4)
Females	Control	12.3	12.1	11.4	11.7
		(11.8-12.9)	(11.3-12.6)	(10.2-15.0)	(10.8-13.0)
	[REDACTED]	13.1	11.6	10.5	11.7
		(11.5-16.8)	(10.4-12.3)	(9.9-11.2)	(10.5-12.4)

10.10. Clinical Chemistry

(Table 6, Appendix 13, and Appendix 14)

10.10.1. Day 3

Globulin was slightly higher (1.2-1.3x fold) and consequently there were lower albumin/globulin ratios in animals receiving [REDACTED] when compared with controls.

There were miscellaneous differences, in some instances statistically significantly different from controls, which were not considered to be related to treatment with [REDACTED]. The differences were considered minor, values were similar to those noted during pretreatment, there was no correlation with other related parameters, and the differences were also noted during pretreatment.

10.10.2. Day 31

Globulin was slightly higher (1.2-1.3x fold) and consequently there were lower albumin/globulin ratios in animals receiving [REDACTED] when compared with controls.

Creatine kinase activities were higher in females, controls and animals receiving [REDACTED] when compared with values measured during pretreatment and on Day 3. There was no obvious explanation for this finding as there was no correlate with clinical signs or local irritation noted in-life, and the histological findings at the injection sites were similar to those recorded in males.

10.10.3. Day 52

Clinical chemistry was unaffected by previous treatment with [REDACTED]

There were miscellaneous differences, in some instances statistically significantly different from controls, which were not considered to be related to treatment with [REDACTED]. The differences were considered minor, were considered to be within normal biological variation and there was no correlation with other related parameters.

10.11. C-Reactive protein

(Table 7, Appendix 13 and Appendix 15)

One day after injection (on Days 2 and 30) there were higher levels, approximately 34-66x fold in males and 8-12x fold in females, of C-reactive protein in animals receiving [REDACTED] when compared with controls. These higher values had returned to similar values to those recorded during pretreatment at the next sample timepoint, either on Day 7 or on Day 52.

Data are summarised in [Text Table 15](#).

Text Table 15
C-reactive protein (mg/L): Group Mean Values

10.12. Immunology

([Appendix 16](#))

[REDACTED] was immunogenic in rabbits (data for which no claim of compliance with GLP is made), and [REDACTED], as measured on Days 14, 31 and 52.

10.13. Organ Weights

([Table 8](#), [Table 9](#), [Table 10](#), [Appendix 17](#), [Appendix 18](#), [Appendix 19](#) and [Appendix 20](#))

10.13.1. Scheduled Euthanasia Animals (Day 31)

Group mean spleen weights were higher in males (up to 1.2x fold) and females (up to 1.4x fold) given [REDACTED] when compared with controls. This achieved statistical significance in females after analysis as a percentage of brain weight. Group mean iliac lymph node weights were statistically significantly higher in males (up to 8.6x fold) and females (up to 10.7x fold) given [REDACTED] when compared with controls.

Test item-related organ weight differences are summarised in [Text Table 16](#).

Text Table 16
Summary Group Mean Organ Weight Data – Scheduled Euthanasia (Day 31)

	Males		Females		
	Group	1	2	1	2
[REDACTED]	Dosage	0	[REDACTED]	0	[REDACTED]
[REDACTED]	No. animals per group	5	5	5	5
Spleen (No. weighed)	(5)	(5)	(5)	(5)	
Absolute value	1.2210	1.2680	1.6214	2.2210	
% of brain weight	12.08496	13.41060	15.73427	22.31558a	
% of body weight	0.03945	0.04549	0.05337	0.07265	
Iliac lymph node (No. weighed)	(5)	(5)	(5)	(5)	
Absolute value	0.0296	0.2300d	0.0378	0.3918d	
% of brain weight	0.29525	2.40250d	0.36805	3.94573d	
% of body weight	0.00098	0.00838d	0.00124	0.01286d	

Significantly different from control group 1 value: a=p≤0.05 (T-test) and d=p≤0.05 (Wilcoxon)

When compared with controls, there were other statistically significant organ weight differences in animals given [REDACTED] which were considered not to be test item related. The differences in absolute weight were considered to be related to the slightly lower terminal body weight in males that were given [REDACTED] and individual variation

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

within the data that was considered to be normal biological variation. There were other isolated organ weight values that were different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. In all cases, the organ weight differences observed were considered incidental and unrelated to test item-administration.

10.13.2. Scheduled Euthanasia Animals (Day 52)

Slightly higher group mean spleen weights in males and females (up to 1.3x fold) and slightly higher iliac lymph node weights (up to 1.7x fold) were noted in males previously given [REDACTED] when compared with controls. There were no differences that were statistically significant.

Test item-related organ weight differences are summarised in [Text Table 17](#).

Text Table 17
Summary Group Mean Organ Weight Data – Scheduled Euthanasia (Day 52)

	Males		Females	
	1	2	1	2
Group	1	2	1	2
[REDACTED] Dosage	0	[REDACTED]	0	[REDACTED]
No. animals per group	5	5	5	5
Spleen (No. weighed)	(5)	(5)	(5)	(5)
Absolute value	1.0392	1.3672	1.3702	1.6460
% of brain weight	10.79100	14.04464	13.33676	17.01429
% of body weight	0.03437	0.04380	0.04342	0.04898
Iliac lymph node No. weighed)	(5)	(5)	(5)	(5)
Absolute value	0.0234	0.0396	-	-
% of brain weight	0.24504	0.41181	-	-
% of body weight	0.00076	0.00131	-	-

There were other isolated organ weight values that were different from their respective controls, including a statistically significant higher liver weight in males (absolute and relative to body weight analysis), but as there were no patterns, trends, or correlating data to suggest these values were toxicologically relevant, they were considered incidental and unrelated to previous administration of the test item.

10.14. Gross Pathology

([Table 11](#) and [Appendix 21](#))

10.14.1. Scheduled Euthanasia Animals (Day 31)

There was only one gross finding that was considered to be related to treatment: bilateral enlargement of the iliac lymph node in one female (2502F) given [REDACTED]. No enlargement of these lymph nodes was noted in controls (group 1).

Findings considered to be procedurally related included the dark discoloration observed at the administration sites at similar incidence in controls and rabbits given [REDACTED]. There was no microscopic correlate for the dark focus recorded in the skeletal muscle of one female given [REDACTED].

Other gross findings observed were of the nature commonly observed in this strain and age of rabbit, or occurred at a similar incidence in control and treated animals, and, therefore, were considered not to be test item-related.

10.14.2. Scheduled Euthanasia Animals (Day 52)

Test item-related gross pathology findings noted at the terminal euthanasia in the iliac lymph node were not observed at the end of the recovery period.

All gross findings observed were of the nature commonly observed in this strain and age of rabbit, or occurred at a similar incidence in control and treated animals, and, therefore, were considered not to be test item-related.

10.15. Histopathology

([Table 12](#), [Appendix 21](#) and [Appendix 22](#))

10.15.1. Scheduled Euthanasia Animals (Day 31)

10.15.1.1. Administration Sites

At Day 29 administration site (site 3), there were clear inflammatory reactions in 4/10 rabbits given [REDACTED]. The reactions in those individuals were characterised by striated muscle necrosis with mixed cell inflammation; and haemorrhage in striated muscle or the fascia. Additionally, in rabbits given [REDACTED] there was also a higher incidence of inflammatory cell infiltration in the fascia/subcutaneous tissue, when compared with controls.

In the administration site injected on Days 1 (site 1) and 15 (site 2), there was higher incidence and slightly higher grade of mononuclear cell infiltration of the fascia/striated muscle, when compared with controls. Minimal striated muscle degeneration/regeneration was noted at one Day 15 administration site.

[Text Table 18](#) summarises the test item-related microscopic findings at the administration sites.

Text Table 18

Summary Test item-related Microscopic Findings at Administration sites – Scheduled Euthanasia Animals
(Day 31)

	Males		Females	
Group	1	2	1	2
Dosage	0	[REDACTED]	0	[REDACTED]
No. animals per group	5	5	5	5
Administration site 1 – Day 1 (No. Examined)	(5)	(5)	(5)	(5)
Infiltration, mononuclear cell, striated muscle/fascia	0	3	1	3
Minimal	0	3	1	2
Mild	0	0	0	1
Administration site 2 – Day 15 (No. Examined)	(5)	(5)	(5)	(5)
Infiltration, mononuclear, striated muscle, mild	0	0	0	1
Degeneration/regeneration, striated muscle, minimal	0	0	0	1
Administration site 3 – Day 29 (No. Examined)	(5)	(5)	(5)	(5)
Necrosis, striated muscle	0	3	0	1
Mild	0	1	0	0
Moderate	0	2	0	1
Inflammation, mixed cell, striated muscle	0	3	0	1
Mild	0	1	0	0
Moderate	0	2	0	1
Inflammation, mixed cell, fascia, mild	0	0	0	1
Haemorrhage, striated muscle, moderate	0	0	0	1
Haemorrhage, fascia, mild	0	2	0	0
Infiltration, mixed cell, fascia/subcutaneous tissue	0	3	0	3
Minimal	0	3	0	1
Mild	0	0	0	2

10.15.1.2. Spleen and Iliac Lymph Nodes

In the iliac lymph node, there was increased lymphoid cellularity of the germinal centre (mild) in all rabbits given [REDACTED] with accompanying increased generalised lymphoid cellularity, (mild or moderate) in 7/10 individuals. This correlated with the bilateral enlargement observed grossly in the lymph node of one female and also correlated with the higher lymph node weight in rabbits given [REDACTED]

In the spleen, there was increased lymphoid cellularity of the germinal centre (minimal or mild) in all rabbits given [REDACTED] correlating with the higher spleen weights recorded.

Test item-related microscopic findings in the spleen and iliac lymph nodes are summarised in [Text Table 19](#).

Text Table 19

Summary Test item-related Microscopic Findings in Spleen and Iliac lymph node –
Scheduled Euthanasia Animals (Day 31)

	Males		Females	
Group	1	2	1	2
Dosage	0	[REDACTED]	0	[REDACTED]
No. animals per group	5	5	5	5
Spleen (No. Examined)	(5)	(5)	(5)	(5)
Increased cellularity, lymphoid, germinal centre	0	5	0	5
Minimal	0	1	0	1
Mild	0	4	0	4
Iliac lymph node (No. Examined)	(5)	(5)	(5)	(5)
Increased cellularity, lymphoid, generalised	0	4	0	3
Mild	0	2	0	1
Moderate	0	2	0	2
Increased cellularity, lymphoid, germinal centre, mild	0	5	0	5

10.15.1.3. Other Findings

There were additional findings at the administration sites which were related to the injection procedure rather than to [REDACTED] including those in the epidermis and subcutaneous haemorrhage/inflammation (occasionally with pigmented macrophages), affecting all sites with a comparable incidence and severity in controls and treated rabbits.

Other microscopic findings observed were of the nature commonly observed in this strain and age of rabbit, or occurred at a similar incidence in control and treated animals, and, therefore, were considered not to be test item-related.

10.15.2. Scheduled Euthanasia Animals (Day 52)

10.15.2.1. Administration Sites

Following the 3-week recovery period, the inflammatory reactions recorded at the administration sites were diminished, comprising only mononuclear inflammatory cell infiltration (minimal and mild) in striated muscle with occasional degeneration/regeneration (minimal). There was no evidence of striated muscle necrosis with mixed cell inflammation, or of any haemorrhage.

Test item-related microscopic findings noted at the terminal euthanasia at the administration sites which were recorded at the end of the recovery period are summarised in [Text Table 20](#).

Text Table 20

Summary Test item-related Microscopic Findings at Administration Sites – Scheduled Euthanasia Animals
(Day 52)

	Males		Females	
Group	1	2	1	2
Dosage	0	[REDACTED]	0	[REDACTED]
No. animals per group	5	5	5	5
Administration site 1 – Day 1 (No. Examined)	(5)	(5)	(5)	(5)
Infiltration, mononuclear, striated muscle, minimal	0	2	0	0
Administration site 2 – Day 15 (No. Examined)	(5)	(5)	(5)	(5)
Infiltration, mononuclear, striated muscle, mild	0	0	0	1
Degeneration/regeneration, striated muscle, minimal	0	0	0	1
Administration site 3 – Day 29 (No. Examined)	(5)	(5)	(5)	(5)
Infiltration, mononuclear, striated muscle, minimal	0	1	0	0

10.15.2.2. Spleen and Iliac Lymph Nodes

Following the 3-week recovery period, findings in the iliac lymph node and spleen (increased lymphoid cellularity of the germinal centre) of animals that had previously been given [REDACTED] persisted; but incidence and severity (minimal or mild) were lower.

Increased generalised lymphoid cellularity was no longer recorded in the iliac lymph node in rabbits previously given [REDACTED]. These findings correlated in males and females with the higher spleen and in males with the higher iliac lymph node weights.

Text Table 21 summarises the test item-related microscopic findings noted at the terminal euthanasia in the spleen and iliac lymph nodes which were recorded at the end of the recovery period.

Text Table 21
Summary Test item-related Microscopic Findings in spleen and iliac lymph node –
Scheduled Euthanasia Animals (Day 52)

	Males		Females	
Group	1	2	1	2
Dosage	0	[REDACTED]	0	[REDACTED]
No. animals per group	5	5	5	5
Spleen (No. Examined)	(5)	(5)	(5)	(5)
Increased cellularity, lymphoid, germinal centre	0	4	0	4
Minimal	0	3	0	3
Mild	0	1	0	1
Iliac lymph node (No. Examined)	(5)	(5)	(5)	(5)
Increased cellularity, lymphoid, germinal centre	0	4	0	2
Minimal	0	2	0	0
Mild	0	2	0	2

Other microscopic findings observed were of the nature commonly observed in this strain and age of rabbit, or occurred at a similar incidence in control and treated animals, and, therefore, were considered not to be test item-related.

11. DISCUSSION

The intramuscular injection on 3 occasions over a 29 day period of [REDACTED]

[REDACTED] to New Zealand White rabbits did not result in any findings that would be considered adverse. There were transient acute phase inflammatory and/or immunologic responses characterised by higher fibrinogen and C-reactive protein, higher iliac lymph node and spleen weights. Microscopic local inflammatory responses at the administration sites, and increased lymphoid cellularity of the germinal centres in the iliac lymph node and spleen, all of which after a 3-week recovery period, had either resolved or were noted to be recovering (as reflected by a generally lower incidence or grade of the findings).

In animals that received [REDACTED] the minimal body weight loss on the day after each injection in some males and at the first injection in some females, and the slightly lower food consumption noted the day after the first and second injection in males were transient effects and considered to be of little toxicological significance.

The slightly higher concentration of fibrinogen and transient increases in C-reactive protein, suggested an acute phase inflammatory reaction which would be regarded as a normal physiological response to injection of the vaccines and of negligible toxicological significance. These findings had recovered at the end of the 21 day treatment free (recovery) period.

Findings of increased lymphoid cellularity in the draining iliac lymph nodes and increased lymphoid cellularity of germinal centres in the spleen correlated with the slightly higher numerical increases in the respective organ weights. The increased lymphoid cellularity reflected an immunologic response to the injections.

The clinical pathology and histological responses noted were considered to reflect a physiological or immunological response to injection of a vaccine. The findings were not considered adverse.

12. CONCLUSION

The intramuscular injection on 3 occasions over a 29 day period of [REDACTED] at [REDACTED] to New Zealand White rabbits resulted in a transient acute phase inflammatory response, slightly higher numbers of monocytes, local inflammatory effects at the administration sites, and increased diffuse and/or germinal centre lymphoid cellularity in the draining iliac lymph node and spleen, which correlated with slightly higher organ weights for these tissues. After a 3-week recovery period, the microscopic findings were still evident, but at a lower frequency and/or grade, and this correlated with slightly higher spleen weights in males and females and lymph node weights in males. The observed findings indicated on-going recovery, were related to the immunologic response to [REDACTED] and were considered not to be adverse.

13. REFERENCES

[REDACTED]

14. COMPLIANCE STATEMENT**Study Number:** [REDACTED]**Study Title:** An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study [REDACTED]
[REDACTED] Vaccine in New Zealand White Rabbits with a 3 Week Recovery Period

I, the undersigned, hereby declare that this study, with the exception of Immunogenicity (antibody analysis), was performed in accordance with the OECD Principles of Good Laboratory Practice as incorporated into the United Kingdom Statutory Instrument for GLP and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA) and Japan (MHLW, MAFF and METI) and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Immunogenicity (antibody analysis) was performed by [REDACTED]

The

[REDACTED] antibody data were generated to confirm the responsiveness of the animals to the vaccine. There was no regulatory requirement for these data to be generated under a claim of compliance with GLP, as they were not generally considered a toxicology safety assessment endpoint. The data generated were not used in the study conclusion. There was no study impact.

This study was conducted in accordance with the procedures described herein. All deviations authorised/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: 29 MAR 2018

Study Director

Ready to use test items were supplied by the Sponsor for use on this study. The production, preparation and any analysis of the test item formulations are not included in the scope of this study.

15. QUALITY ASSURANCE STATEMENT

Study Number: [REDACTED]

Study Title: **An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study [REDACTED] Vaccine in New Zealand White Rabbits with a 3 Week Recovery Period**

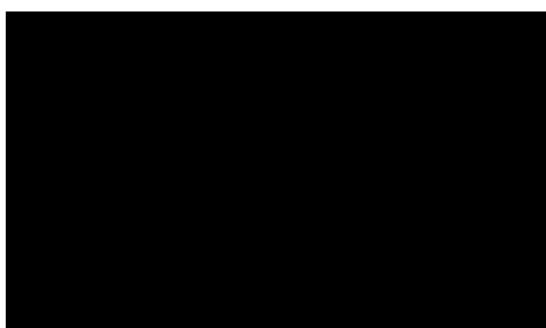
The Charles River Quality Assurance Unit conducted a protocol review, protocol amendment reviews, study-based inspections and report audits on this study, as detailed below.

Dates Findings Submitted to:			
Date(s) of Audit	Phase(s) Audited	Study Director	Study Director Management
29-Sep-2017	Final Protocol	29-Sep-2017	29-Sep-2017
04-Oct-2017	Dose Dispensing	04-Oct-2017	04-Oct-2017
04-Oct-2017	Dose Administration	04-Oct-2017	04-Oct-2017
02-Nov-2017	Ophthalmology	03-Nov-2017	03-Nov-2017
17-Nov-2017	Protocol Amendment 01	17-Nov-2017	17-Nov-2017
22-Nov-2017	Protocol Amendment 02	22-Nov-2017	22-Nov-2017
17-Jan-2018 19-Jan-2018	Draft Report	24-Jan-2018	24-Jan-2018
22-Jan-2018 - 24-Jan-2018	Data Review - Animal Care	24-Jan-2018	24-Jan-2018
17-Jan-2018 19-Jan-2018	Data Review - Formulations	24-Jan-2018	24-Jan-2018
22-Jan-2018 - 24-Jan-2018	Data Review - Clinical Pathology	24-Jan-2018	24-Jan-2018
19-Jan-2018	Data Review - Pathology	24-Jan-2018	24-Jan-2018
22-Jan-2018 - 24-Jan-2018	Protocol Amendment 03	09-Mar-2018	09-Mar-2018
14-Mar-2018 - 15-Mar-2018	Final Report	15-Mar-2018	15-Mar-2018

Process-based inspections relevant to this study are scheduled once every quarter. The outcome of each inspection is reported to Management and, where relevant, the Study Director.

Facilities relevant to this study are included in Charles River's annual facility inspection programme. The outcome of each inspection is reported to Management.

This report is considered to describe accurately and completely the procedures used in the study and the results obtained.



Quality Assurance Auditor

Figure 1**Graphical Representation of Body Weights (g) Pretreatment and Dosing Period Males**

Group 1 - Control

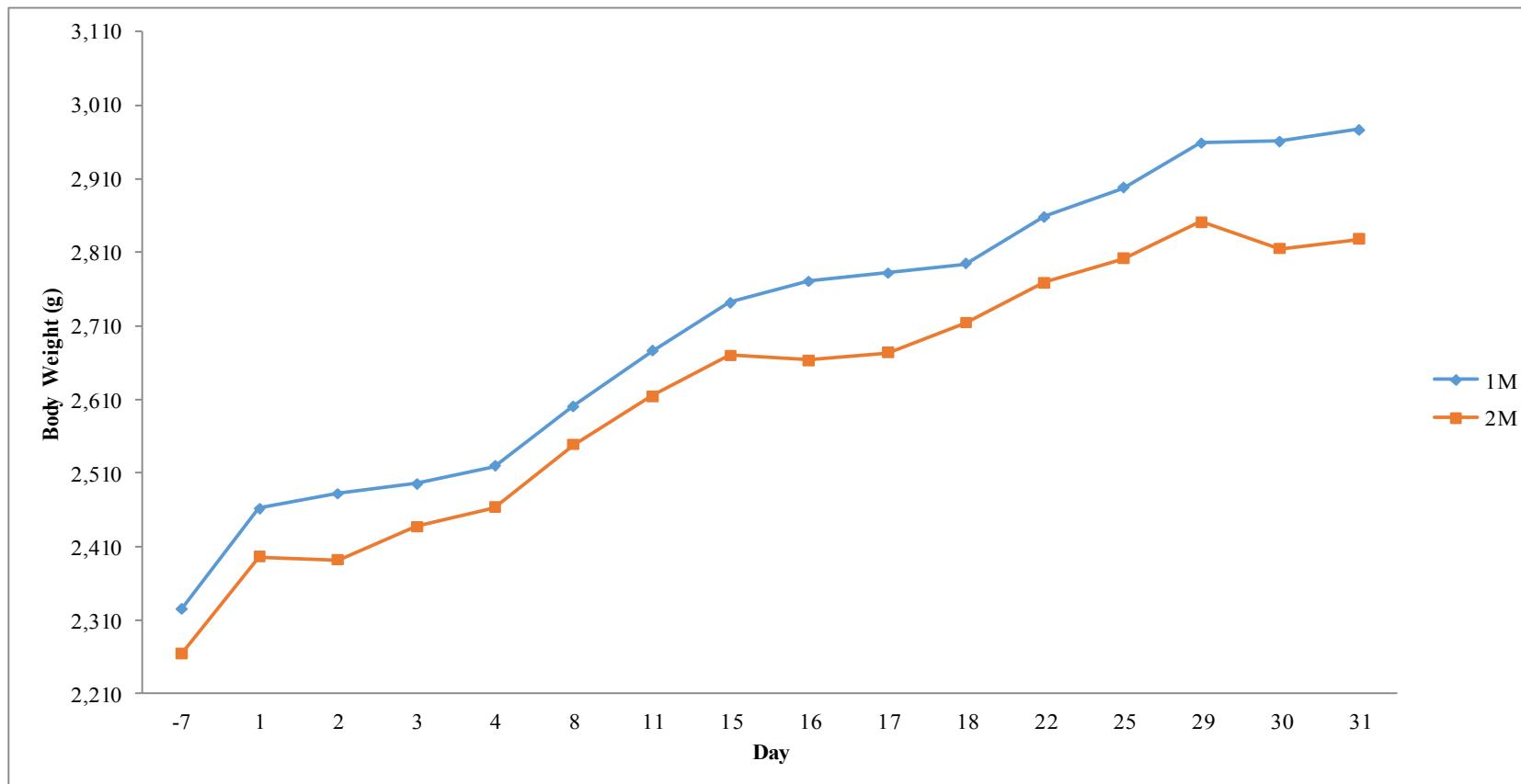
Group 2 - [REDACTED] 1×10^{11} VP

Figure 1**Graphical Representation of Body Weights (g) Pretreatment and Dosing Period Females**

Group 1 - Control

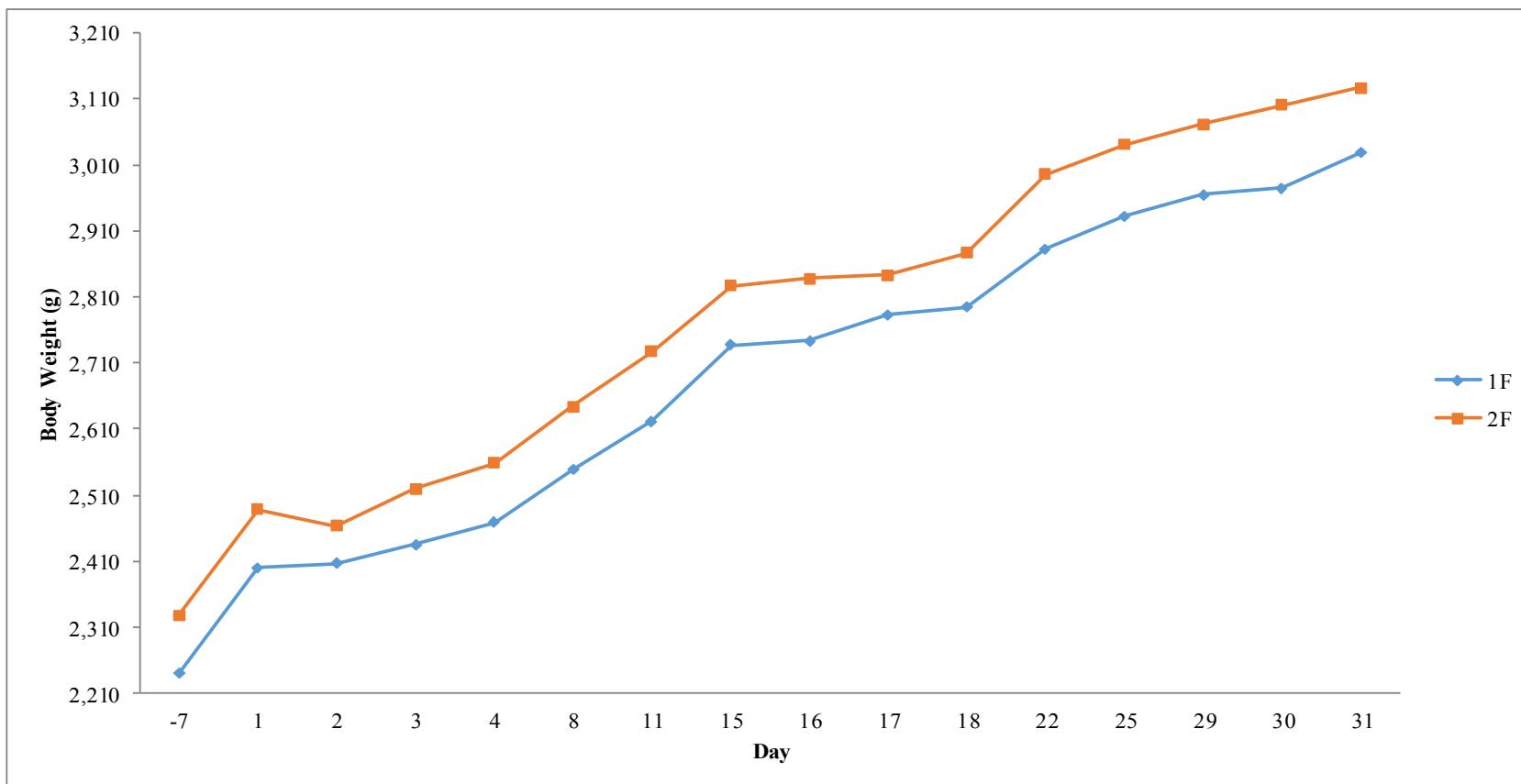
Group 2 - [REDACTED] 1×10^{11} VP

Figure 2**Graphical Representation of Body Weights (g) Recovery Period Males**

Group 1 - Control

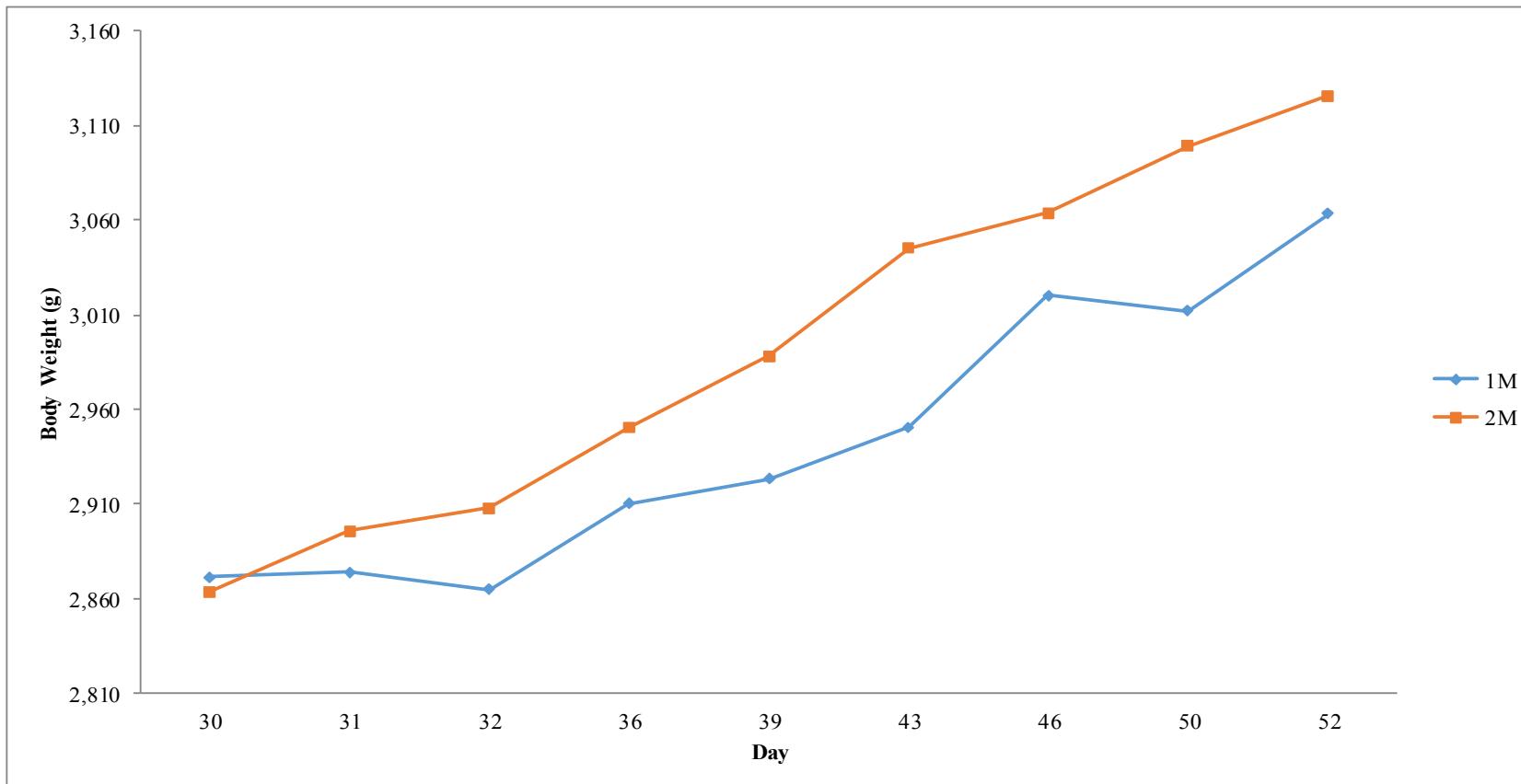
Group 2 - [REDACTED] 1×10^{11} VP

Figure 2**Graphical Representation of Body Weights (g) Recovery Period Females**

Group 1 - Control

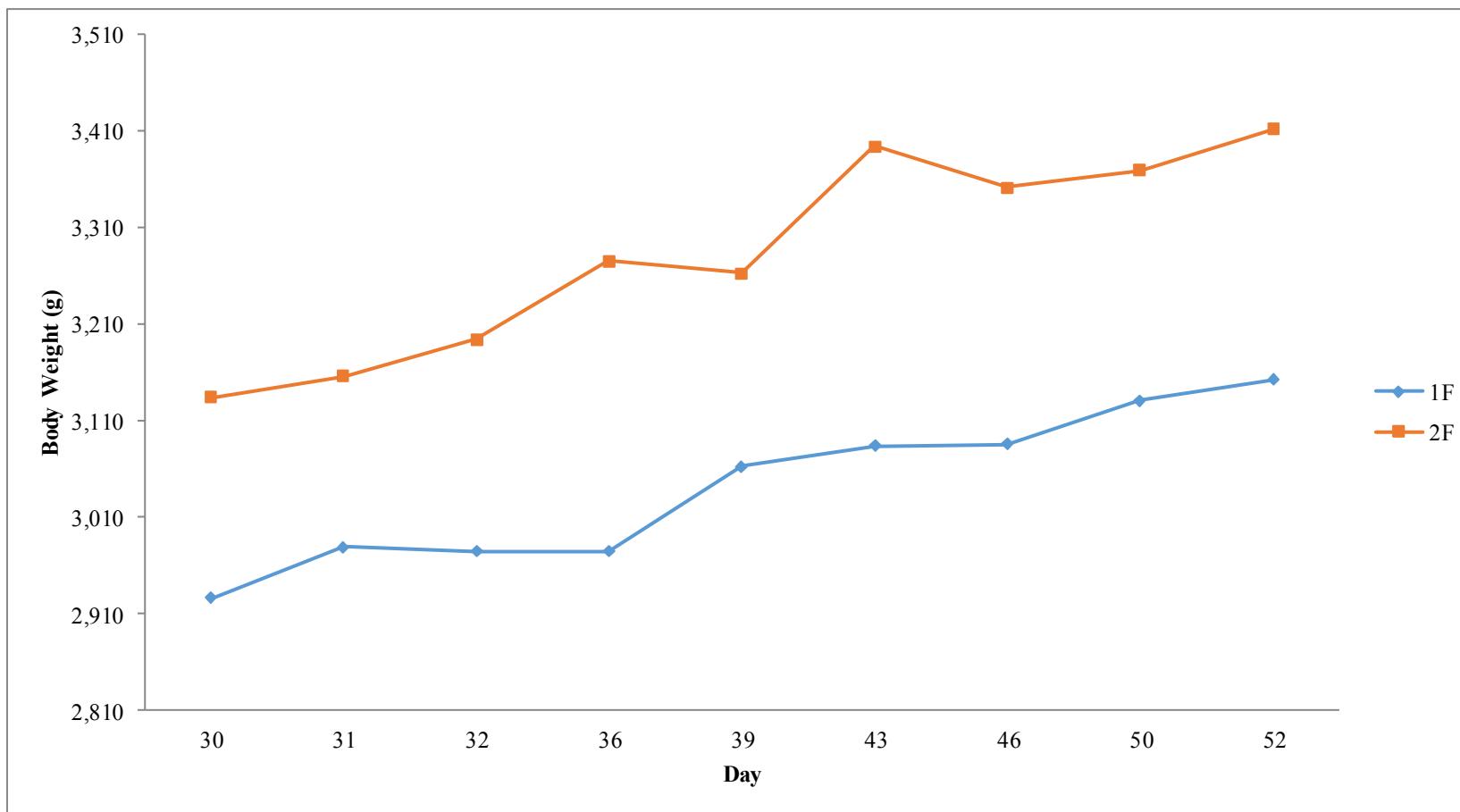
Group 2 - [REDACTED] 1×10^{11} VP

Table 1

Summary of Clinical Observations Pretreatment and Dosing Period

[REDACTED]

Day numbers relative to Start Date

Sex: Male

0 1×10^{11}
VP

Skin, Scab

Number of Observations	8	.
Number of Animals	1	.
Days from - to	-1 29	.

Table 1

Summary of Clinical Observations Pretreatment and Dosing Period

[REDACTED]

Day numbers relative to Start Date

Sex: Female

0 1×10^{11}
VP

Skin, Scab

Number of Observations	3	.
Number of Animals	1	.
Days from - to	1 15	.

Table 2
Summary of Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		Day						
		-7	1	2	3	4	8	11
1M	Mean	2324.1	2462.3	2482.5	2495.2	2519.1	2600.9	2675.9
	SD	185.1	216.2	225.0	213.6	226.2	231.0	249.2
	N	10	10	10	10	10	10	10
2M	Mean	2264.1	2395.7	2391.6	2437.5	2463.0	2548.4	2613.7
	SD	252.1	246.7	257.6	245.3	246.5	257.2	260.9
	N	10	10	10	10	10	10	10

Table 2
Summary of Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		Day					
		15	16	17	18	22	25
1M	Mean	2741.6	2771.0	2781.7	2794.8	2858.1	2896.9
	SD	248.4	248.1	243.4	262.3	269.2	277.7
	N	10	10	10	10	10	10
2M	Mean	2670.4	2663.8	2673.2	2713.4	2768.0	2800.9
	SD	276.9	283.5	276.0	277.6	274.3	275.8
	N	10	10	10	10	10	10

Table 2
Summary of Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		30	31	Day Change 1 - 31
1M	Mean	2960.6	2976.4	514.1
	SD	292.4	298.3	112.5
	N	10	10	10
2M	Mean	2814.4	2827.6	431.9
	SD	299.2	308.4	106.5
	N	10	10	10

Table 2
Summary of Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	-7	1	2	Day				
				3	4	8	11	
1F	Mean	2240.3	2400.7	2406.3	2435.7	2468.8	2548.9	2621.2
	SD	64.6	81.0	83.2	82.5	93.6	90.1	101.4
	N	10	10	10	10	10	10	10
2F	Mean	2328.7b	2489.3a	2463.3	2520.4	2558.7a	2644.2a	2727.3a
	SD	71.9	83.3	87.8	110.5	96.2	110.1	110.8
	N	10	10	10	10	10	10	10

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

Table 2
Summary of Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	15	16	17	Day				
				18	22	25	29	
1F	Mean	2737.3	2744.0	2783.9	2794.9	2882.6	2932.7	2964.3
	SD	96.3	100.6	118.1	134.5	125.8	116.8	140.3
	N	10	10	10	10	10	10	10
2F	Mean	2827.2	2837.9	2843.5	2877.2	2995.8a	3040.5a	3072.3
	SD	118.4	115.5	117.6	111.1	110.2	111.5	106.0
	N	10	10	10	10	10	10	10

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

Table 2
Summary of Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		30	31	Day Change 1 - 31
1F	Mean	2975.3	3027.9	627.2
	SD	132.2	125.7	87.8
	N	10	10	10
2F	Mean	3100.0a	3126.7	637.4
	SD	101.7	94.3	38.0
	N	10	10	10

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

Table 2
Summary of Body Weights (g) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		30	31	32	Day 36	39	43	46
1M	Mean	2871.6	2874.0	2865.0	2910.2	2923.2	2950.8	3020.4
	SD	153.3	174.7	157.7	174.5	184.3	194.5	195.3
	N	5	5	5	5	5	5	5
2M	Mean	2863.8	2896.0	2908.0	2950.0	2988.2	3045.2	3063.8
	SD	303.1	305.2	319.3	287.7	309.9	300.9	282.4
	N	5	5	5	5	5	5	5

Table 2
Summary of Body Weights (g) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		50	52	Day Change 31 - 52
1M	Mean	3011.8	3063.2	189.2
	SD	227.1	220.8	83.7
	N	5	5	5
2M	Mean	3099.0	3125.4	229.4
	SD	281.9	270.6	53.8
	N	5	5	5

Table 2
Summary of Body Weights (g) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		Day					
		30	31	32	36	39	43
1F	Mean	2925.6	2979.0	2974.6	2974.6	3062.2	3083.4
	SD	124.4	115.1	117.0	124.2	206.6	197.5
	N	5	5	5	5	5	5
2F	Mean	3134.0a	3155.6a	3194.0a	3275.2b	3262.4	3394.4a
	SD	127.2	123.3	145.8	90.9	121.4	182.2
	N	5	5	5	5	5	5

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



Table 2
Summary of Body Weights (g) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		50	52	Day Change 31 - 52
1F	Mean	3130.8	3152.4	173.4
	SD	211.3	190.3	106.3
	N	5	5	5
2F	Mean	3368.8	3412.0	256.4
	SD	235.8	237.2	129.1
	N	5	5	5

Table 3
Summary of Food Consumption (g/animal/day) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Day (From/To)					
	-7/1	1/2	2/3	3/4	4/8	8/11
1M	Mean	106.51	116.40	122.00	113.60	122.58
	SD	16.50	21.31	16.01	19.27	19.41
	N	10	10	10	10	10
2M	Mean	111.09	102.40	116.40	119.10	119.40
	SD	16.66	28.80	14.19	15.15	16.38
	N	10	10	10	10	10

Table 3
Summary of Food Consumption (g/animal/day) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Day (From/To)					
	11/15	15/16	16/17	17/18	18/22	22/25
1M	Mean	130.29	130.30	119.60	135.60	127.44
	SD	21.14	21.01	14.74	25.89	23.15
	N	10	10	10	10	10
2M	Mean	127.75	103.70a	114.60	121.40	127.08
	SD	18.85	26.45	17.35	18.39	15.53
	N	10	10	10	10	10

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 Food Consumption (g/animal/day) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Day (From/To)		
	25/29	29/30	30/31
1M	Mean	141.09	123.80
	SD	20.36	20.62
	N	10	10
2M	Mean	133.33	111.70
	SD	13.15	32.38
	N	10	10

Table 3
Summary of Food Consumption (g/animal/day) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Day (From/To)					
	30/31	31/32	32/36	36/39	39/43	43/46
1M	Mean	99.60	113.00	112.58	114.32	116.14
	SD	19.24	11.25	9.91	16.23	21.01
	N	5	5	5	5	5
2M	Mean	112.80	138.20a	122.36	125.74	128.42
	SD	15.50	21.31	8.33	18.16	19.14
	N	5	5	5	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 Food Consumption (g/animal/day) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Day (From/To)	
	46/50	50/52
1M	Mean	120.22
	SD	21.91
	N	5
1M	Mean	122.00
2M	Mean	134.64
	SD	16.81
	N	5
2M	Mean	127.80
	SD	16.38
	N	5

Table 4
Summary of Body Temperature (°C)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		Day -7 pr	Day 1 p6	Day 2 p	Day 15 pr	Day 16 p6	Day 16 p
1M	Mean	39.3	39.4	39.0	39.1	39.2	39.2
	SD	0.1	0.2	0.2	0.2	0.1	0.1
	N	10	10	10	10	10	10
2M	Mean	39.1a	39.4	39.1	39.3	39.1	39.1
	SD	0.2	0.2	0.2	0.3	0.1	0.1
	N	10	10	10	10	10	10

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

Table 4
Summary of Body Temperature (°C)

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		Day 29 pr	Day 30 p6	Day 30 p	Day 31 p	Day 52 p
1M	Mean	39.3	39.0	39.3	39.1	39.0
	SD	0.1	0.1	0.3	0.2	0.2
	N	10	10	10	10	5
2M	Mean	39.2	39.2	39.0a	39.1	39.1
	SD	0.1	0.3	0.2	0.3	0.1
	N	10	10	10	10	5

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

Table 4
Summary of Body Temperature (°C)

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		Day -7 pr	Day 1 p6	Day 2 p	Day 15 pr	Day 16 p6	Day 16 p
1F	Mean	39.4	39.5	39.2	39.1	39.5	39.4
	SD	0.1	0.1	0.2	0.1	0.3	0.3
	N	10	10	10	10	10	10
2F	Mean	39.2	39.3d	39.0	39.4b	39.3	39.5
	SD	0.2	0.3	0.2	0.2	0.1	0.3
	N	10	10	10	10	10	10

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 4
Summary of Body Temperature (°C)

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		Day 29 pr	Day 30 p6	Day 30 p	Day 31 p	Day 52 p
1F	Mean	39.3	39.3	39.6	39.4	39.2
	SD	0.1	0.1	0.3	0.2	0.2
	N	10	10	10	10	5
2F	Mean	39.3	39.1	39.1b	39.3	39.1
	SD	0.2	0.1	0.3	0.2	0.1
	N	10	10	10	10	5

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



Table 5
Summary of Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
1M	Mean	5.738	1.205	3.899	0.051	0.133	0.433	0.021
	SD	0.650	0.517	0.384	0.015	0.041	0.031	0.014
	N	8	8	8	8	8	8	8
2M	Mean	5.413	1.124	3.623	0.105a	0.121	0.426	0.015
	SD	0.879	0.319	0.771	0.063	0.038	0.111	0.005
	N	8	8	8	8	8	8	8
	XFold G1	0.943	0.933	0.929	2.049	0.915	0.986	0.706

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

Table 5
Summary of Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1M	Mean	6.376	13.11	0.4053	63.66	20.61	32.35
	SD	0.357	0.58	0.0207	3.14	1.05	0.55
	N	8	8	8	8	8	8
2M	Mean	6.464	13.54	0.4149	64.15	20.95	32.64
	SD	0.271	0.69	0.0196	1.14	0.48	0.24
	N	8	8	8	8	8	8
	XFold G1	1.014	1.03	1.0238	1.01	1.02	1.03

Table 5
Summary of Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L
1M	Mean	297.9	127.75	12.20	13.04	2.28
	SD	65.7	40.36	0.78	0.60	0.28
	N	7	8	7	7	7
2M	Mean	256.3	124.01	12.86	11.93a	2.41
	SD	83.4	26.17	1.88	0.85	0.77
	N	8	8	8	8	8
	XFold G1	0.9	0.97	1.05	0.91	1.06

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

Table 5
Summary of Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1×10^{11} vp

Group / Sex		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
1F	Mean	5.800	1.306	3.818	0.084	0.120	0.451	0.020
	SD	1.293	0.456	0.766	0.054	0.046	0.152	0.015
	N	8	8	8	8	8	8	8
2F	Mean	5.564	1.390	3.500	0.090	0.132	0.432	0.020
	SD	1.243	0.504	0.674	0.051	0.028	0.155	0.016
	N	9	9	9	9	9	9	9
	XFold G1	0.959	1.064	0.917	1.075	1.102	0.958	1.000

Table 5
Summary of Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1F	Mean	6.181	12.98	0.3966	64.20	21.01	32.70
	SD	0.286	0.36	0.0118	1.50	0.52	0.23
	N	8	8	8	8	8	8
2F	Mean	6.491a	12.94	0.4001	61.71a	19.96d	32.33
	SD	0.304	0.34	0.0115	2.75	1.03	0.46
	N	9	9	9	9	9	9
XFold G1	1.050	1.00	1.0088	0.96	0.95	0.99	1.03

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 Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L
1F	Mean	292.0	100.20	12.30	13.12	1.84
	SD	89.0	21.95	0.36	0.68	0.21
	N	8	8	6	6	6
2F	Mean	299.4	104.81	13.11	13.01	1.78
	SD	69.4	23.58	1.86	0.99	0.42
	N	8	9	9	9	9
	XFold G1	1.0	1.05	1.07	0.99	0.97

Table 5
Summary of Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
1M	Mean	5.494	0.969	3.938	0.069	0.111	0.393
	SD	0.453	0.241	0.363	0.052	0.056	0.100
	N	10	10	10	10	10	10
2M	Mean	5.106	0.851	3.619	0.183a	0.082	0.350
	SD	0.619	0.308	0.598	0.160	0.022	0.074
	N	9	9	9	9	9	9
	XFold G1	0.929	0.878	0.919	2.657	0.741	0.891
							1.111

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

Table 5
Summary of Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	RBC 10^12/L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1M	Mean	5.928	12.27	0.3817	64.50	20.75	32.14
	SD	0.284	0.41	0.0139	2.73	0.73	0.47
	N	10	10	10	10	10	10
2M	Mean	5.736	12.02	0.3707	64.63	20.99	32.48
	SD	0.225	0.57	0.0153	1.86	0.74	0.54
	N	9	9	9	9	9	9
	XFold G1	0.968	0.98	0.9711	1.00	1.01	1.01

Table 5
Summary of Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L
1M	Mean	240.9	249.04	12.06	12.64	2.28
	SD	77.1	48.37	1.30	1.03	0.50
	N	10	10	10	10	10
2M	Mean	266.8	202.49a	11.26	12.40	4.49c
	SD	86.8	40.61	0.61	0.86	0.34
	N	9	9	10	10	10
	XFold G1	1.1	0.81	0.93	0.98	1.96

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

Table 5
Summary of Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
1F	Mean	5.892	1.392	3.870	0.080	0.100	0.419
	SD	1.137	0.509	0.649	0.039	0.024	0.139
	N	9	9	9	9	9	9
2F	Mean	5.330	1.296	3.260	0.241b	0.092	0.404
	SD	1.031	0.629	0.821	0.140	0.051	0.157
	N	10	10	10	10	10	8
XFold G1	0.905	0.931	0.842	3.013	0.920	0.964	1.527

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

Table 5
Summary of Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	RBC 10^12/L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1F	Mean	5.804	12.06	0.3763	64.84	20.74	13.69
	SD	0.156	0.48	0.0126	1.76	0.64	0.49
	N	9	9	9	9	9	9
2F	Mean	5.900	11.68	0.3650	61.92a	19.83a	13.48
	SD	0.344	0.41	0.0144	2.58	1.05	0.54
	N	10	10	10	10	10	10
XFold G1	1.016	0.97	0.9699	0.95	0.96	1.00	0.98

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

Table 5
Summary of Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L
1F	Mean	305.7	224.79	12.07	13.27	2.09
	SD	50.4	36.87	0.37	1.27	0.33
	N	9	9	10	10	10
2F	Mean	255.7	195.92	11.63a	12.90	4.16c
	SD	100.5	31.82	0.54	0.63	0.31
	N	10	10	10	10	10
	XFold G1	0.8	0.87	0.96	0.97	2.00

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

Table 5
Summary of Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
1M	Mean	6.582	1.678	4.012	0.140	0.142	0.570	0.038
	SD	1.550	0.972	0.521	0.100	0.073	0.152	0.024
	N	5	5	5	5	5	5	5
2M	Mean	6.074	1.146	4.046	0.154	0.102	0.540	0.088
	SD	0.991	0.403	0.742	0.112	0.029	0.141	0.098
	N	5	5	5	5	5	5	5
	XFold G1	0.923	0.683	1.008	1.100	0.718	0.947	2.316

Table 5
Summary of Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1M	Mean	6.134	12.90	0.3950	64.52	21.12	32.72
	SD	0.395	0.44	0.0112	3.00	0.91	0.29
	N	5	5	5	5	5	5
2M	Mean	6.040	12.98	0.3956	65.54	21.50	32.82
	SD	0.289	0.47	0.0140	1.68	0.85	0.81
	N	5	5	5	5	5	5
XFold G1	0.985	1.01	1.0015	1.02	1.02	1.00	1.03

Table 5
Summary of Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L
1M	Mean	310.2	165.42	10.74	12.56	2.47
	SD	38.6	23.82	0.39	0.74	0.65
	N	5	5	5	5	5
2M	Mean	380.2	149.78	10.08b	11.94	4.32b
	SD	99.3	9.02	0.19	0.80	0.55
	N	5	5	5	5	5
	XFold G1	1.2	0.91	0.94	0.95	1.75

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

Table 5
Summary of Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
1F	Mean	6.332	1.822	3.766	0.108	0.124	0.028
	SD	1.373	0.591	0.922	0.026	0.032	0.010
	N	5	5	5	5	5	4
2F	Mean	6.864	1.648	4.276	0.222c	0.108	0.065
	SD	1.761	0.766	0.876	0.038	0.043	0.034
	N	5	5	5	5	5	4
XFold G1	1.084	0.905	1.135	2.056	0.871	1.139	2.364

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

Table 5
Summary of Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1F	Mean	5.844	12.52	0.3880	66.46	21.48	32.32
	SD	0.430	0.72	0.0234	1.58	0.37	0.48
	N	5	5	5	5	5	5
2F	Mean	6.044	12.08	0.3750	62.20a	20.04d	32.22
	SD	0.337	0.24	0.0085	3.17	0.89	0.68
	N	5	5	5	5	5	5
XFold G1	1.034	0.96	0.9665	0.94	0.93	1.00	1.02

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 Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L
1F	Mean	303.8	179.96	11.42	12.96	1.93
	SD	49.6	39.89	2.02	1.38	0.65
	N	5	5	5	5	5
2F	Mean	333.8	173.58	10.52	13.30	3.18a
	SD	60.5	34.50	0.53	0.59	0.57
	N	5	5	5	5	5
	XFold G1	1.1	0.96	0.92	1.03	1.65

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

Table 5
Summary of Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
1M	Mean	6.806	1.186	4.906	0.060	0.126	0.508	0.020
	SD	0.691	0.233	0.695	0.007	0.040	0.150	0.007
	N	5	5	5	5	5	5	5
2M	Mean	5.464	0.978	3.892	0.050	0.108	0.424	0.010
	SD	1.724	0.425	1.288	0.020	0.053	0.128	0.007
	N	5	5	5	5	5	5	5
	XFold G1	0.803	0.825	0.793	0.833	0.857	0.835	0.500

Table 5
Summary of Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1M	Mean	6.544	13.86	0.4296	65.70	21.22	12.72
	SD	0.308	0.25	0.0121	2.40	0.66	0.70
	N	5	5	5	5	5	5
2M	Mean	6.380	13.62	0.4154	65.16	21.42	13.16
	SD	0.249	0.38	0.0139	1.89	0.70	0.53
	N	5	5	5	5	5	5
	XFold G1	0.975	0.98	0.9669	0.99	1.01	1.03

Table 5
Summary of Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L
1M	Mean	275.4	157.92	10.80	12.14	2.05
	SD	63.3	30.03	0.54	0.82	0.26
	N	5	5	5	5	5
2M	Mean	297.0	147.70	11.44	12.36	2.03
	SD	65.8	18.21	0.78	0.86	0.21
	N	5	5	5	5	5
	XFold G1	1.1	0.94	1.06	1.02	0.99

Table 5
Summary of Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
1F	Mean	5.406	1.088	3.606	0.056	0.134	0.014
	SD	0.585	0.131	0.422	0.030	0.021	0.005
	N	5	5	5	5	5	5
2F	Mean	5.806	1.550	3.478	0.066	0.128	0.022
	SD	0.713	0.695	0.286	0.038	0.004	0.018
	N	5	5	5	5	5	5
XFold G1	1.074	1.425	0.965	1.179	0.955	1.098	1.571

Table 5
Summary of Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1F	Mean	6.434	13.36	0.4096	63.70	20.76	11.78
	SD	0.141	0.30	0.0088	1.73	0.70	0.37
	N	5	5	5	5	5	5
2F	Mean	6.752b	13.40	0.4174	61.82	19.82	13.00b
	SD	0.125	0.48	0.0100	1.96	0.83	0.58
	N	5	5	5	5	5	5
XFold G1	1.049	1.00	1.0190	0.97	0.95	0.98	1.10

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



Table 5
Summary of Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L
1F	Mean	330.8	110.12	11.66	15.58	1.68
	SD	68.7	29.27	0.85	1.41	0.27
	N	5	5	5	5	5
2F	Mean	314.0	123.24	11.70	14.10	2.07
	SD	31.1	23.67	0.78	0.90	0.51
	N	5	5	5	5	5
	XFold G1	0.9	1.12	1.00	0.91	1.23

Table 6
Summary of Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1M	Mean	14.5	30.2	221.7	7.6	673.4	1.30	5.62
	SD	3.0	6.1	58.1	2.1	472.0	0.00	1.01
	N	10	10	10	10	10	10	10
2M	Mean	14.3	36.5	248.6	7.7	597.4	1.30	5.13
	SD	4.0	13.8	63.9	2.1	201.7	0.00	1.00
	N	10	10	10	10	10	10	10
XFold G1		1.0	1.2	1.1	1.0	0.9	1.00	0.91

Table 6
Summary of Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1M	Mean	62.0	8.025	0.87	1.475	58.0	44.7	13.1
	SD	8.3	0.383	0.22	0.387	2.1	1.5	1.6
	N	10	10	10	10	10	10	10
2M	Mean	65.7	8.632b	1.01	1.919	59.2	45.7	13.5
	SD	13.9	0.507	0.31	1.457	4.1	2.5	2.2
	N	10	10	10	10	10	10	10
XFold G1		1.1	1.076	1.16	1.301	1.0	1.0	1.0

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 Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	3.46	3.897	2.037	142.3	4.68
	SD	0.45	0.102	0.090	1.1	0.22
	N	10	10	10	10	10
2M	Mean	3.43	3.860	2.203b	142.2	4.96a
	SD	0.50	0.152	0.134	1.7	0.35
	N	10	10	10	10	10
	XFold G1	0.99	0.991	1.081	1.0	1.06

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 Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1F	Mean	13.5	29.4	240.2	8.7	495.6	1.30
	SD	2.4	8.3	36.1	1.5	89.3	0.00
	N	10	10	10	10	10	10
2F	Mean	11.6	29.7	241.3	8.4	895.6	1.30
	SD	2.0	5.3	46.4	1.2	942.6	0.00
	N	10	10	10	10	10	10
XFold G1	0.9	1.0	1.0	1.0	1.8	1.00	1.02

Table 6
Summary of Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1F	Mean	71.0	8.558	1.31	1.522	55.8	43.3	12.5
	SD	5.2	0.512	0.24	0.875	2.6	1.6	1.6
	N	10	10	10	10	10	10	10
2F	Mean	72.2	9.009	1.37	1.180	56.7	43.7	13.0
	SD	6.8	0.671	0.25	0.229	3.1	1.9	1.5
	N	10	10	10	10	10	10	10
XFold G1		1.0	1.053	1.05	0.775	1.0	1.0	1.0

Table 6
Summary of Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	3.51	3.893	2.005	140.8	4.54
	SD	0.46	0.101	0.113	0.6	0.38
	N	10	10	10	10	10
2F	Mean	3.40	3.867	2.232c	141.1	4.77
	SD	0.31	0.138	0.141	1.5	0.32
	N	10	10	10	10	10
XFold G1	0.97	0.993	1.113	1.0	1.05	1.0

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 Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1M	Mean	10.5	26.8	189.6	7.9	605.9	1.30	5.63
	SD	3.0	4.6	40.2	2.5	210.3	0.00	0.75
	N	10	10	10	10	10	10	10
2M	Mean	13.0	33.9a	174.3	8.2	895.6a	1.30	5.16
	SD	2.9	8.8	31.1	2.5	285.6	0.00	0.66
	N	10	10	10	10	10	10	10
XFold G1		1.2	1.3	0.9	1.0	1.5	1.00	0.92

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 Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1M	Mean	61.6	7.986	0.74	1.458	55.7	44.1	11.9
	SD	4.3	0.537	0.22	0.396	1.8	1.4	1.2
	N	10	10	10	10	10	10	10
2M	Mean	63.6	8.611a	0.91	1.668	58.8c	43.6	15.1c
	SD	7.0	0.428	0.25	0.853	1.2	1.1	0.6
	N	10	10	10	10	10	10	10
XFold G1		1.0	1.078	1.23	1.144	1.1	1.0	1.3

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 Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	3.72	3.803	1.954	142.9	4.68
	SD	0.33	0.103	0.120	1.7	0.21
	N	10	10	10	10	10
2M	Mean	2.91c	3.754	2.030	141.9	4.79
	SD	0.15	0.059	0.110	1.4	0.37
	N	10	10	10	10	10
XFold G1	0.78	0.987	1.039	1.0	1.02	1.0

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 Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1F	Mean	9.9	30.6	224.9	8.9	841.5	5.66
	SD	4.2	8.0	33.2	1.3	465.6	0.64
	N	10	10	10	10	10	10
2F	Mean	12.7	30.5	196.8	8.5	988.4	5.49
	SD	3.9	5.6	30.9	1.3	310.5	0.51
	N	10	10	10	10	10	10
XFold G1	1.3	1.0	0.9	1.0	1.2	1.00	0.97

Table 6
Summary of Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1F	Mean	70.9	8.517	1.32	1.187	55.4	43.4	11.7
	SD	6.6	0.334	0.11	0.591	1.5	1.2	1.1
	N	10	10	10	10	10	10	10
2F	Mean	72.2	9.176b	1.48	1.210	56.8	42.6	14.1c
	SD	7.5	0.598	0.23	0.326	2.3	2.0	1.0
	N	10	10	10	10	10	10	10
XFold G1		1.0	1.077	1.12	1.019	1.0	1.0	1.2

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 Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	3.69	3.766	1.995	141.8	4.56
	SD	0.30	0.094	0.166	0.9	0.39
	N	10	10	10	10	10
2F	Mean	3.01c	3.812	1.996	141.7	4.62
	SD	0.21	0.107	0.257	1.3	0.25
	N	10	10	10	10	10
XFold G1	0.82	1.012	1.001	1.0	1.01	1.0

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 Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1M	Mean	10.2	30.6	148.2	5.8	679.0	1.30	6.22
	SD	3.8	8.5	32.7	1.3	241.6	0.00	0.78
	N	5	5	5	5	5	5	5
2M	Mean	10.8	38.4	128.6	6.0	893.2	1.30	5.54
	SD	1.9	13.4	26.0	1.2	452.7	0.00	0.85
	N	5	5	5	5	5	5	5
	XFold G1	1.1	1.3	0.9	1.0	1.3	1.00	0.89

Table 6
Summary of Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1M	Mean	64.4	8.198	0.50	1.600	58.2	45.8	12.6
	SD	5.1	0.157	0.16	0.639	2.2	1.3	1.3
	N	5	5	5	5	5	5	5
2M	Mean	64.6	8.648a	0.64	1.032	60.8	44.8	16.0b
	SD	4.8	0.257	0.27	0.146	2.3	1.1	1.4
	N	5	5	5	5	5	5	5
	XFold G1	1.0	1.055	1.28	0.645	1.0	1.0	1.3

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 Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	3.66	3.802	1.684	148.2	5.02
	SD	0.32	0.097	0.096	1.1	0.22
	N	5	5	5	5	5
2M	Mean	2.86b	3.658d	1.608	145.4	4.74
	SD	0.21	0.044	0.129	4.0	0.29
	N	5	5	5	5	5
	XFold G1	0.78	0.962	0.955	1.0	0.94

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 6
Summary of Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1F	Mean	15.4	42.6	179.4	9.6	2301.2	6.82
	SD	6.1	7.7	30.3	0.5	1152.6	0.61
	N	5	5	5	5	5	5
2F	Mean	11.6	40.6	152.0	8.6	1414.6	7.40
	SD	4.0	5.1	27.7	1.8	1066.3	0.79
	N	5	5	5	5	5	5
XFold G1	0.8	1.0	0.8	0.9	0.6	1.00	1.09

Table 6
Summary of Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1F	Mean	79.0	8.254	1.42	0.770	57.0	44.4	12.6
	SD	8.3	0.537	0.24	0.204	1.4	1.5	0.5
	N	5	5	5	5	5	5	5
2F	Mean	80.2	8.512	1.38	1.014	57.8	43.2	14.8b
	SD	10.1	0.393	0.23	0.254	3.2	2.2	1.3
	N	5	5	5	5	5	5	5
XFold G1		1.0	1.031	0.97	1.317	1.0	1.0	1.2

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 Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	3.52	3.746	1.644	142.2	4.64
	SD	0.16	0.139	0.243	3.8	0.51
	N	5	5	5	5	5
2F	Mean	2.90c	3.752	1.540	143.0	4.56
	SD	0.16	0.128	0.135	4.1	0.32
	N	5	5	5	5	5
	XFold G1	0.82	1.002	0.937	1.0	0.98

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 Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1M	Mean	12.2	38.4	127.2	7.0	665.0	1.30	7.16
	SD	2.4	4.6	14.9	1.6	274.8	0.00	1.09
	N	5	5	5	5	5	5	5
2M	Mean	16.6	56.6	119.8	6.0	706.2	1.30	7.22
	SD	5.3	24.0	13.2	1.6	156.0	0.00	1.02
	N	5	5	5	5	5	5	5
	XFold G1	1.4	1.5	0.9	0.9	1.1	1.00	1.01

Table 6
Summary of Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1M	Mean	71.2	7.776	0.56	1.784	60.0	47.0	13.0
	SD	6.6	0.745	0.11	0.690	1.2	1.2	1.2
	N	5	5	5	5	5	5	5
2M	Mean	72.4	7.962	0.64	2.788	59.6	46.0	13.8
	SD	5.9	0.394	0.21	1.458	1.8	0.7	1.3
	N	5	5	5	5	5	5	5
	XFold G1	1.0	1.024	1.14	1.563	1.0	1.0	1.1

Table 6
Summary of Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1M	Mean	3.68	3.872	1.496	143.6	4.50
	SD	0.35	0.105	0.090	1.1	0.12
	N	5	5	5	5	5
2M	Mean	3.36	3.860	1.496	144.4	4.70
	SD	0.27	0.089	0.094	3.2	0.34
	N	5	5	5	5	5
	XFold G1	0.91	0.997	1.000	1.0	1.04

Table 6
Summary of Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1F	Mean	11.0	33.6	134.6	7.4	825.2	8.28
	SD	1.2	8.6	15.2	2.5	395.5	0.86
	N	5	5	5	5	5	5
2F	Mean	12.4	43.0	108.2a	7.8	1128.6	7.70
	SD	1.1	9.7	19.1	1.3	623.0	0.53
	N	5	5	5	5	5	5
XFold G1	1.1	1.3	0.8	1.1	1.4	1.00	0.93

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 Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1F	Mean	82.8	8.166	0.96	1.082	55.0	42.8	12.2
	SD	5.5	0.749	0.21	0.390	2.4	1.6	1.1
	N	5	5	5	5	5	5	5
2F	Mean	84.0	8.028	1.20	0.716	57.2	43.4	13.8
	SD	12.3	0.446	0.32	0.194	2.7	1.1	1.6
	N	5	5	5	5	5	5	5
	XFold G1	1.0	0.983	1.25	0.662	1.0	1.0	1.1

Table 6
Summary of Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1F	Mean	3.58	3.756	1.264	140.6	4.08
	SD	0.29	0.116	0.035	1.1	0.16
	N	5	5	5	5	5
2F	Mean	3.20	3.768	1.270	142.4	4.32a
	SD	0.41	0.113	0.097	3.2	0.11
	N	5	5	5	5	5
	XFold G1	0.89	1.003	1.005	1.0	1.06

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 C-Reactive Protein Values (mg/L)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		Day -5	Day 2	Day 7	Day 30	Day 52
1M	Mean	1.70	1.31	1.38	2.54	1.88
	SD	1.56	1.89	1.43	3.44	1.41
	N	10	10	10	10	5
2M	Mean	3.52	85.82	1.65	85.02	2.10
	SD	4.26	52.12	1.04	41.96	1.29
	N	10	10	10	10	5

Table 7
Summary of C-Reactive Protein Values (mg/L)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		Day -5	Day 2	Day 7	Day 30	Day 52
1F	Mean	4.61	8.38	7.48	9.15	3.50
	SD	3.35	8.24	6.42	7.20	2.69
	N	10	10	10	10	5
2F	Mean	4.53	97.85	8.26	74.18	9.25
	SD	2.99	67.98	8.31	42.38	9.63
	N	10	10	10	10	5

Table 8
Summary of Absolute Organ Weights Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Body Weight kg	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	Mean	3.06	10.1114	2.2326	0.3036	0.0374	0.6570
	SD	0.36	0.1789	0.1085	0.0747	0.0120	0.2953
	N	5	5	5	5	5	5
2M	Mean	2.76	9.3884d	1.8610	0.2650	0.0362	0.7640
	SD	0.34	0.6088	0.3693	0.0379	0.0055	0.1457
	N	5	5	5	5	5	5

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 8
Summary of Absolute Organ Weights Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	HEART g	KIDNEY g	LIVER g	LYMPH NODE g	SPLEEN g	TESTIS g	THYMUS g
1M	Mean	9.1412	19.2578	124.8700	0.0296	1.2210	4.6868
	SD	1.5554	3.1604	12.1195	0.0252	0.3590	0.9744
	N	5	5	5	5	5	5
2M	Mean	7.4334	17.4888	99.4314a	0.2300d	1.2680	3.6142
	SD	0.8711	1.5438	17.2988	0.1006	0.4060	0.5724
	N	5	5	5	5	5	5

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 8
Summary of Absolute Organ Weights Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Body Weight kg	BRAIN g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND THYROID g	HEART g	KIDNEY g
1F	Mean	3.06	10.3256	0.2212	0.0382	0.3114	7.9444
	SD	0.11	0.3706	0.0589	0.0079	0.0373	0.6244
	N	5	5	5	5	5	5
2F	Mean	3.06	9.9316	0.2738	0.0298	0.2962	7.9530
	SD	0.05	0.5206	0.0409	0.0029	0.0366	0.7397
	N	5	5	5	5	5	5

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 Absolute Organ Weights Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		LIVER g	LYMPH NODE g	OVARY g	SPLEEN g	THYMUS g
1F	Mean	115.6996	0.0378	0.3222	1.6214	3.6456
	SD	8.4853	0.0181	0.0859	0.5588	0.8205
	N	5	5	5	5	5
2F	Mean	108.1686	0.3918a	0.3574	2.2210	3.3860
	SD	12.3001	0.2318	0.0793	0.3298	0.7610
	N	5	5	5	5	5

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

Table 8
Summary of Absolute Organ Weights Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		Body Weight kg	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	Mean	3.04	9.7156	2.3076	0.2792	0.0218	0.6792	0.2848
	SD	0.19	0.5519	0.3127	0.0585	0.0082	0.1628	0.0383
	N	5	5	5	5	4	5	5
2M	Mean	3.14	9.7704	2.6296	0.3116	0.0338	1.0922	0.3336
	SD	0.25	0.3869	0.4119	0.0654	0.0171	0.4014	0.1011
	N	5	5	5	5	5	5	5

Table 8
Summary of Absolute Organ Weights Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	HEART g	KIDNEY g	LIVER g	LYMPH NODE g	SPLEEN g	TESTIS g	THYMUS g
1M	Mean	8.2944	16.8582	110.5824	0.0234	1.0392	5.1996
	SD	1.3078	0.8056	8.2111	0.0201	0.1643	0.4787
	N	5	5	5	5	5	5
2M	Mean	8.7446	18.1716	127.8836a	0.0396	1.3672	5.2442
	SD	0.6587	1.4875	10.6730	0.0245	0.4543	0.5818
	N	5	5	5	5	5	5

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 Absolute Organ Weights Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Body Weight kg	BRAIN g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND THYROID g	HEART g	KIDNEY g
1F	Mean	3.16	10.3334	0.2876	0.0360	0.3442	8.2918
	SD	0.21	0.4550	0.0361	0.0058	0.0642	0.2378
	N	5	5	5	5	5	4
2F	Mean	3.38	9.6526	0.2644	0.0364	0.3143	8.6506
	SD	0.26	0.4931	0.0490	0.0089	0.0539	0.4453
	N	5	5	5	5	5	5

Table 8
Summary of Absolute Organ Weights Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		LIVER g	LYMPH NODE g	OVARY g	SPLEEN g	THYMUS g
1F	Mean	103.9782	0.0364	0.5076	1.3702	3.3280
	SD	17.7077	0.0197	0.2177	0.3223	0.6503
	N	5	5	5	5	5
2F	Mean	101.1402	0.0242	0.4746	1.6460	3.2094
	SD	17.9384	0.0124	0.1531	0.2250	0.3208
	N	5	5	5	5	5

Table 9
Summary of Organ Weights Relative to Body Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.33412	0.07369	0.01011	0.00123	0.02192	0.01303
	SD	0.03944	0.00861	0.00305	0.00042	0.01116	0.00131
	N	5	5	5	5	5	5
2M	Mean	0.34390	0.06833	0.00979	0.00134	0.02788	0.01101
	SD	0.04191	0.01535	0.00215	0.00034	0.00569	0.00201
	N	5	5	5	5	5	5

Table 9
Summary of Organ Weights Relative to Body Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	KIDNEY %	LIVER %	LYMPH NODE %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.62849	4.09801	0.00098	0.03945	0.15508
	SD	0.06304	0.31242	0.00084	0.00812	0.04001
	N	5	5	5	5	5
2M	Mean	0.63684	3.60586	0.00838a	0.04549	0.13178
	SD	0.04241	0.53586	0.00351	0.01051	0.02113
	N	5	5	5	5	5

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

Table 9
Summary of Organ Weights Relative to Body Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	BRAIN %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND THYROID %	HEART %	KIDNEY %	LIVER %
1F	Mean	0.33760	0.00724	0.00125	0.01018	0.25962	0.53266
	SD	0.01124	0.00193	0.00027	0.00118	0.01765	0.05076
	N	5	5	5	5	5	5
2F	Mean	0.32483	0.00895	0.00097	0.00970	0.26006	0.48068
	SD	0.02200	0.00136	0.00010	0.00134	0.02622	0.01250
	N	5	5	5	5	5	5

Table 9
Summary of Organ Weights Relative to Body Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	LYMPH NODE %	OVARY %	SPLEEN %	THYMUS %
1F	Mean	0.00124	0.01061	0.05337
	SD	0.00059	0.00316	0.01933
	N	5	5	5
2F	Mean	0.01286a	0.01167	0.07265
	SD	0.00776	0.00249	0.01140
	N	5	5	5

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

Table 9
Summary of Organ Weights Relative to Body Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	Mean	0.32009	0.07566	0.00929	0.00070	0.02246	0.00943
	SD	0.01773	0.00620	0.00247	0.00026	0.00601	0.00160
	N	5	5	5	4	5	5
2M	Mean	0.31206	0.08346	0.00984	0.00106	0.03451	0.01053
	SD	0.01526	0.00890	0.00130	0.00048	0.01177	0.00275
	N	5	5	5	5	5	5

Table 9
Summary of Organ Weights Relative to Body Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	KIDNEY %	LIVER %	LYMPH NODE %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	0.55567	3.64394	0.00076	0.03437	0.17096
	SD	0.03094	0.28073	0.00064	0.00653	0.00924
	N	5	5	5	5	5
2M	Mean	0.58162	4.07860a	0.00131	0.04380	0.16673
	SD	0.06560	0.26202	0.00093	0.01498	0.00646
	N	5	5	5	5	5

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

Table 9
Summary of Organ Weights Relative to Body Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	BRAIN %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND THYROID %	HEART %	KIDNEY %	LIVER %
1F	Mean	0.32759	0.00913	0.00114	0.01096	0.26328	0.50667
	SD	0.01585	0.00123	0.00022	0.00227	0.01827	0.04687
	N	5	5	5	5	4	5
2F	Mean	0.28742	0.00788	0.00110	0.00920	0.25689	0.46363
	SD	0.03258	0.00163	0.00034	0.00207	0.01970	0.07229
	N	5	5	5	4	5	5

Table 9
Summary of Organ Weights Relative to Body Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		LYMPH NODE %	OVARY %	SPLEEN %	THYMUS %
1F	Mean	0.00115	0.01592	0.04342	0.10481
	SD	0.00063	0.00606	0.01059	0.01443
	N	5	5	5	5
2F	Mean	0.00074	0.01438	0.04898	0.09521
	SD	0.00042	0.00574	0.00807	0.01041
	N	5	5	5	5

Table 10
Summary of Organ Weights Relative to Brain Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	22.07408	3.01326	0.37128	6.47915	3.95302	90.37330
	SD	0.83865	0.79974	0.12530	2.90022	0.70136	15.09531
	N	5	5	5	5	5	5
2M	Mean	19.74476	2.81700	0.38953	8.19519	3.23228	79.43129
	SD	3.14616	0.31168	0.08206	1.79561	0.63537	10.57141
	N	5	5	5	5	5	5

Table 10
Summary of Organ Weights Relative to Brain Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		LIVER %	LYMPH NODE %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	1234.36958	0.29525	12.08496	46.34610	42.96375
	SD	110.14645	0.25593	3.55845	9.59820	9.33269
	N	5	5	5	5	5
2M	Mean	1057.66475	2.40250a	13.41060	38.63915	34.66163
	SD	166.83571	0.93699	3.67461	6.54321	11.29142
	N	5	5	5	5	5

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

Table 10
Summary of Organ Weights Relative to Brain Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	GLAND ADRENAL %	GLAND PITUITARY %	GLAND THYROID %	HEART %	KIDNEY %	LIVER %	LYMPH NODE %
1F	Mean	2.14829	0.37031	3.01337	76.98459	157.74767	1120.43077
	SD	0.60019	0.07593	0.31973	6.14059	13.75823	69.49083
	N	5	5	5	5	5	5
2F	Mean	2.75569	0.30053	2.97933	80.01685	148.38424	1092.02000
	SD	0.37857	0.03223	0.30687	4.82676	8.19474	143.38425
	N	5	5	5	5	5	5

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

Table 10
Summary of Organ Weights Relative to Brain Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		OVARY %	SPLEEN %	THYMUS %
1F	Mean	3.14395	15.73427	35.34286
	SD	0.93157	5.31198	8.14521
	N	5	5	5
2F	Mean	3.60634	22.31558a	34.09578
	SD	0.83435	2.54242	7.67563
	N	5	5	5

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

Table 10
Summary of Organ Weights Relative to Brain Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex		EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	Mean	23.75116	2.90790	0.21887	7.05192	2.93971	85.26969	174.03994
	SD	3.00626	0.78417	0.07700	1.96794	0.42122	11.90819	14.28462
	N	5	5	4	5	5	5	5
2M	Mean	26.88014	3.17641	0.34131	11.17815	3.39406	89.48511	186.05795
	SD	3.90575	0.56995	0.16129	4.19027	0.94827	5.33303	14.37260
	N	5	5	5	5	5	5	5

Table 10
Summary of Organ Weights Relative to Brain Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		LIVER %	LYMPH NODE %	SPLEEN %	TESTIS %	THYMUS %
1M	Mean	1142.54326	0.24504	10.79100	53.58277	34.50993
	SD	124.19669	0.21986	2.27937	4.69226	11.21323
	N	5	5	5	5	5
2M	Mean	1309.46599	0.41181	14.04464	53.59017	35.34080
	SD	107.54091	0.27123	4.82859	4.38291	5.90175
	N	5	5	5	5	5

Table 10
Summary of Organ Weights Relative to Brain Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	GLAND ADRENAL %	GLAND PITUITARY %	GLAND THYROID %	HEART %	KIDNEY %	LIVER %	LYMPH NODE %
1F	Mean	2.78237	0.34823	3.33401	80.36723	153.85880	1006.20229
	SD	0.31702	0.05201	0.61183	4.22496	6.48717	162.65410
	N	5	5	5	5	5	5
2F	Mean	2.74999	0.37485	3.28796	89.94427	163.21749	1054.45818
	SD	0.56803	0.07630	0.45250	8.62752	34.90264	227.07013
	N	5	5	4	5	5	5

Table 10
Summary of Organ Weights Relative to Brain Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex		OVARY %	SPLEEN %	THYMUS %
1F	Mean	4.88885	13.33676	32.12119
	SD	1.98160	3.55068	5.37424
	N	5	5	5
2F	Mean	4.89782	17.01429	33.35608
	SD	1.48379	1.72262	4.14153
	N	5	5	5

Table 11

[REDACTED] Summary of Necropsy Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5			5	5		
ARTERY, AORTA								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BODY CAVITY, NASAL								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE, FEMUR								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE, STERNUM								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE MARROW, FEMUR								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE MARROW, STERNUM								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE MARROW SMEAR								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BRAIN								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
CERVIX								
Submitted	-	-			5	5		
No Visible Lesions	-	-			5	5		
EPIDIDYMIS								
Submitted	5	5			-	-		
No Visible Lesions	5	5			-	-		
ESOPHAGUS								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
EYE								
Submitted	5	5			5	5		

Table 11

[REDACTED] Summary of Necropsy Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
EYE (Continued...)								
No Visible Lesions	5	5					5	5
GALLBLADDER								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GALT								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, ADRENAL								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, LACRIMAL								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, MAMMARY								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, PARATHYROID								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, PITUITARY								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, PROSTATE								
Submitted	5	5					-	-
No Visible Lesions	4	4					-	-
Small	1	1					-	-
GLAND, SALIVARY, MANDIBULAR								
Submitted	5	5					5	5
No Visible Lesions	5	4					5	5
Discoloration; dark	0	1					0	0
GLAND, SEMINAL VESICLE								
Submitted	5	5					-	-
No Visible Lesions	5	4					-	-
Small	0	1					-	-

Table 11

[REDACTED] Summary of Necropsy Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
GLAND, THYROID								
Submitted	5	5					5	5
No Visible Lesions	4	4					5	5
Enlargement	0	1					0	0
Discoloration; dark	1	0					0	0
HEART								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
KIDNEY								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, APPENDIX								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, CECUM								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, COLON								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, RECTUM								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARYNX								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LIVER								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LUNG								
Submitted	5	5					5	5
No Visible Lesions	0	3					3	2
Focus; dark	1	0					0	1
Discoloration; dark	0	0					1	0
Discoloration; mottled	4	2					1	2

Table 11

[REDACTED] Summary of Necropsy Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5			5	5		
LUNG (Continued...)								
Abnormal consistency	0	1			0	0		
LYMPH NODE, ILIAC								
Submitted	5	5			5	5		
No Visible Lesions	5	5			3	3		
Discoloration; dark	0	0			2	1		
Enlargement	0	0			0	1		
LYMPH NODE, MANDIBULAR								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
LYMPH NODE, MESENTERIC								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
MUSCLE, DIAPHRAGM								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
MUSCLE, SKELETAL								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	4		
Focus; dark	0	0			0	1		
NERVE, OPTIC								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
NERVE, SCIATIC								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
OVARY								
Submitted	-	-			5	5		
No Visible Lesions	-	-			5	5		
OVIDUCT								
Submitted	-	-			5	5		
No Visible Lesions	-	-			4	5		
Cyst; clear	-	-			1	0		
PANCREAS								
Submitted	5	5			5	5		

Table 11

[REDACTED] Summary of Necropsy Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
PANCREAS (Continued...)								
No Visible Lesions	5	5					5	5
SKIN								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, DUODENUM								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, ILEUM								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, JEJUNUM								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, SACculus ROTUNDUS								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
SPINAL CORD								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
SPLEEN								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
STOMACH								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
TESTIS								
Submitted	5	5					-	-
No Visible Lesions	5	5					-	-
THYMUS								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
TONGUE								
Submitted	5	5					5	5

Table 11

[REDACTED] Summary of Necropsy Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
TONGUE (Continued...)								
No Visible Lesions	5	5					5	5
TRACHEA								
Submitted	5	5					5	5
No Visible Lesions	5	4					4	5
Fluid accumulation	0	1					0	0
Fluid accumulation; dark	0	0					1	0
URETER								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
URINARY BLADDER								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
UTERUS								
Submitted	-	-					5	5
No Visible Lesions	-	-					5	5
VAGINA								
Submitted	-	-					5	5
No Visible Lesions	-	-					5	5
SITE, ADMINISTRATION, 1								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	3
Discoloration; dark	0	0					0	2
SITE, ADMINISTRATION, 2								
Submitted	5	5					5	5
No Visible Lesions	5	5					2	5
Discoloration; dark	0	0					3	0
SITE, ADMINISTRATION, 3								
Submitted	5	5					5	5
No Visible Lesions	5	3					3	4
Discoloration; dark	0	2					2	1

Table 11

[REDACTED] Summary of Necropsy Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5			5	5		
ARTERY, AORTA								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BODY CAVITY, NASAL								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE, FEMUR								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE, STERNUM								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE MARROW, FEMUR								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE MARROW, STERNUM								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BONE MARROW SMEAR								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
BRAIN								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
CERVIX								
Submitted	-	-			5	5		
No Visible Lesions	-	-			5	5		
EPIDIDYMIS								
Submitted	5	5			-	-		
No Visible Lesions	5	5			-	-		
ESOPHAGUS								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
EYE								
Submitted	5	5			5	5		

Table 11

[REDACTED] Summary of Necropsy Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
EYE (Continued...)								
No Visible Lesions	5	5					5	5
GALLBLADDER								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GALT								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, ADRENAL								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, LACRIMAL								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	4
Discoloration; pale	0	0					0	1
GLAND, MAMMARY								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, PARATHYROID								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, PITUITARY								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, PROSTATE								
Submitted	5	5					-	-
No Visible Lesions	5	5					-	-
GLAND, SALIVARY, MANDIBULAR								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, SEMINAL VESICLE								
Submitted	5	5					-	-
No Visible Lesions	5	5					-	-
GLAND, THYROID								
Submitted	5	5					5	5

Table 11

[REDACTED] Summary of Necropsy Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
GLAND, THYROID (Continued...)								
No Visible Lesions	5	5					5	5
HEART								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
KIDNEY								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, APPENDIX								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, CECUM								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, COLON								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, RECTUM								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LARYNX								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LIVER								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
LUNG								
Submitted	5	5					5	5
No Visible Lesions	3	4					2	2
Focus; dark	0	0					1	0
Discoloration; dark	1	0					2	0
Discoloration; mottled	1	1					0	2
Abnormal consistency	0	1					1	2
LYMPH NODE, ILIAC								
Submitted	5	5					5	5

Table 11

[REDACTED] Summary of Necropsy Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5			5	5		
LYMPH NODE, ILIAC (Continued...)								
No Visible Lesions	5	4			4	4		
Discoloration; dark	0	1			1	1		
LYMPH NODE, MANDIBULAR								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
LYMPH NODE, MESENTERIC								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	4		
Discoloration; dark	0	0			0	1		
MUSCLE, DIAPHRAGM								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
MUSCLE, SKELETAL								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
NERVE, OPTIC								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
NERVE, SCIATIC								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
OVARY								
Submitted	-	-			5	5		
No Visible Lesions	-	-			4	5		
Enlargement	-	-			1	0		
OVIDUCT								
Submitted	-	-			5	5		
No Visible Lesions	-	-			3	5		
Cyst; clear	-	-			2	0		
PANCREAS								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
SKIN								
Submitted	5	5			5	5		

Table 11

[REDACTED] Summary of Necropsy Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5			5	5		
SKIN (Continued...)								
No Visible Lesions	5	5			5	5		
SMALL INTESTINE, DUODENUM								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
SMALL INTESTINE, ILEUM								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
SMALL INTESTINE, JEJUNUM								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
SMALL INTESTINE, SACculus ROTUNDUS								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
SPINAL CORD								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
SPLEEN								
Submitted	5	5			5	5		
No Visible Lesions	5	5			4	5		
Abnormal appearance	0	0			1	0		
STOMACH								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		
TESTIS								
Submitted	5	5			-	-		
No Visible Lesions	5	5			-	-		
THYMUS								
Submitted	5	5			5	5		
No Visible Lesions	5	5			4	5		
Discoloration; mottled	0	0			1	0		
TONGUE								
Submitted	5	5			5	5		
No Visible Lesions	5	5			5	5		

Table 11

[REDACTED] Summary of Necropsy Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
TRACHEA								
Submitted	5	5					5	5
No Visible Lesions	5	5					4	4
Fluid accumulation; pale	0	0					1	1
URETER								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
URINARY BLADDER								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
UTERUS								
Submitted	-	-					5	5
No Visible Lesions	-	-					4	5
Abnormal appearance	-	-					1	0
VAGINA								
Submitted	-	-					5	5
No Visible Lesions	-	-					5	5
SITE, ADMINISTRATION, 1								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
SITE, ADMINISTRATION, 2								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5
SITE, ADMINISTRATION, 3								
Submitted	5	5					5	5
No Visible Lesions	5	5					5	5

Table 12

[REDACTED] Summary of Histopathological Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
ARTERY, AORTA								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
BONE, FEMUR								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
BONE, STERNUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
BONE MARROW								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
BRAIN								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
CERVIX								
Examined	-	-					5	5
No Visible Lesions	-	-					5	5
EPIDIDYMIS								
Examined	5	5					-	-
No Visible Lesions	5	5					-	-
ESOPHAGUS								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
EYE								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
GALLBLADDER								
Examined	3	5					5	5
No Visible Lesions	3	5					5	5
Not Examined: Postmortem Change Precludes Evaluation.	2	0					0	0
GALT								
Examined	4	4					5	5
No Visible Lesions	4	4					5	5

Table 12

[REDACTED] Summary of Histopathological Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
GALT (Continued...)								
Not Examined: Insufficient Tissue Available For Evaluation.	1	1					0	0
GLAND, ADRENAL								
Examined	5	5					5	5
No Visible Lesions	5	5					4	5
Hypertrophy; cortex	0	0					1	0
.... minimal	0	0					1	0
GLAND, LACRIMAL								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, MAMMARY								
Examined	0	0					5	5
No Visible Lesions	-	-					5	5
GLAND, PARATHYROID								
Examined	3	2					4	4
No Visible Lesions	3	2					4	4
Not Examined: Not Present In Section.	2	3					1	1
GLAND, PITUITARY								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, PROSTATE								
Examined	5	5					-	-
No Visible Lesions	4	4					-	-
Immaturity	1	1					-	-
GLAND, SALIVARY, MANDIBULAR								
Examined	5	5					5	5
No Visible Lesions	5	4					5	5
Congestion; agonal	0	1					0	0
.... mild	0	1					0	0
GLAND, SEMINAL VESICLE								
Examined	5	5					-	-
No Visible Lesions	5	5					-	-
GLAND, THYROID								
Examined	5	5					5	5

Table 12

[REDACTED] Summary of Histopathological Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
GLAND, THYROID (Continued...)								
No Visible Lesions	5	5					5	5
HEART								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
KIDNEY								
Examined	5	5					5	5
No Visible Lesions	4	3					4	5
Mineralization; cortical	1	2					1	0
.... minimal	1	2					1	0
Basophilia; cortical	1	1					0	0
.... minimal	1	1					0	0
Infiltration, mononuclear cell; cortical	0	1					0	0
.... minimal	0	1					0	0
LARGE INTESTINE, APPENDIX								
Examined	5	5					5	5
No Visible Lesions	4	5					5	5
Abscess	1	0					0	0
.... minimal	1	0					0	0
LARGE INTESTINE, CECUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, COLON								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, RECTUM								
Examined	5	5					5	5
No Visible Lesions	5	5					4	5
Infiltration, heterophilic; in adjacent tissue	0	0					1	0
.... minimal	0	0					1	0
LARYNX								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5

Table 12

[REDACTED] Summary of Histopathological Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
LIVER								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
LUNG								
Examined	5	5					5	5
No Visible Lesions	0	2					3	1
Congestion; agonal	5	3					2	4
.... mild	1	1					0	3
.... moderate	3	1					1	1
.... marked	1	1					1	0
Cyst; alveolar	0	0					1	0
.... moderate	0	0					1	0
LYMPH NODE, ILIAC								
Examined	5	5					5	5
No Visible Lesions	5	0					3	0
Erythrocytosis; sinusoid	0	0					2	1
.... mild	0	0					0	1
.... moderate	0	0					2	0
Increased cellularity; lymphoid, germinal center	0	5					0	5
.... mild	0	5					0	5
Increased cellularity; lymphoid, generalised	0	4					0	3
.... mild	0	2					0	1
.... moderate	0	2					0	2
LYMPH NODE, MANDIBULAR								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
LYMPH NODE, MESENTERIC								
Examined	5	4					5	5
No Visible Lesions	5	4					4	4
Not Examined: Insufficient Tissue Available For Evaluation.	0	1					0	0
Decreased cellularity; lymphoid	0	0					1	1
.... mild	0	0					1	1

Table 12

[REDACTED] Summary of Histopathological Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
MUSCLE, DIAPHRAGM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
MUSCLE, SKELETAL								
Examined	5	5					5	5
No Visible Lesions	5	5					5	4
Infiltration, mononuclear cell	0	0					0	1
.... minimal	0	0					0	1
NERVE, OPTIC								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
NERVE, SCIATIC								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
OVARY								
Examined	-	-					5	5
No Visible Lesions	-	-					5	5
OVIDUCT								
Examined	-	-					5	5
No Visible Lesions	-	-					4	5
Cyst	-	-					1	0
.... mild	-	-					1	0
PANCREAS								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SKIN								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, DUODENUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, ILEUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5

Table 12

[REDACTED] Summary of Histopathological Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5			5	5		
SMALL INTESTINE, JEJUNUM								
Examined	5	5			5	5		
No Visible Lesions	5	5			5	5		
SMALL INTESTINE, SACculus ROTUNDUS								
Examined	5	5			5	5		
No Visible Lesions	5	5			5	5		
SPINAL CORD								
Examined	5	5			5	5		
No Visible Lesions	5	5			5	5		
SPLEEN								
Examined	5	5			5	5		
No Visible Lesions	5	0			5	0		
Increased cellularity; lymphoid, germinal center	0	5			0	5		
.... minimal	0	1			0	1		
.... mild	0	4			0	4		
Macrophage aggregation	0	0			0	1		
.... minimal	0	0			0	1		
STOMACH								
Examined	5	5			5	5		
No Visible Lesions	5	5			5	5		
TESTIS								
Examined	5	5			-	-		
No Visible Lesions	4	2			-	-		
Atrophy; seminiferous tubule	1	3			-	-		
.... minimal	1	1			-	-		
.... mild	0	2			-	-		
THYMUS								
Examined	5	5			5	5		
No Visible Lesions	5	5			4	4		
Atrophy; cortical	0	0			1	1		
.... minimal	0	0			1	1		
TONGUE								
Examined	5	5			5	5		

Table 12

[REDACTED] Summary of Histopathological Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
TONGUE (Continued...)								
No Visible Lesions	5	5					5	5
TRACHEA								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
URETER								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
URINARY BLADDER								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
UTERUS								
Examined	-	-					5	5
No Visible Lesions	-	-					5	5
VAGINA								
Examined	-	-					5	5
No Visible Lesions	-	-					4	5
Infiltration, mixed cell; in adjacent tissue	-	-					1	0
.... mild	-	-					1	0
SITE, ADMINISTRATION, 1								
Examined	5	5					5	5
No Visible Lesions	5	1					4	1
Infiltration, mononuclear cell; fascia	0	3					0	0
.... minimal	0	3					0	0
Infiltration, mononuclear cell; striated muscle	0	0					1	3
.... minimal	0	0					1	2
.... mild	0	0					0	1
Hemorrhage; subcutaneous tissue	0	1					0	1
.... minimal	0	1					0	1
Infiltration, heterophilic; subcutaneous tissue	0	0					0	1
.... minimal	0	0					0	1

Table 12

[REDACTED] Summary of Histopathological Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
SITE, ADMINISTRATION, 2								
Examined	5	5					5	5
No Visible Lesions	5	5					3	4
Hemorrhage; subcutaneous tissue	0	0					2	0
.... minimal	0	0					2	0
Pigmented macrophage; subcutaneous tissue	0	0					1	0
.... minimal	0	0					1	0
Degeneration/regeneration; striated muscle	0	0					0	1
.... minimal	0	0					0	1
Infiltration, mononuclear cell; striated muscle	0	0					0	1
.... mild	0	0					0	1
SITE, ADMINISTRATION, 3								
Examined	5	5					5	5
No Visible Lesions	4	0					1	0
Ulceration; epidermis	0	0					2	0
.... minimal	0	0					1	0
.... mild	0	0					1	0
Inflammation, mixed cell; fascia	0	0					0	1
.... mild	0	0					0	1
Inflammation, mixed cell; striated muscle	0	3					0	1
.... moderate	0	2					0	1
.... mild	0	1					0	0
Inflammation, mixed cell; subcutaneous tissue	0	1					1	0
.... mild	0	1					1	0
Hemorrhage; fascia	0	2					0	0
.... mild	0	2					0	0
Hemorrhage; striated muscle	0	0					0	1
.... moderate	0	0					0	1
Hemorrhage; subcutaneous tissue	0	1					2	1
.... mild	0	1					2	1

Table 12

[REDACTED] Summary of Histopathological Findings Main

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5			5	5		
SITE, ADMINISTRATION, 3 (Continued...)								
Infiltration, mixed cell; fascia	0	1			0	2		
.... minimal	0	1			0	1		
.... mild	0	0			0	1		
Infiltration, mixed cell; striated muscle	0	0			0	1		
.... minimal	0	0			0	1		
Infiltration, mixed cell; subcutaneous tissue	0	2			0	1		
.... minimal	0	2			0	0		
.... mild	0	0			0	1		
Infiltration, mononuclear cell; striated muscle	0	0			0	2		
.... minimal	0	0			0	2		
Necrosis; striated muscle	0	3			0	1		
.... moderate	0	2			0	1		
.... mild	0	1			0	0		
Inflammation, mononuclear cell; striated muscle	1	0			1	0		
.... minimal	1	0			1	0		
Cellular debris; epidermis	0	1			0	0		
.... minimal	0	1			0	0		

Table 12

[REDACTED] Summary of Histopathological Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
ARTERY, AORTA								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
BONE, FEMUR								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
BONE, STERNUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
BONE MARROW								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
BRAIN								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
CERVIX								
Examined	-	-					5	5
No Visible Lesions	-	-					5	5
EPIDIDYMIS								
Examined	5	5					-	-
No Visible Lesions	5	5					-	-
ESOPHAGUS								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
EYE								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
GALLBLADDER								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
GALT								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, ADRENAL								
Examined	5	5					5	5

Table 12

[REDACTED] Summary of Histopathological Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
GLAND, ADRENAL (Continued...)								
No Visible Lesions	5	5					5	5
GLAND, LACRIMAL								
Examined	1	4					1	4
No Visible Lesions	1	4					1	4
Not Examined: Insufficient Tissue Available For Evaluation.	4	1					4	1
GLAND, MAMMARY								
Examined	0	0					5	5
No Visible Lesions	-	-					5	5
GLAND, PARATHYROID								
Examined	3	4					2	3
No Visible Lesions	3	4					2	3
Not Examined: Not Present In Section.	2	1					3	2
GLAND, PITUITARY								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, PROSTATE								
Examined	5	5					-	-
No Visible Lesions	5	5					-	-
GLAND, SALIVARY, MANDIBULAR								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
GLAND, SEMINAL VESICLE								
Examined	5	5					-	-
No Visible Lesions	5	5					-	-
GLAND, THYROID								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
HEART								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
KIDNEY								
Examined	5	5					5	5
No Visible Lesions	3	3					2	5

Table 12

[REDACTED] Summary of Histopathological Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10^11		0		1x10^11	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
KIDNEY (Continued...)								
Mineralization; cortical	1	1					2	0
.... minimal	1	1					2	0
Basophilia; cortical	2	2					2	0
.... minimal	2	1					2	0
.... mild	0	1					0	0
LARGE INTESTINE, APPENDIX								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, CECUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
LARGE INTESTINE, COLON								
Examined	4	5					5	5
No Visible Lesions	4	5					5	5
Not Examined: Not Present In Section.	1	0					0	0
LARGE INTESTINE, RECTUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
LARYNX								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
LIVER								
Examined	5	5					5	5
No Visible Lesions	5	5					4	5
Fatty change; hepatocellular	0	0					1	0
.... minimal	0	0					1	0
LUNG								
Examined	5	5					5	5
No Visible Lesions	2	4					3	2
Congestion; agonal	3	1					2	3
.... mild	2	0					0	0
.... moderate	1	1					2	3
LYMPH NODE, ILIAC								
Examined	5	5					5	4

Table 12

Summary of Histopathological Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male			Female	
	0 Group 1		1x10^11 VP Group 2	0 Group 1	
	Number of Animals:	5	5	5	5
LYMPH NODE, ILIAC (Continued...)					
No Visible Lesions	5	1		4	2
Not Examined: Insufficient Tissue Available For Evaluation.	0	0		0	1
Erythrocytosis; sinusoid	0	1		1	1
.... minimal	0	1		1	1
Increased cellularity; lymphoid, germinal center	0	4		0	2
.... minimal	0	2		0	0
.... mild	0	2		0	2
LYMPH NODE, MANDIBULAR					
Examined	5	5		5	5
No Visible Lesions	5	5		5	5
LYMPH NODE, MESENTERIC					
Examined	5	4		5	5
No Visible Lesions	5	4		5	5
Not Examined: Insufficient Tissue Available For Evaluation.	0	1		0	0
MUSCLE, DIAPHRAGM					
Examined	5	5		4	5
No Visible Lesions	5	5		4	5
Not Examined: Lost During Necropsy.	0	0		1	0
MUSCLE, SKELETAL					
Examined	5	5		5	5
No Visible Lesions	5	5		5	5
NERVE, OPTIC					
Examined	5	5		5	5
No Visible Lesions	5	5		5	5
NERVE, SCIATIC					
Examined	5	5		5	5
No Visible Lesions	5	5		5	5
OVARY					
Examined	-	-		5	5
No Visible Lesions	-	-		5	5
OVIDUCT					

Table 12

[REDACTED] Summary of Histopathological Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
OVIDUCT (Continued...)								
Examined	-	-					5	5
No Visible Lesions	-	-					4	5
Cyst	-	-					1	0
.... moderate	-	-					1	0
PANCREAS								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SKIN								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, DUODENUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, ILEUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, JEJUNUM								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SMALL INTESTINE, SACculus ROTUNDUS								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SPINAL CORD								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
SPLEEN								
Examined	5	5					5	5
No Visible Lesions	5	1					5	1
Increased cellularity; lymphoid, germinal center	0	4					0	4
.... minimal	0	3					0	3
.... mild	0	1					0	1

Table 12

[REDACTED] Summary of Histopathological Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5					5	5
STOMACH								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
TESTIS								
Examined	5	5					-	-
No Visible Lesions	4	3					-	-
Atrophy; seminiferous tubule	1	2					-	-
.... mild	1	2					-	-
THYMUS								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
TONGUE								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
TRACHEA								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
URETER								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
URINARY BLADDER								
Examined	5	5					5	5
No Visible Lesions	5	5					5	5
UTERUS								
Examined	-	-					5	5
No Visible Lesions	-	-					4	5
Congenital anomaly	-	-					1	0
VAGINA								
Examined	-	-					5	5
No Visible Lesions	-	-					5	5
SITE, ADMINISTRATION, 1								
Examined	5	5					5	5
No Visible Lesions	5	3					5	5
Infiltration, mononuclear cell; striated muscle	0	2					0	0

Table 12

[REDACTED] Summary of Histopathological Findings Recovery

Removal Reason: RECOVERY EUTHANASIA	Male				Female			
	0		1x10 ¹¹		0		1x10 ¹¹	
	Group 1	VP	Group 2	Group 1	VP	Group 2	Group 1	VP
Number of Animals:	5	5			5	5		
SITE, ADMINISTRATION, 1 (Continued...)								
.... minimal	0	2			0	0		
SITE, ADMINISTRATION, 2								
Examined	5	5			5	5		
No Visible Lesions	5	5			5	4		
Degeneration/regeneration; striated muscle	0	0			0	1		
.... minimal	0	0			0	1		
Infiltration, mononuclear cell; striated muscle	0	0			0	1		
.... mild	0	0			0	1		
SITE, ADMINISTRATION, 3								
Examined	5	5			5	5		
No Visible Lesions	5	4			5	5		
Infiltration, mononuclear cell; striated muscle	0	1			0	0		
.... minimal	0	1			0	0		

Appendix 1



FINAL PROTOCOL

Test Facility Study No. [REDACTED]

Sponsor Reference No. [REDACTED]

**An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance
Study [REDACTED] Vaccine in New
Zealand White Rabbits with a 3 Week Recovery Period**

Study Status: Good Laboratory Practice (GLP)

SPONSOR:

[REDACTED]

TEST FACILITY:

Charles River Laboratories [REDACTED]

[REDACTED]

Appendix 1

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Appendix 1

1. OBJECTIVE(S)

The test item under investigation in this study is [REDACTED]

[REDACTED]
[REDACTED] The objectives of this study are to determine the potential toxicity and local tolerance of [REDACTED] when given by intramuscular injection on 3 occasions (Days 1, 15 and 29) to rabbits, and to evaluate the potential reversibility of any findings during a 3-week recovery period.

1.1. Study Classification

Study Category:	Toxicology
Study Type:	Local Tolerance; Repeat Dose Toxicity
Study Design:	Parallel
Primary Treatment CAS Registry Number:	Not Available
Primary Treatment Unique Ingredient ID:	Not Available
Class of Compound:	Vaccine

2. PROPOSED STUDY SCHEDULE

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

Experimental Start Date:	27 Sep 2017 (First date of study-specific data collection)
Experimental Completion Date:	Jan 2018 (Last date data are collected from the study)
Animal Arrival/Transfer:	19 Sep 2017
Initiation of Dosing:	04 Oct 2017
Completion of In-life:	Main Study - 03 Nov 2017 Recovery Study – 24 Nov 2017 (Last dates of necropsy)
In-life data available (main study animals):	13 Nov 2017 (including clinical pathology data) (Expected ship date from RS to Study Director)
Immunology Draft Report:	To be added by protocol amendment (Expected ship date from RS to Study Director)
Histopathology Draft Report:	18 Dec 2017 (Expected ship date from IS to Study Director)
Pathology Peer Review:	To be added by protocol amendment

Appendix 1

Histopathology Final Report:	To be added by protocol amendment (Expected ship date from IS to Study Director)
Data Review Meeting:	29 Jan 2018
Draft Tox Report for Sponsor Review:	09 Feb 2018
Sponsor agreed Final Draft Report:	26 Feb 2018
Final Report:	09 Mar 2018 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99rev1.
- WHO Guideline on nonclinical evaluation of vaccines, Nov 2003 and WHO Guideline on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines Oct 2013.
- OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring. Number 13. *Consensus Document of the Working Group on Good Laboratory Practice. The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies*.

4. REGULATORY COMPLIANCE

This study with the exception of the Immunogenicity assessment will be performed in accordance with the OECD Principles of Good Laboratory Practice as incorporated into the United Kingdom Statutory Instrument for GLP and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA) and Japan (MHLW, MAFF and METI), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Immunogenicity analysis (See Section 5.2)

5. QUALITY ASSURANCE

5.1. Test Facility

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

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 1

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

[REDACTED]

5.2. Sponsor

The following study phase will be conducted according to the best scientific principles and the data and report will be subjected to Test Site QA procedures, but is not intended to be in full GLP compliance:

Immunogenicity measurement at [REDACTED]
[REDACTED]

6. SPONSOR

Sponsor Representative

[REDACTED]
[REDACTED]
[REDACTED]

Alternative Sponsor Contact

[REDACTED]
[REDACTED]

Pathology Peer Review

[REDACTED]
[REDACTED]
[REDACTED]

7. RESPONSIBLE PERSONNEL

Study Director

[REDACTED]
[REDACTED]

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

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Appendix 1

Management Contact



Individual Scientists (IS) at the Test Facility

Pathology To be added by amendment

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

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

Responsible Scientist (RS) at Sponsor

Immunology [REDACTED]



The RS's reference number for this phase of the study will be added by amendment.

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

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

Appendix 1

8. TEST AND CONTROL ITEMS

8.1. Test Item(s)

Identification: [REDACTED]

Batch (Lot) Number: [REDACTED]

Expiration Date: 12 Jan 2018

Physical Description: Clear to slightly opalescent, colourless to yellowish solution and essentially free of visible particulate matter

Concentration: [REDACTED] mL

Purity: 100 %

Storage Conditions: Kept frozen in a freezer set to maintain -80°C, protected from light.

8.2. Control Item

Identification: [REDACTED]

Supplier: Test Facility

Details of the batch(es) used will be recorded in the study raw data.

8.3. Test Item Characterisation

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity, composition, and stability for the test item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report.

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

8.4. Analysis of Test Item

Information to support the stability of each lot of the bulk test item will be provided by the Sponsor.

8.5. Reserve Samples

For each batch (lot) of test item, a reserve sample (1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

8.6. Test and Control Item Inventory and Disposition

Records of the receipt, distribution, and storage of test and control items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied test item will be returned to the Sponsor after completion of the scheduled programme of work.

Appendix 1

9. SAFETY

Safety instructions for this study are provided on the Sponsor supplied safety data sheet. COSHH assessment and classification will be carried out at the Test Facility on a Chemical Classification Spreadsheet.

10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Test Item

[REDACTED] vaccine vials will be removed from the freezer on the day of dosing and allowed to reach room temperature. Details on handling and preparation of the test item are provided in Attachment 1.

The product from the compounded vial must be dosed within 4 hours after start of thawing of the vials.

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

10.2. Preparation of Control Item

The control item, sodium chloride solution, will be administered as received. For each day of dosing an adequate volume will be dispensed to the animal unit for administration to Group 1 control animals.

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

10.3. Sample Collection and Analysis

The test and control items will be used as received; therefore, samples for dose formulation analysis will not be collected by the Test Facility.

11. TEST SYSTEM

Species:	Rabbit
Strain:	New Zealand White
Source:	[REDACTED]
Number of Males Ordered:	20
Number of Females Ordered:	20
Target Age at the Initiation of Dosing:	At least 12 weeks, acceptable up to 16 weeks
Target Weight at the Initiation of Dosing:	<i>ca</i> 2.5-4 kg
The actual age and weight of animals received will be listed in the Final Report.	

Appendix 1

11.1. Justification of Test System and Number of Animals

The rabbit was chosen as the animal model for this study as it is a species accepted by regulatory agencies for toxicity testing.

The New Zealand White (NZW) rabbit is selected for this study because it is a widely used species to assess preclinical toxicity and local tolerance of vaccine candidates, for which sufficient historical control data exist. Rabbits have sufficient muscle mass to receive a full human dose (of up to 1.0 mL) via the intramuscular route. In addition, NZW rabbits have been used in the past to assess preclinical safety of [REDACTED] vaccine candidates. Such studies showed that these vaccines induced an immune response following intramuscular injection in NZW rabbits.

The total number of animals to be used in this study is considered to be the minimum required to properly characterise 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.

11.2. Animal Identification

At study assignment, each animal will be identified using a subcutaneously implanted electronic cylindrical, 'glass-sealed' TROVAN microchip.

11.3. Environmental Acclimation

The animals will be allowed to acclimate to the Test Facility rabbit toxicology accommodation for a period of up to 3 weeks before the commencement of dosing.

11.4. Selection, Assignment and Disposition of Animals

Animals will be removed in random order from their transport boxes and allocated to dose group on arrival by placing them in pens. Cages/pens will be labelled with the study number, animal number and group number.

Control animals will be housed on a separate rack.

Animals suspected of being diseased will be culled from the study. If significant numbers of animals are unsuitable, the entire batch will be rejected by the Study Director and a new batch obtained.

During the week before the commencement of dosing, the animals will be approved for entry into the experiment on the basis of satisfactory clinical observation records and body weight profile. At the start of pretreatment, female body weight group means will be checked to ensure that they are similar between groups.

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

Appendix 1

12. HUSBANDRY

12.1. Housing

Males will be housed individually in appropriately sized stainless steel cages with a 'Noryl' dual level interior and perforated floor. Beneath each cage will be a suspended tray containing absorbent paper.

Females (where behaviour allows) will be socially housed in groups of at least 10 animals (unless reduced by mortality) in pens with adequate floor space. Bedding will be placed on each pen floor. If behaviour does not permit social housing, animals will be housed individually.

Bedding material will be provided with a certificate of analysis for significant contaminants. An analytical certificate for each batch of bedding used will be retained at the Test Facility.

There are no known contaminants in the bedding that would interfere with the objectives of the study.

12.2. Environmental Conditions

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

Temperature: 16 - 20°C

Humidity: 40 - 70%

Ventilation: A minimum of 10 air changes per hour

Light Cycle: 12 hours light and 12 hours dark (except when interrupted by study procedures/activities).

There will be automatic control of temperature and humidity which will be continuously monitored and recorded. Information on actual temperature and humidity ranges versus target ranges will be presented in the study report.

There will be automatic control of light cycle.

12.3. Food

Envigo Diet will be available to the animals *ad libitum*. Each animal will also be offered a supplement of hay at least 3 times per week.

The diet will be supplied with a batch analysis for major nutritive components and significant contaminants and will be used within the manufacturers' designated shelf-life. The hay is not analysed.

An analytical certificate for each batch of diet used will be retained at the Test Facility.

There are no known contaminants in the feed that would interfere with the objectives of the study.

12.4. Water

The animals will have access to water *ad libitum* from the public supply.

Appendix 1

The water used by Charles River [REDACTED] is analysed at regular intervals for dissolved materials, heavy metals, pesticide residues, pH, nitrates and nitrites. Microbiological screening is also conducted. An analytical certificate for each analysis will be retained at the Test Facility.

There are no known contaminants in the water that would interfere with the objectives of the study.

12.5. Animal Enrichment

Females will be socially housed for psychological/environmental enrichment and all animals will be provided with items such as a device for hiding in and an object for chewing, except when interrupted by study procedures/activities. Males will be allowed a period of exercise (generally weekly) in a separate pen. Details will be documented.

Objects for chewing and devices for hiding in will be provided with a certificate of analysis for significant contaminants. An analytical certificate for each batch of chewing objects and hiding devices used will be retained at the Test Facility.

12.6. Veterinary Care

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

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

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13. EXPERIMENTAL DESIGN

Experimental Design

Group No.	Treatment	Dosage	Dose Volume	Animal Numbers			
				Main Study		Recovery Study	
				Males	Females	Males	Females
1	Control	0	1 mL	1001-1005	1501-1505	1006-1010	1506-1510
2	[REDACTED]	[REDACTED]	1 mL	2001-2005	2501-2505	2006-2010	2506-2510

VP =Virus particles

Dose Sites

Group No.	Treatment	Dosing days (dosing site)		
		1	15	29
1	Control	Site 1	Site 2	Site 3
2	[REDACTED]	Site 1	Site 2	Site 3

Site 1: Day 1= right thigh (posterior)

Site 2: Day 15 = left thigh

Site 3: Day 29 = right thigh (anterior)

Dose sites will be discrete and adequately spaced from each other.

13.1. Administration of Test and Control Items

The first day of dosing for each individual animal will be designated as Day 1. The dosing volume will be 1 mL per injection.

The injection sites will be clipped free from fur before injection.

The test and control items will be administered to the appropriate animals by intramuscular injection on Days 1, 15 and 29 where appropriate. The doses will be given using a graduated polycarbonate syringe (BD Syringe) and needle (BD 25G Microlance). The injection of the test item will occur within 4 h of removal of test item from the freezer. The injection site will be marked at each administration, and this marking will remain throughout the study. The last injection site (site 3) will be marked by a X to ease collection at necropsy. Further clipping and marking will occur as necessary to maintain visibility of each site.

13.2. Justification of Route and Dosage Levels

The intramuscular route is the intended route of administration of the [REDACTED] vaccine in humans.

The dose level for [REDACTED] is selected on the basis of available data from previous animal studies and is equivalent to the maximum anticipated dosage that will be used in human clinical studies (i.e. a full human dose will be administered to the animals).

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all animals.

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14.1. Mortality/Moribundity Checks

- Frequency: Twice daily, once at the start and once towards the end of the working day throughout the study.
- Procedure: Animals will be observed for general health/mortality and moribundity. Animals will not be removed from the cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

- Frequency: Weekly, beginning Week -1, and to include each dosing day. Animals will be removed from the cage for examination. The animals will be examined for general appearance including movement and behaviour pattern. Other examinations will include the eyes, ears and external genitalia for discharge, redness or other abnormalities; the skin, coat and feet for the presence of abnormalities or injuries; and an observation for any abnormalities of respiration.

- Procedure: Animals removed from the cage for examination.

14.2.2. Postdose Observations

- Frequency: At least twice on each day of dosing (Days 1, 15 and 29), including before dose administration and a target of 1 h and 6 h after injection. On non-dosing days, signs will be recorded once.
- Procedure: All the animals will be examined for reaction to treatment. The onset, intensity and duration of these signs will be recorded (if appropriate), particular attention being paid to the animals during and for the first hour after dosing.

14.3. Dermal Scoring

- Frequency: Injection sites will be evaluated before each dose, 6 h (\pm 30 min) after the injection, 24 h, 48 h, 72 h (all \pm 1 h) after dosing and weekly thereafter. In case injection site effects are observed, the daily observations will be continued until scores returned to 0.
- Injection sites will be evaluated prior to necropsy.
- Procedure: Skin will be assessed for erythema and eschar formation, oedema formation and any other reaction to treatment.

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Erythema and Eschar Formation	Grade
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Oedema Formation	Grade
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

14.4. Body Weights

- Frequency: Once pretreatment, day of dosing (before each dose), daily for 3 days post dose, twice weekly at other times and on each day of necropsy.
- Procedure: Animals will be individually weighed. Weight will be recorded in grams.

14.5. Food Consumption (males only)

- Frequency: Once pretreatment, day of dose, daily for 3 days post dose, twice weekly at other times and on each day of necropsy.
- Procedure: Food consumption will be quantitatively measured.
Female food consumption will be assessed by visual inspection of the food bowls. These assessments will be recorded.

14.6. Ophthalmic Examinations

- Frequency: Pretreatment – All animals once
Dosing Period – All animals after end of dosing before main study necropsy.
Recovery Period - All recovery animals towards the end of the of recovery period.
- Procedure: The eyes will be examined using an indirect ophthalmoscope after the application of a mydriatic agent (1% Tropicamide, Mydriacyl®). The anterior, lenticular and fundic areas will be examined.
The eyes will also be examined with a slit lamp ophthalmoscope after the application of fluorescein to the eyes for epithelial staining. Anterior and medium segments of the

Appendix 1

eye with conjunctiva, cornea, anterior chamber, iris, lens and vitreous body will be examined.

14.7. Body Temperature

Frequency:

Pretreatment – All animals once

Dosing Period – Day of dose (before each dose), $6 \pm 0.5\text{h}$ and $24 \pm 1\text{h}$ after each dose. If body temperature is $\geq \pm 1^\circ\text{C}$ from mean pretreatment value that is the pretreatment and predose Day 1 value, additional measurements will be conducted daily until body temperature returns to the mean value recorded from both pretreatment values. A body temperature will also be recorded on each day of necropsy.

Procedure:

The body temperature of each animal will be recorded using a digital thermometer in the rectum.

15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

Blood will be collected from an auricular artery. Additional blood samples may be obtained (e.g. due to clotting of non-serum samples) if permissible sampling frequency and blood volume are not exceeded. After collection, samples will be transferred to the appropriate laboratory for processing.

Animals will not be deprived of food prior to blood sampling. Samples will be collected according to the following table.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Haematology	Coagulation	Clinical Chemistry	C-Reactive Protein
All animals	Pretreatment	X	X	X	X
All animals	Day 2 ^a	-	-	-	X
All animals	Day 3	X	X	X	-
All animals	Day 7	-	-	-	X
All animals	Day 30	-	-	-	X
Main animals	Day 31 (necropsy)	X	X	X	-
Recovery animals	Day 52 (necropsy)	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X	X

X = sample to be collected; - = not applicable; ^a = 24 h ($\pm 2\text{ h}$)

Day 1 = first dose administered.

15.1.2. Haematology

Target Volume: 0.5 mL

Appendix 1Anticoagulant: K₂EDTA

Haematology Parameters

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

A blood smear will be prepared from each haematology sample. Blood smears will be labelled, stained, and stored. Individual blood smears may be examined to confirm certain analyser results, as required by SOP.

If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a protocol amendment.

15.1.3. Coagulation

Target Volume: 0.9 mL

Anticoagulant: 3.8% (w/v) trisodium citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 1.5 mL

Anticoagulant: Lithium Heparin

Processing: To plasma

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Clinical Chemistry Parameters

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine kinase	Glucose
Total bilirubin ^a	Cholesterol
Urea	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphate	Chloride

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

15.1.5. C-Reactive Protein

Target Volume: 0.6 mL (2 x 0.6 mL at pretreatment*)

Tubes: Plain with gel separator

Anticoagulant: None

* One sample is for method re-establishment.

Serum will be analysed at the Test Facility using ELISA methodology established under [REDACTED].

15.1.6. Bone Marrow Smear Evaluation

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (Section 16.5).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. Immunogenicity Sample Collection, Processing, and Analysis

Blood will be collected from an auricular artery once during pretreatment (all animals), Days 14 and 31 (all animals) and Day 52 (Recovery) and from unscheduled euthanasia (when possible).

Target Volume: 2 mL

Tubes: Plain with gel separator

Anticoagulant: None

Processing: Allow to stand for at least 1 hour before centrifugation to serum (1500 g/10 min /4°C)

2 aliquots of approximately 0.5 mL serum (into clear polypropylene tubes).

Sample Storage: In a freezer set to maintain -20 °C.

Serum shipment To the Responsible Scientist

Shipment conditions: On dry ice, with temperature monitoring.

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Residual samples will be discarded before issue of the final report and after approval of the Study Director.

The presence of [REDACTED] specific antibodies will be determined in serum obtained before first dosing, at Day 14 post dose, at termination (at main and recovery necropsy) and at unscheduled euthanasia (when possible), using an ELISA analytical method, with all details on the procedure being reported in the Responsible Scientist report. This work will not be conducted in full compliance with GLP.

16. TERMINAL PROCEDURES

Terminal procedures are summarised in the following table:

Terminal Procedures for All Animals

Group Number	Number of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology ^a	Histopathology ^a
	M	F		Necropsy	Tissue Collection ^a	Organ Weights ^a		
1	5	5	31	X	X	X	Full Tissue Gross Lesions	Full Tissue Gross Lesions
2	5	5					Full Tissue Gross Lesions	Full Tissue Gross Lesions
1	5	5	52	X	X	X	Full Tissue Gross Lesions	Full Tissue Gross Lesions
2	5	5					Full Tissue Gross Lesions	Full Tissue Gross Lesions
Unscheduled Deaths				X	X	-	Full Tissue Gross Lesions	Full Tissue Gross Lesions

X = procedure to be conducted; - = not applicable

^a See Tissue Collection and Preservation table for listing of tissues and weights.

16.1. Unscheduled Deaths

If an animal dies on study, a necropsy will be conducted and specified tissues will be saved. If necessary, the animal will be refrigerated to minimise autolysis.

Animals may be euthanised for humane reasons as per Test Facility SOPs. The body weight will be recorded and samples for evaluation of clinical pathology parameters and immunology will be obtained if possible as specified in Section 15. These animals will undergo necropsy, and specified tissues will be retained. If necessary, the animal will be refrigerated to minimise autolysis.

16.2. Scheduled Euthanasia

Animals surviving until scheduled euthanasia will have a terminal body weight recorded, and will be euthanised by an intravenous overdose of a barbiturate, followed by exsanguination. When possible, the animals will be euthanised in a rotating order across dose groups such that similar numbers of animals from each group, including controls will be necropsied throughout the day. Animals will not be fasted before their scheduled necropsy.

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16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table will be collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

Tissue Collection and Preservation

Tissue	Weigh	Collect	Microscopic Evaluation	Comment
Administration site	-	X	X	3 sites (see Section 13 for injection sites). Include skin. Identify individually and identify retained. 2 levels per site prepared for histological examination.
Animal identification	-	X	-	-
Artery, aorta	-	X	X	From thoracic segment.
Bone marrow smear	-	X	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanised moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are fixed in Methanol. Both smears will be stained using May-Grunwald-Giemsa as soon as practical after necropsy.
Bone marrow	-	X	X	Collect with bone, femur and sternum.
Bone, femur with articulating surface	-	X	X	Collect distal end to include femorotibial joint.

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Tissue	Weigh	Collect	Microscopic Evaluation	Comment
Bone, sternum	-	X	X	-
Brain	X	X	X	Forebrain, midbrain, cerebellum, and medulla oblongata.
Cervix	-	X	X	Collect with uterus.
Diaphragm	-	X	X	-
Epididymis x 2	X	X	X	-
Eye x 2	-	X	X	Preserve in Davidson's fixative.
Gallbladder	-	X	X	-
Gland, adrenal x 2	X	X	X	-
Gland, lacrimal x 2	-	X	X	-
Gland, mammary	-	X	X	Collect with skin and include nipple. Gland, mammary will be examined in females only.
Gland, parathyroid x 2	-	X	X	Collect with gland, thyroid. Examine only if present in the routine section of thyroid.
Gland, pituitary	X	X	X	-
Gland, prostate	X	X	X	-
Gland, salivary x 2	-	X	X	Mandibular.
Gland, seminal vesicle	-	X	X	-
Gland, thyroid x 2	X	X	X	Weight includes gland, parathyroid.
Gut-associated lymphoid tissue (Peyer's Patches)	-	X	X	Collect with jejunum or ileum.
Heart	X	X	X	-
Kidney x 2	X	X	X	-
Large intestine, appendix	-	X	X	-
Large intestine, caecum	-	X	X	-
Large intestine, colon	-	X	X	-
Large intestine, rectum	-	X	X	-
Larynx	-	X	X	-
Lesions/masses	-	X	X	Include local draining lymph nodes to masses.
Liver	X	X	X	Drain gallbladder before weighing.
Lung	-	X	X	Infuse with 10% neutral buffered formalin
Lymph node, mandibular	-	X	X	-
Lymph node, mesenteric	-	X	X	-
Lymph node, medial iliac x2	X	X	X	Individually identify.
Muscle, skeletal	-	X	X	From thigh.
Nasal cavity	-	X	-	-
Nerve, optic x 2	-	X	X	Preserve in Davidson's fixative. Examine only if present in the routine section of the eye.
Nerve, sciatic x 2	-	X	X	-
Oesophagus	-	X	X	-
Ovary x 2	X	X	X	-
Oviduct x 2	-	X	X	Collect with uterus.
Pancreas	-	X	X	-
Skin	-	X	X	Collect with gland, mammary.
Small intestine, duodenum	-	X	X	-
Small intestine, ileum	-	X	X	-
Small intestine, jejunum	-	X	X	-
Small intestine, sacculus rotundus	-	X	X	-

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Tissue	Weigh	Collect	Microscopic Evaluation	Comment
Spinal cord	-	X	X	Cervical, thoracic and lumbar. Examine one transverse from each area.
Spleen	X	X	X	-
Stomach	-	X	X	Fundus, body and pylorus
Testis x 2	X	X	X	Preserve in Modified Davidson's fixative.
Thymus	X	X	X	-
Tongue	-	X	X	-
Trachea	-	X	X	-
Ureter x 2	-	X	X	-
Urinary bladder	-	X	X	Distend contracted bladders by infusing with 10% neutral buffered formalin.
Uterus	-	X	X	-
Vagina	-	X	X	-

X = procedure to be conducted; - = not applicable.

17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist or a veterinary pathologist with training and experience in laboratory animal pathology.

Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by protocol amendment following discussion with the Study Director and in consultation with the Sponsor.

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

17.3. Pathology Peer Review

A pathology peer review will be performed by the Sponsor according to the Sponsor's standard operating procedures. The peer review memorandum and any related correspondence will be provided to the Test Facility. The signed peer review form will be included in the final report.

18. COMPUTERISED SYSTEMS

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

Data for parameters not required by protocol, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are

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generated by the program but are not required by protocol and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

Critical Computerised Systems

System Name	Description of Data Collected and/or Analysed
Dispense 8	Test item receipt, accountability and/or formulation activities.
Provantis 8	Applicable In-life, clinical pathology and postmortem
In-house reporting software Nevis (using SAS)	Applicable In-life, clinical pathology and postmortem

19. CONSTRUCTED VARIABLES

Body Weight Gains:	calculated between appropriate scheduled intervals
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

20. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Food Consumption (males only)	X
Body Temperature	X
Haematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Organ Weights	X
Body Weight Change	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparison will be made:

Group 2 vs. Group 1

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20.1. Parametric/Non-Parametric

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

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

21. AMENDMENTS AND DEVIATIONS

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

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

22. RETENTION OF RECORDS, SAMPLES AND SPECIMENS

All study-specific raw data, electronic data, documentation, protocol, protocol amendments, retained samples and specimens, and interim (if applicable) and final reports generated by Charles River from this study will be transferred to a Charles River archive. Two years after issue of the final report, the Sponsor will be contacted to determine the disposition of materials associated with the study. The original signed copy of the final report will be archived indefinitely at the Test Facility.

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

- Protocol, protocol amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Test and control item receipt, identification and preparation
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Immunology sample collection
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

Data generated at the Sponsor-designated Test Site will be archived at the Test Site for the period stated in the phase report.

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23. REPORTING

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

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

A tabulated data summary following the appropriate format as outlined in the ICH Harmonised Tripartite Guideline, *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety – M4S (R2), Nonclinical Overview and Nonclinical Summaries of Module 2, Organisation of Module 4* will be included within the study report, and also provided as a separate Microsoft Word document.

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

24. ANIMAL WELFARE

The UK Home Office controls scientific procedures on animals in the UK and does so by the issue of licences under the Animals (Scientific Procedures) Act 1986. The regulations conform to EU Directive 2010/63/EU and achieve the standard of care required by the US Department of Health and Human Services' Guide for the Care and Use of Laboratory Animals.

The Home Office licence governing this study strictly specifies the limits of severity of effects on the animals. From the available information, the procedures described in the protocol are not anticipated to cause any effects which exceed the severity limit of the procedure. Any animal which shows unacceptable reactions may be euthanised or other actions taken as required by the Home Office to alleviate distress.

24.1. Home Office Project Licence No.

[REDACTED]

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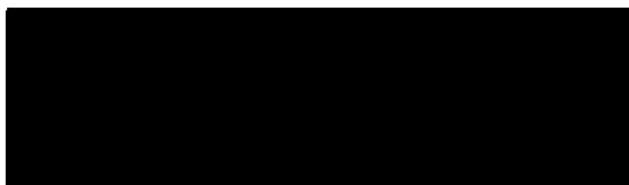
25. REFERENCES

None.

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TEST FACILITY APPROVAL

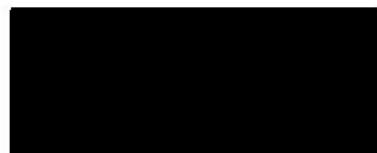
The signature below acknowledges Test Facility Management's responsibility to the study as defined by the relevant GLP regulations.



Date: 26 SEPT 2017

Test Facility Management

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



Date: 26 Sep 2017

Study Director

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SPONSOR APPROVAL

The protocol was approved by the Sponsor by email on 26 Sep 2017. The signature below confirms the approval of the protocol by the Sponsor Representative.



Date: 28 Sep 2017

Sponsor Representative

Appendix 1**ATTACHMENTS****Attachment 1: Preparation and Administration of the Test Item**

1. Prepare work space as per site procedure.
2. Remove appropriate number of vials of [REDACTED] DP, [REDACTED] mL. Record details as per site procedure.
3. Record the time of removal from freezer (thaw start time). Do not force thawing by holding the vial in your hand.
4. Keep the vials of [REDACTED] at ambient temperature until completely thawed. Minimum thaw time to get the vial to ambient temperature will be at least 30 minutes. Thawing should take no longer than 2 hours. Verify complete thawing and record this time.
5. Gently mix the contents of the [REDACTED] vials by swirling both vials carefully for 30 seconds. Check contents of vial. [REDACTED] should be a colourless to slightly yellowish, clear to slightly opalescent solution, free from particulate matter.
6. Remove the flip-off cap from the [REDACTED] vials. Wipe the rubber closure of the vial with a disinfectant swab and allow drying.
7. Extract the contents of one vial and add to a second vial of [REDACTED]. Record completion time and complete paperwork as per site procedure. Despatch vials to the animal facility.
8. Before administration, mix the contents of each [REDACTED] vial by swirling carefully for 30 seconds. Remove an appropriate amount to allow for dosing of 1 mL. This should include dead space needle and syringe volume.
9. Use a new needle for dosing, prime needle and dose the required 1 mL. Discard needle as per site procedure.

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PROTOCOL AMENDMENT 3

Test Facility Study No. [REDACTED]

Sponsor Reference No. [REDACTED]

**An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance
Study [REDACTED] Vaccine in New
Zealand White Rabbits with a 3 Week Recovery Period**

Study Status: Good Laboratory Practice (GLP)

SPONSOR:

[REDACTED]

TEST FACILITY:

Charles River Laboratories [REDACTED]

[REDACTED]

EH33 2NE
UK

Appendix 1**SUMMARY OF CHANGES AND JUSTIFICATIONS****Protocol effective date: 26 Sep 2017**

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

Item or Section(s)	Justification
Amendment 1	Date: 15 Nov 2017
7. Responsible Personnel	To provide details of Individual Scientist for pathology at Test Facility.
Amendment 2	Date: 21 Nov 2017
2. Proposed Study Schedule	To include required dates.
7. Responsible Personnel	From 21 Nov 2017, [REDACTED] will take over as Study Director due to the absence of the original Study Director.
Amendment 3	
2. Proposed Study Schedule	Date amended to allow sufficient time for sponsor review, and update and issue at the Test Facility.
15.2. Immunogenicity Sample Collection, Processing, and Analysis	The Sponsor intends to use residual immunogenicity samples for research purposes. The protocol is updated accordingly.

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Appendix 1

1. OBJECTIVE(S)

The test item under investigation in this study is [REDACTED]
[REDACTED]

[REDACTED] The objectives of this study are to determine the potential toxicity and local tolerance of [REDACTED] [REDACTED] when given by intramuscular injection on 3 occasions (Days 1, 15 and 29) to rabbits, and to evaluate the potential reversibility of any findings during a 3-week recovery period.

1.1. Study Classification

Study Category: Toxicology
Study Type: Local Tolerance; Repeat Dose Toxicity
Study Design: Parallel
Primary Treatment CAS Registry Number: Not Available
Primary Treatment Unique Ingredient ID: Not Available
Class of Compound: Vaccine

2. PROPOSED STUDY SCHEDULE

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

Experimental Start Date:	27 Sep 2017 (First date of study-specific data collection)
Experimental Completion Date:	Jan 2018 (Last date data are collected from the study)
Animal Arrival/Transfer:	19 Sep 2017
Initiation of Dosing:	04 Oct 2017
Completion of In-life:	Main Study - 03 Nov 2017 Recovery Study – 24 Nov 2017 (Last dates of necropsy)
In-life data available (main study animals):	13 Nov 2017 (including clinical pathology data) (Expected ship date from RS to Study Director)
Immunology Draft Report:	To be added by protocol amendment (Expected ship date from RS to Study Director)
Histopathology Draft Report:	18 Dec 2017 (Expected ship date from IS to Study Director)
Pathology Peer Review:	06-08 Dec 2017
Histopathology Final Report:	23 Feb 2018 (Expected ship date from IS to Study Director)

Appendix 1

Data Review Meeting:	29 Jan 2018
Draft Tox Report for Sponsor Review:	09 Feb 2018
Sponsor agreed Final Draft Report:	26 Feb 2018
Final Report:	09 30 Mar 2018 (Expected date of Study Director signature)

3. GUIDELINES FOR STUDY DESIGN

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

- Committee for Medicinal Products for Human Use (CHMP). *Note for Guidance on Repeated Dose Toxicity*. CPMP/SWP/1042/99rev1.
- WHO Guideline on nonclinical evaluation of vaccines, Nov 2003 and WHO Guideline on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines Oct 2013.
- OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring. Number 13. *Consensus Document of the Working Group on Good Laboratory Practice. The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies*.

4. REGULATORY COMPLIANCE

This study with the exception of the Immunogenicity assessment will be performed in accordance with the OECD Principles of Good Laboratory Practice as incorporated into the United Kingdom Statutory Instrument for GLP and as accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA) and Japan (MHLW, MAFF and METI), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions to GLPs include the following study elements:

- Immunogenicity analysis (See Section 5.2)

5. QUALITY ASSURANCE

5.1. Test Facility

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

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

Appendix 1

Tel: +44 (0) 1875 618480
[REDACTED]
[REDACTED]

5.2. Sponsor

The following study phase will be conducted according to the best scientific principles and the data and report will be subjected to Test Site QA procedures, but is not intended to be in full GLP compliance:

Immunogenicity measurement at [REDACTED]
[REDACTED]

6. SPONSOR

Sponsor Representative

[REDACTED]
[REDACTED]
[REDACTED]

Alternative Sponsor Contact

[REDACTED]
[REDACTED]
[REDACTED]

Pathology Peer Review

[REDACTED]
[REDACTED]
[REDACTED]

7. RESPONSIBLE PERSONNEL

Study Director

[REDACTED]
[REDACTED]
[REDACTED]

Appendix 1

[REDACTED]

Management Contact

[REDACTED]

Individual Scientists (IS) at the Test Facility

[REDACTED]

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

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

Responsible Scientist (RS) at Sponsor

Immunology

[REDACTED]

The RS's reference number for this phase of the study will be added by amendment.

Appendix 1

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

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

8. TEST AND CONTROL ITEMS

8.1. Test Item(s)

Identification: [REDACTED]

Batch (Lot) Number: [REDACTED]

Expiration Date: 12 Jan 2018

Physical Description: Clear to slightly opalescent, colourless to yellowish solution and essentially free of visible particulate matter

Concentration: [REDACTED] mL

Purity: 100 %

Storage Conditions: Kept frozen in a freezer set to maintain -80°C, protected from light.

8.2. Control Item

Identification: [REDACTED]

Supplier: Test Facility

Details of the batch(es) used will be recorded in the study raw data.

8.3. Test Item Characterisation

The Sponsor will provide to the Test Facility documentation of the identity, strength, purity, composition, and stability for the test item. A Certificate of Analysis or equivalent documentation will be provided for inclusion in the Final Report.

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

Appendix 1

8.4. Analysis of Test Item

Information to support the stability of each lot of the bulk test item will be provided by the Sponsor.

8.5. Reserve Samples

For each batch (lot) of test item, a reserve sample (1 vial) will be collected and maintained under the appropriate storage conditions by the Test Facility.

8.6. Test and Control Item Inventory and Disposition

Records of the receipt, distribution, and storage of test and control items will be maintained. With the exception of reserve samples, all unused Sponsor-supplied test item will be returned to the Sponsor after completion of the scheduled programme of work.

9. SAFETY

Safety instructions for this study are provided on the Sponsor supplied safety data sheet. COSHH assessment and classification will be carried out at the Test Facility on a Chemical Classification Spreadsheet.

10. DOSE FORMULATION AND ANALYSIS

10.1. Preparation of Test Item

[REDACTED] vaccine vials will be removed from the freezer on the day of dosing and allowed to reach room temperature. Details on handling and preparation of the test item are provided in Attachment 1.

The product from the compounded vial must be dosed within 4 hours after start of thawing of the vials.

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

10.2. Preparation of Control Item

The control item, sodium chloride solution, will be administered as received. For each day of dosing an adequate volume will be dispensed to the animal unit for administration to Group 1 control animals.

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

10.3. Sample Collection and Analysis

The test and control items will be used as received; therefore, samples for dose formulation analysis will not be collected by the Test Facility.

11. TEST SYSTEM

Species: Rabbit

Appendix 1

Strain: New Zealand White
Source: [REDACTED]
Number of Males Ordered: 20
Number of Females Ordered: 20
Target Age at the Initiation of Dosing: At least 12 weeks, acceptable up to 16 weeks
Target Weight at the Initiation of Dosing: ca 2.5-4 kg

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

11.1. Justification of Test System and Number of Animals

The rabbit was chosen as the animal model for this study as it is a species accepted by regulatory agencies for toxicity testing.

The New Zealand White (NZW) rabbit is selected for this study because it is a widely used species to assess preclinical toxicity and local tolerance of vaccine candidates, for which sufficient historical control data exist. Rabbits have sufficient muscle mass to receive a full human dose (of up to 1.0 mL) via the intramuscular route. In addition, NZW rabbits have been used in the past to assess preclinical safety of [REDACTED]. Such studies showed that these vaccines induced an immune response following intramuscular injection in NZW rabbits.

The total number of animals to be used in this study is considered to be the minimum required to properly characterise 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.

11.2. Animal Identification

At study assignment, each animal will be identified using a subcutaneously implanted electronic cylindrical, 'glass-sealed' TROVAN microchip.

11.3. Environmental Acclimation

The animals will be allowed to acclimate to the Test Facility rabbit toxicology accommodation for a period of up to 3 weeks before the commencement of dosing.

11.4. Selection, Assignment and Disposition of Animals

Animals will be removed in random order from their transport boxes and allocated to dose group on arrival by placing them in pens. Cages/pens will be labelled with the study number, animal number and group number.

Control animals will be housed on a separate rack.

Animals suspected of being diseased will be culled from the study. If significant numbers of animals are unsuitable, the entire batch will be rejected by the Study Director and a new batch obtained.

Appendix 1

During the week before the commencement of dosing, the animals will be approved for entry into the experiment on the basis of satisfactory clinical observation records and body weight profile. At the start of pretreatment, female body weight group means will be checked to ensure that they are similar between groups.

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

12. HUSBANDRY

12.1. Housing

Males will be housed individually in appropriately sized stainless steel cages with a 'Noryl' dual level interior and perforated floor. Beneath each cage will be a suspended tray containing absorbent paper.

Females (where behaviour allows) will be socially housed in groups of at least 10 animals (unless reduced by mortality) in pens with adequate floor space. Bedding will be placed on each pen floor. If behaviour does not permit social housing, animals will be housed individually.

Bedding material will be provided with a certificate of analysis for significant contaminants. An analytical certificate for each batch of bedding used will be retained at the Test Facility.

There are no known contaminants in the bedding that would interfere with the objectives of the study.

12.2. Environmental Conditions

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

Temperature:	16 - 20°C
Humidity:	40 - 70%
Ventilation:	A minimum of 10 air changes per hour
Light Cycle:	12 hours light and 12 hours dark (except when interrupted by study procedures/activities).

There will be automatic control of temperature and humidity which will be continuously monitored and recorded. Information on actual temperature and humidity ranges versus target ranges will be presented in the study report.

There will be automatic control of light cycle.

12.3. Food

Envigo Diet will be available to the animals *ad libitum*. Each animal will also be offered a supplement of hay at least 3 times per week.

The diet will be supplied with a batch analysis for major nutritive components and significant contaminants and will be used within the manufacturers' designated shelf-life. The hay is not analysed.

Appendix 1

An analytical certificate for each batch of diet used will be retained at the Test Facility.

There are no known contaminants in the feed that would interfere with the objectives of the study.

12.4. Water

The animals will have access to water *ad libitum* from the public supply.

The water used by Charles River [REDACTED] is analysed at regular intervals for dissolved materials, heavy metals, pesticide residues, pH, nitrates and nitrites. Microbiological screening is also conducted. An analytical certificate for each analysis will be retained at the Test Facility.

There are no known contaminants in the water that would interfere with the objectives of the study.

12.5. Animal Enrichment

Females will be socially housed for psychological/environmental enrichment and all animals will be provided with items such as a device for hiding in and an object for chewing, except when interrupted by study procedures/activities. Males will be allowed a period of exercise (generally weekly) in a separate pen. Details will be documented.

Objects for chewing and devices for hiding in will be provided with a certificate of analysis for significant contaminants. An analytical certificate for each batch of chewing objects and hiding devices used will be retained at the Test Facility.

12.6. Veterinary Care

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

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

Appendix 1**13. EXPERIMENTAL DESIGN**

Experimental Design

Group No.	Treatment	Dosage	Dose Volume	Animal Numbers			
				Main Study		Recovery Study	
				Males	Females	Males	Females
1	Control	0	1 mL	1001-1005	1501-1505	1006-1010	1506-1510
2	[REDACTED]	[REDACTED]	1 mL	2001-2005	2501-2505	2006-2010	2506-2510

VP =Virus particles

Dose Sites

Group No.	Treatment	Dosing days (dosing site)		
		1	15	29
1	Control	Site 1	Site 2	Site 3
2	[REDACTED]	Site 1	Site 2	Site 3

Site 1: Day 1= right thigh (posterior)

Site 2: Day 15 = left thigh

Site 3: Day 29 = right thigh (anterior)

Dose sites will be discrete and adequately spaced from each other.

13.1. Administration of Test and Control Items

The first day of dosing for each individual animal will be designated as Day 1. The dosing volume will be 1 mL per injection.

The injection sites will be clipped free from fur before injection.

The test and control items will be administered to the appropriate animals by intramuscular injection on Days 1, 15 and 29 where appropriate. The doses will be given using a graduated polycarbonate syringe (BD Syringe) and needle (BD 25G Microlance). The injection of the test item will occur within 4 h of removal of test item from the freezer. The injection site will be marked at each administration, and this marking will remain throughout the study. The last injection site (site 3) will be marked by an X to ease collection at necropsy. Further clipping and marking will occur as necessary to maintain visibility of each site.

13.2. Justification of Route and Dosage Levels

The intramuscular route is the intended route of administration of the [REDACTED] vaccine in humans.

The dose level for [REDACTED] is selected on the basis of available data from previous animal studies and is equivalent to the maximum anticipated dosage that will be used in human clinical studies (i.e. a full human dose will be administered to the animals).

14. IN-LIFE PROCEDURES, OBSERVATIONS, AND MEASUREMENTS

The in-life procedures, observations, and measurements listed below will be performed for all animals.

Appendix 1

14.1. Mortality/Moribundity Checks

- Frequency: Twice daily, once at the start and once towards the end of the working day throughout the study.
- Procedure: Animals will be observed for general health/mortality and moribundity. Animals will not be removed from the cage during observation, unless necessary for identification or confirmation of possible findings.

14.2. Clinical Observations

14.2.1. Detailed Clinical Observations

- Frequency: Weekly, beginning Week -1, and to include each dosing day. Animals will be removed from the cage for examination. The animals will be examined for general appearance including movement and behaviour pattern. Other examinations will include the eyes, ears and external genitalia for discharge, redness or other abnormalities; the skin, coat and feet for the presence of abnormalities or injuries; and an observation for any abnormalities of respiration.

- Procedure: Animals removed from the cage for examination.

14.2.2. Postdose Observations

- Frequency: At least twice on each day of dosing (Days 1, 15 and 29), including before dose administration and a target of 1 h and 6 h after injection. On non-dosing days, signs will be recorded once.
- Procedure: All the animals will be examined for reaction to treatment. The onset, intensity and duration of these signs will be recorded (if appropriate), particular attention being paid to the animals during and for the first hour after dosing.

14.3. Dermal Scoring

- Frequency: Injection sites will be evaluated before each dose, 6 h (\pm 30 min) after the injection, 24 h, 48 h, 72 h (all \pm 1 h) after dosing and weekly thereafter. In case injection site effects are observed, the daily observations will be continued until scores returned to 0.
- Injection sites will be evaluated prior to necropsy.
- Procedure: Skin will be assessed for erythema and eschar formation, oedema formation and any other reaction to treatment.

Appendix 1

Erythema and Eschar Formation	Grade
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Oedema Formation	Grade
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

14.4. Body Weights

- Frequency: Once pretreatment, day of dosing (before each dose), daily for 3 days post dose, twice weekly at other times and on each day of necropsy.
- Procedure: Animals will be individually weighed. Weight will be recorded in grams.

14.5. Food Consumption (males only)

- Frequency: Once pretreatment, day of dose, daily for 3 days post dose, twice weekly at other times and on each day of necropsy.
- Procedure: Food consumption will be quantitatively measured.
Female food consumption will be assessed by visual inspection of the food bowls. These assessments will be recorded.

14.6. Ophthalmic Examinations

- Frequency: Pretreatment – All animals once
Dosing Period – All animals after end of dosing before main study necropsy.
Recovery Period - All recovery animals towards the end of the of recovery period.
- Procedure: The eyes will be examined using an indirect ophthalmoscope after the application of a mydriatic agent (1% Tropicamide, Mydriacyl®). The anterior, lenticular and fundic areas will be examined.
The eyes will also be examined with a slit lamp ophthalmoscope after the application of fluorescein to the eyes for epithelial staining. Anterior and medium segments of the

Appendix 1

eye with conjunctiva, cornea, anterior chamber, iris, lens and vitreous body will be examined.

14.7. Body Temperature

Frequency:

Pretreatment – All animals once

Dosing Period – Day of dose (before each dose), $6 \pm 0.5\text{h}$ and $24 \pm 1\text{h}$ after each dose. If body temperature is $\geq \pm 1^\circ\text{C}$ from mean pretreatment value that is the pretreatment and predose Day 1 value, additional measurements will be conducted daily until body temperature returns to the mean value recorded from both pretreatment values. A body temperature will also be recorded on each day of necropsy.

Procedure:

The body temperature of each animal will be recorded using a digital thermometer in the rectum.

15. LABORATORY EVALUATIONS

15.1. Clinical Pathology

15.1.1. Sample Collection

Blood will be collected from an auricular artery. Additional blood samples may be obtained (e.g. due to clotting of non-serum samples) if permissible sampling frequency and blood volume are not exceeded. After collection, samples will be transferred to the appropriate laboratory for processing.

Animals will not be deprived of food prior to blood sampling. Samples will be collected according to the following table.

Samples for Clinical Pathology Evaluation

Group Nos.	Time Point	Haematology	Coagulation	Clinical Chemistry	C-Reactive Protein
All animals	Pretreatment	X	X	X	X
All animals	Day 2 ^a	-	-	-	X
All animals	Day 3	X	X	X	-
All animals	Day 7	-	-	-	X
All animals	Day 30	-	-	-	X
Main animals	Day 31 (necropsy)	X	X	X	-
Recovery animals	Day 52 (necropsy)	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia	X	X	X	X

X = sample to be collected; - = not applicable; ^a = 24 h ($\pm 2\text{ h}$)

Day 1 = first dose administered.

15.1.2. Haematology

Target Volume: 0.5 mL

Appendix 1Anticoagulant: K₂EDTA

Haematology Parameters

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

A blood smear will be prepared from each haematology sample. Blood smears will be labelled, stained, and stored. Individual blood smears may be examined to confirm certain analyser results, as required by SOP.

If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated and this evaluation will be described in a protocol amendment.

15.1.3. Coagulation

Target Volume: 0.9 mL

Anticoagulant: 3.8% (w/v) trisodium citrate

Processing: To plasma

Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample Quality

15.1.4. Clinical Chemistry

Target Volume: 1.5 mL

Anticoagulant: Lithium Heparin

Processing: To plasma

Appendix 1

Clinical Chemistry Parameters

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine kinase	Glucose
Total bilirubin ^a	Cholesterol
Urea	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphate	Chloride

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

15.1.5. C-Reactive Protein

Target Volume: 0.6 mL (2 x 0.6 mL at pretreatment*)

Tubes: Plain with gel separator

Anticoagulant: None

* One sample is for method re-establishment.

Serum will be analysed at the Test Facility using ELISA methodology established under Charles River [REDACTED].

15.1.6. Bone Marrow Smear Evaluation

Bone marrow smears will be collected and prepared as described in the Tissue Collection and Preservation table (Section 16.5).

Evaluation of stained smears may be added by amendment at the discretion of the Study Director in consultation with the pathologist and the Sponsor.

15.2. Immunogenicity Sample Collection, Processing, and Analysis

Blood will be collected from an auricular artery once during pretreatment (all animals), Days 14 and 31 (all animals) and Day 52 (Recovery) and from unscheduled euthanasia (when possible).

Target Volume: 2 mL

Tubes: Plain with gel separator

Anticoagulant: None

Processing: Allow to stand for at least 1 hour before centrifugation to serum (1500 g/10 min /4°C)
2 aliquots of approximately 0.5 mL serum (into clear polypropylene tubes).

Sample Storage: In a freezer set to maintain -20 °C.

Serum shipment To the Responsible Scientist

Shipment conditions: On dry ice, with temperature monitoring.

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Residual samples will be **discarded before issue of the final report and after approval of the Study Director retained by the Test Site and used for research purposes. Results from any analysis are outside the scope of this present study, and will have no influence on the study objectives or conclusions drawn.**

The presence of [REDACTED] specific antibodies will be determined in serum obtained before first dosing, at Day 14 post dose, at termination (at main and recovery necropsy) and at unscheduled euthanasia (when possible), using an ELISA analytical method, with all details on the procedure being reported in the Responsible Scientist report. This work will not be conducted in full compliance with GLP.

16. TERMINAL PROCEDURES

Terminal procedures are summarised in the following table:

Terminal Procedures for All Animals

Group Number	Number of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology ^a	Histopathology ^a
	M	F		Necropsy	Tissue Collection ^a	Organ Weights ^a		
1	5	5	31	X	X	X	Full Tissue Gross Lesions	Full Tissue Gross Lesions
2	5	5					Full Tissue Gross Lesions	Full Tissue Gross Lesions
1	5	5	52	X	X	X	Full Tissue Gross Lesions	Full Tissue Gross Lesions
2	5	5					Full Tissue Gross Lesions	Full Tissue Gross Lesions
Unscheduled Deaths				X	X	-	Full Tissue Gross Lesions	Full Tissue Gross Lesions

X = procedure to be conducted; - = not applicable

^a See Tissue Collection and Preservation table for listing of tissues and weights.

16.1. Unscheduled Deaths

If an animal dies on study, a necropsy will be conducted and specified tissues will be saved. If necessary, the animal will be refrigerated to minimise autolysis.

Animals may be euthanised for humane reasons as per Test Facility SOPs. The body weight will be recorded and samples for evaluation of clinical pathology parameters and immunology will be obtained if possible as specified in Section 15. These animals will undergo necropsy, and specified tissues will be retained. If necessary, the animal will be refrigerated to minimise autolysis.

16.2. Scheduled Euthanasia

Animals surviving until scheduled euthanasia will have a terminal body weight recorded, and will be euthanised by an intravenous overdose of a barbiturate, followed by exsanguination. When possible, the animals will be euthanised in a rotating order across dose groups such that similar numbers of animals from each group, including controls will be necropsied throughout the day. Animals will not be fasted before their scheduled necropsy.

Appendix 1

16.3. Necropsy

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

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

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

16.4. Organ Weights

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

16.5. Tissue Collection and Preservation

Representative samples of the tissues identified in the Tissue Collection and Preservation table will be collected from all animals and preserved in 10% neutral buffered formalin, unless otherwise indicated. Additional tissue samples may be collected to elucidate abnormal findings.

Tissue Collection and Preservation

Tissue	Weigh	Collect	Microscopic Evaluation	Comment
Administration site	-	X	X	3 sites (see Section 13 for injection sites). Include skin. Identify individually and identify retained. 2 levels per site prepared for histological examination.
Animal identification	-	X	-	-
Artery, aorta	-	X	X	From thoracic segment.
Bone marrow smear	-	X	-	Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanised moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are fixed in Methanol. Both smears will be stained using May-Grunwald-Giemsa as soon as practical after necropsy.
Bone marrow	-	X	X	Collect with bone, femur and sternum.
Bone, femur with articulating surface	-	X	X	Collect distal end to include femorotibial joint.

Appendix 1

Tissue	Weigh	Collect	Microscopic Evaluation	Comment
Bone, sternum	-	X	X	-
Brain	X	X	X	Forebrain, midbrain, cerebellum, and medulla oblongata.
Cervix	-	X	X	Collect with uterus.
Diaphragm	-	X	X	-
Epididymis x 2	X	X	X	-
Eye x 2	-	X	X	Preserve in Davidson's fixative.
Gallbladder	-	X	X	-
Gland, adrenal x 2	X	X	X	-
Gland, lacrimal x 2	-	X	X	-
Gland, mammary	-	X	X	Collect with skin and include nipple. Gland, mammary will be examined in females only.
Gland, parathyroid x 2	-	X	X	Collect with gland, thyroid. Examine only if present in the routine section of thyroid.
Gland, pituitary	X	X	X	-
Gland, prostate	X	X	X	-
Gland, salivary x 2	-	X	X	Mandibular.
Gland, seminal vesicle	-	X	X	-
Gland, thyroid x 2	X	X	X	Weight includes gland, parathyroid.
Gut-associated lymphoid tissue (Peyer's Patches)	-	X	X	Collect with jejunum or ileum.
Heart	X	X	X	-
Kidney x 2	X	X	X	-
Large intestine, appendix	-	X	X	-
Large intestine, caecum	-	X	X	-
Large intestine, colon	-	X	X	-
Large intestine, rectum	-	X	X	-
Larynx	-	X	X	-
Lesions/masses	-	X	X	Include local draining lymph nodes to masses.
Liver	X	X	X	Drain gallbladder before weighing.
Lung	-	X	X	Infuse with 10% neutral buffered formalin
Lymph node, mandibular	-	X	X	-
Lymph node, mesenteric	-	X	X	-
Lymph node, medial iliac x2	X	X	X	Individually identify.
Muscle, skeletal	-	X	X	From thigh.
Nasal cavity	-	X	-	-
Nerve, optic x 2	-	X	X	Preserve in Davidson's fixative. Examine only if present in the routine section of the eye.
Nerve, sciatic x 2	-	X	X	-
Oesophagus	-	X	X	-
Ovary x 2	X	X	X	-
Oviduct x 2	-	X	X	Collect with uterus.
Pancreas	-	X	X	-
Skin	-	X	X	Collect with gland, mammary.
Small intestine, duodenum	-	X	X	-
Small intestine, ileum	-	X	X	-
Small intestine, jejunum	-	X	X	-
Small intestine, sacculus rotundus	-	X	X	-

Appendix 1

Tissue	Weigh	Collect	Microscopic Evaluation	Comment
Spinal cord	-	X	X	Cervical, thoracic and lumbar. Examine one transverse from each area.
Spleen	X	X	X	-
Stomach	-	X	X	Fundus, body and pylorus
Testis x 2	X	X	X	Preserve in Modified Davidson's fixative.
Thymus	X	X	X	-
Tongue	-	X	X	-
Trachea	-	X	X	-
Ureter x 2	-	X	X	-
Urinary bladder	-	X	X	Distend contracted bladders by infusing with 10% neutral buffered formalin.
Uterus	-	X	X	-
Vagina	-	X	X	-

X = procedure to be conducted; - = not applicable.

17. HISTOLOGY AND HISTOPATHOLOGY

17.1. Histology

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

17.2. Histopathology

Histopathological evaluation will be performed by a board-certified veterinary pathologist or a veterinary pathologist with training and experience in laboratory animal pathology.

Any additional stains or evaluations, if deemed necessary by the pathologist, will be added by protocol amendment following discussion with the Study Director and in consultation with the Sponsor.

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

17.3. Pathology Peer Review

A pathology peer review will be performed by the Sponsor according to the Sponsor's standard operating procedures. The peer review memorandum and any related correspondence will be provided to the Test Facility. The signed peer review form will be included in the final report.

18. COMPUTERISED SYSTEMS

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

Data for parameters not required by protocol, which are automatically generated by analytical devices used will be retained on file but not reported. Statistical analysis results that are

Appendix 1

generated by the program but are not required by protocol and/or are not scientifically relevant will be retained on file but will not be included in the tabulations.

Critical Computerised Systems

System Name	Description of Data Collected and/or Analysed
Dispense 8	Test item receipt, accountability and/or formulation activities.
Provantis 8	Applicable In-life, clinical pathology and postmortem
In-house reporting software Nevis (using SAS)	Applicable In-life, clinical pathology and postmortem

19. CONSTRUCTED VARIABLES

Body Weight Gains:	calculated between appropriate scheduled intervals
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

20. STATISTICAL ANALYSIS

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

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

Statistical Matrix

Variables for Inferential Analysis	Statistical Method
	Parametric/ Non-Parametric
Body Weight	X
Food Consumption (males only)	X
Body Temperature	X
Haematology Variables	X
Coagulation Variables	X
Clinical Chemistry Variables	X
Organ Weights	X
Body Weight Change	X
Organ Weight relative to Body Weight	X
Organ Weight relative to Brain Weight	X

The following pairwise comparison will be made:

Group 2 vs. Group 1

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20.1. Parametric/Non-Parametric

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

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

21. AMENDMENTS AND DEVIATIONS

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

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

22. RETENTION OF RECORDS, SAMPLES AND SPECIMENS

All study-specific raw data, electronic data, documentation, protocol, protocol amendments, retained samples and specimens, and interim (if applicable) and final reports generated by Charles River from this study will be transferred to a Charles River archive. Two years after issue of the final report, the Sponsor will be contacted to determine the disposition of materials associated with the study. The original signed copy of the final report will be archived indefinitely at the Test Facility.

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

- Protocol, protocol amendments, and deviations
- Study schedule
- Study-related correspondence
- Test system receipt, health, and husbandry
- Test and control item receipt, identification and preparation
- In-life measurements and observations
- Clinical pathology sample collection and evaluation
- Immunology sample collection
- Gross and microscopic observations and related data
- Organ weight measurements
- Statistical analysis results

Data generated at the Sponsor-designated Test Site will be archived at the Test Site for the period stated in the phase report.

Appendix 1

23. REPORTING

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

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

A tabulated data summary following the appropriate format as outlined in the ICH Harmonised Tripartite Guideline, *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety – M4S (R2), Nonclinical Overview and Nonclinical Summaries of Module 2, Organisation of Module 4* will be included within the study report, and also provided as a separate Microsoft Word document.

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

24. ANIMAL WELFARE

The UK Home Office controls scientific procedures on animals in the UK and does so by the issue of licences under the Animals (Scientific Procedures) Act 1986. The regulations conform to EU Directive 2010/63/EU and achieve the standard of care required by the US Department of Health and Human Services' Guide for the Care and Use of Laboratory Animals.

The Home Office licence governing this study strictly specifies the limits of severity of effects on the animals. From the available information, the procedures described in the protocol are not anticipated to cause any effects which exceed the severity limit of the procedure. Any animal which shows unacceptable reactions may be euthanised or other actions taken as required by the Home Office to alleviate distress.

24.1. Home Office Project Licence No.

[REDACTED]

Appendix 1

25. REFERENCES

None.

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 1

AMENDMENT APPROVAL

[REDACTED]
Study Director

Date: 08 MAR 2018

Appendix 1

SPONSOR APPROVAL

The protocol amendment was approved by the Sponsor Monitor on 06 Mar 2018.

Appendix 1**ATTACHMENTS****Attachment 1: Preparation and Administration of the Test Item**

1. Prepare work space as per site procedure.
2. Remove appropriate number of vials of [REDACTED] DP, [REDACTED] mL. Record details as per site procedure.
3. Record the time of removal from freezer (thaw start time). Do not force thawing by holding the vial in your hand.
4. Keep the vials of [REDACTED] at ambient temperature until completely thawed. Minimum thaw time to get the vial to ambient temperature will be at least 30 minutes. Thawing should take no longer than 2 hours. Verify complete thawing and record this time.
5. Gently mix the contents of the [REDACTED] vials by swirling both vials carefully for 30 seconds. Check contents of vial. [REDACTED] should be a colourless to slightly yellowish, clear to slightly opalescent solution, free from particulate matter.
6. Remove the flip-off cap from the [REDACTED] vials. Wipe the rubber closure of the vial with a disinfectant swab and allow drying.
7. Extract the contents of one vial and add to a second vial of [REDACTED]. Record completion time and complete paperwork as per site procedure. Despatch vials to the animal facility.
8. Before administration, mix the contents of each [REDACTED] vial by swirling carefully for 30 seconds. Remove an appropriate amount to allow for dosing of 1 mL. This should include dead space needle and syringe volume.
9. Use a new needle for dosing, prime needle and dose the required 1 mL. Discard needle as per site procedure.

Appendix 1

Protocol Deviations and Other Events

The image consists of a series of horizontal black bars of varying lengths and positions, set against a white background. The bars are composed of multiple segments, creating a stepped or jagged appearance. They are arranged in a descending staircase pattern from left to right. The first bar is at the top left, followed by a shorter one below it, then a longer one further down, and so on. The bars are irregular in width and position, giving them a digital or processed signal appearance.

Appendix 1

Protocol Deviations and Other Events

A large black rectangular redaction box covers the majority of the page content, from approximately y=106 to y=890. The redaction is irregular at the bottom right corner, where a small white triangular area is visible.

Appendix 1

Protocol Deviations and Other Events

[REDACTED]

[REDACTED]

[REDACTED]

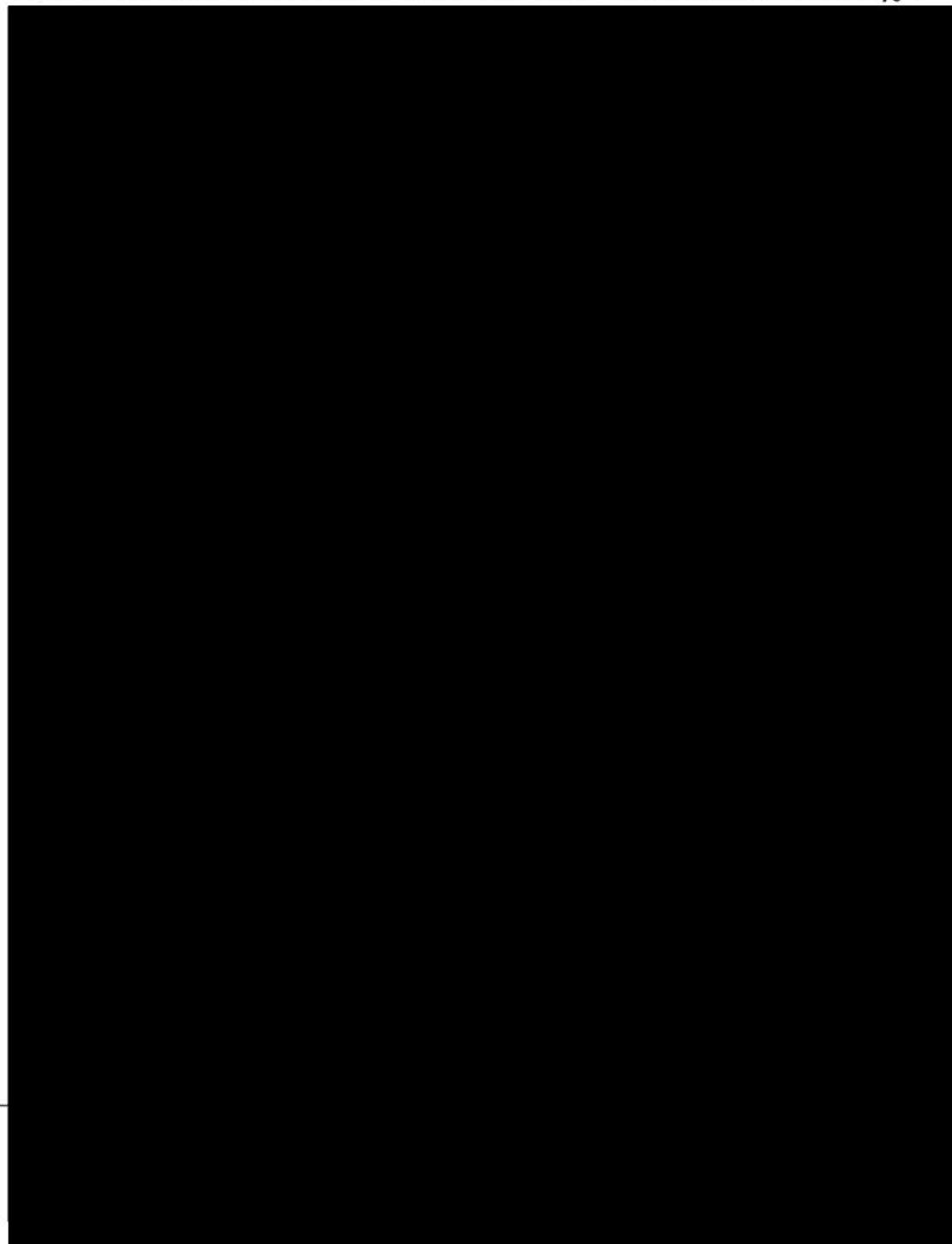
[REDACTED]

Appendix 2
Certificate of Analysis

[REDACTED] Certificate of Analysis [REDACTED] D [REDACTED]

MATERIAL NUMBER:
BATCH NUMBER:

[REDACTED] Page 1 of 2
Print Date: 21 Sep. 2017
EF-11182



Appendix 2
Certificate of Analysis

[REDACTED]
Certificate of Analysis
[REDACTED]

MATERIAL NUMBER:
BATCH NUMBER:

Page 2 of 2

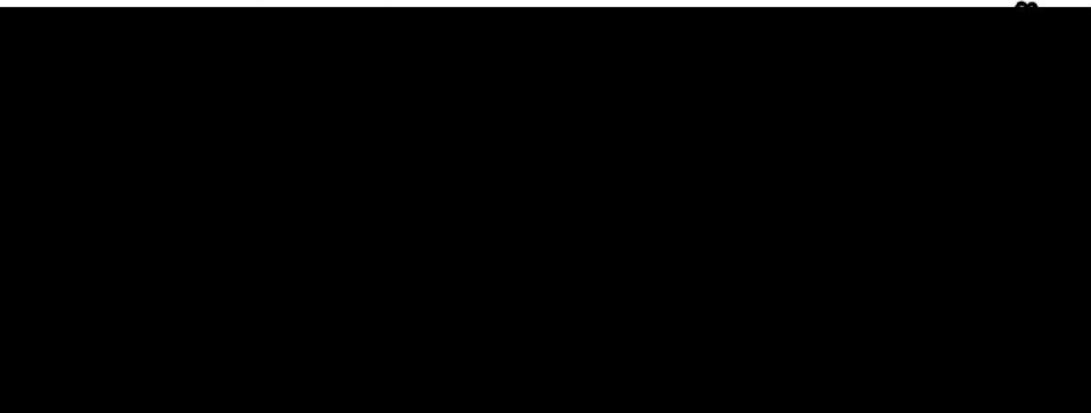
Print Date: 21 Sep, 2017

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**Appendix 3
Individual Mortality****Explanation Page**

Abbreviation	Description	Abbreviation	Description
FD	Found dead	NR	Not recorded
TE or TERM	Terminal euthanasia	UE or UNSC	Unscheduled euthanasia
REC	Recovery euthanasia		

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

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

Appendix 3**Individual Mortality**

[REDACTED]

Group	Dose	Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
1	0		Male	1001	1	31	5	03NOV2017	8:57	.	.	TERM
				1002	2	31	5	03NOV2017	10:04	.	.	TERM
				1003	3	31	5	03NOV2017	11:14	.	.	TERM
				1004	4	31	5	03NOV2017	12:06	.	.	TERM
				1005	5	31	5	03NOV2017	14:11	.	.	TERM
				1006	6	52	8	24NOV2017	8:53	.	.	REC
				1007	7	52	8	24NOV2017	8:54	.	.	REC
				1008	8	52	8	24NOV2017	11:24	.	.	REC
				1009	9	52	8	24NOV2017	12:34	.	.	REC
				1010	10	52	8	24NOV2017	14:39	.	.	REC
1	0		Female	1501	21	31	5	03NOV2017	9:24	.	.	TERM
				1502	21	31	5	03NOV2017	10:35	.	.	TERM
				1503	21	31	5	03NOV2017	11:39	.	.	TERM
				1504	21	31	5	03NOV2017	12:34	.	.	TERM
				1505	21	31	5	03NOV2017	14:39	.	.	TERM
				1506	21	52	8	24NOV2017	9:35	.	.	REC
				1507	21	52	8	24NOV2017	10:42	.	.	REC
				1508	21	52	8	24NOV2017	11:54	.	.	REC
				1509	21	52	8	24NOV2017	15:12	.	.	REC
				1510	21	52	8	24NOV2017	14:07	.	.	REC
2	1x10^11	VP	Male	2001	11	31	5	03NOV2017	8:50	.	.	TERM
				2002	12	31	5	03NOV2017	10:01	.	.	TERM
				2003	13	31	5	03NOV2017	11:04	.	.	TERM
				2004	14	31	5	03NOV2017	12:11	.	.	TERM
				2005	15	31	5	03NOV2017	14:10	.	.	TERM
				2006	16	52	8	24NOV2017	10:12	.	.	REC
				2007	17	52	8	24NOV2017	10:27	.	.	REC
				2008	18	52	8	24NOV2017	11:56	.	.	REC
				2009	19	52	8	24NOV2017	14:04	.	.	REC
				2010	20	52	8	24NOV2017	15:13	.	.	REC
2	1x10^11	VP	Female	2501	22	31	5	03NOV2017	9:32	.	.	TERM
				2502	22	31	5	03NOV2017	11:37	.	.	TERM

Appendix 3Individual Mortality
[REDACTED]

Group	Dose	Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
2	1x10^11	VP	Female	2503	22	31	5	03NOV2017	10:34	.	.	TERM
				2504	22	31	5	03NOV2017	12:37	.	.	TERM
				2505	22	31	5	03NOV2017	14:46	.	.	TERM
				2506	22	52	8	24NOV2017	9:44	.	.	REC
				2507	22	52	8	24NOV2017	11:09	.	.	REC
				2508	22	52	8	24NOV2017	12:27	.	.	REC
				2509	22	52	8	24NOV2017	14:38	.	.	REC
				2510	22	52	8	24NOV2017	15:44	.	.	REC

Appendix 4

Individual Clinical Observations

Explanation Page

Abbreviation	Description	Abbreviation	Description
PreRx or pr	Predose	PostRx or p	Immediately postdose
PostRx1 or p1	1 hour postdose	PostRx2 or p2	2 hours postdose
PostRx3 or p3	2 to 3 hours postdose	PostRx4 or p4	3 to 4 hours postdose
PostRx5	4 to 8 hours posdose	PostRx6	8 to 12 hours postdose
SIRT	Detailed clinical observations on non-dosing days		
CSO	Cage side observations on non-dosing days		
.	No abnormality detected, animal not examined or animal deceased		
*	Comment present.		

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

Only animals with clinical observations on at least one occasion are presented in this appendix.

Appendix 4Individual Clinical Observations Pretreatment and Dosing Period
[REDACTED]

Day numbers relative to Start Date												
Group	Sex	Animal	Clinical Sign	Site	-1	1	2	3	8	15	22	29
					PreRx	PreRx	PreRx	SIRT	PreRx	SIRT	PreRx	PreRx
1	m	1006	Skin, Scab	Pinna, Left	X	X	X	X	X	X	X	X

Severity Codes: X = Present

Group 1 - 0

Appendix 4Individual Clinical Observations Pretreatment and Dosing Period
[REDACTED]

Day numbers relative to Start Date

Group	Sex	Animal	Clinical		Site	1 PreRx	8 SIRT	15 PreRx
			Sign	Site				
1	f	1507	Skin, Scab	Eyelid, Left		X	X	X

Severity Codes: X = Present

Group 1 - 0

Appendix 5
Individual Dermal Scoring
Explanation Page

Abbreviation	Description	Abbreviation	Description
SIRT Pre	Predose	SIRT PostRx6	6 hour postdose
SIRT	Dermal scoring on non-dosing days		
.	Not applicable or animal deceased		
*	Comment present.		

The skin was assessed and graded as follows:

Erythema and Eschar Formation	Grade
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Oedema Formation	Grade
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

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

Treatment Site No.01 = right thigh (posterior)

Treatment Site No.02 = left thigh

Treatment Site No.03 = right thigh (anterior)

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period

[REDACTED]

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date									
					1 SIRT Pre	1 SIRT PostRx6	2 SIRT	3 SIRT	4 SIRT	8 SIRT	15 SIRT	15 SIRT Pre	15 SIRT PostRx6	
1	m	1001	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1002			Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1003			Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1004			Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1005			Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date								
					16 SIRT	17 SIRT	18 SIRT	22 SIRT	29 SIRT	29 SIRT Pre	29 SIRT PostRx6	30 SIRT	31 SIRT
1	m	1001	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	m	1002	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
	f	1002	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0	0
1	f	1003	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
	f	1003	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0	0
	f	1004	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
1	f	1004	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0	0
	f	1005	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1×10^{11} VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date									
					1 SIRT Pre	1 SIRT PostRx6	2 SIRT	3 SIRT	4 SIRT	8 SIRT	15 SIRT	15 SIRT Pre	15 SIRT PostRx6	
1	m	1006	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
	m	1007	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
	m	1008	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
1	m	1009	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
	m	1010	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
	m	1010	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date								
					16 SIRT	17 SIRT	18 SIRT	22 SIRT	29 SIRT	29 SIRT Pre	29 SIRT PostRx6	30 SIRT	31 SIRT
1	m	1006	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	m	1007	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
	m	1008	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
1	m	1009	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0
	m	1010	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	m	1010	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1×10^{11} VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



			Day numbers relative to Start Date											
Group	Sex	Animal	Clinical Sign	Site	1	1	2	3	4	8	15	15	15	
					SIRT Pre	SIRT PostRx6	SIRT	SIRT	SIRT	SIRT	SIRT	SIRT Pre	SIRT PostRx6	
2	m	2001	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	0	
			Erythema	Treatment Site No.03	
	2002		Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	0	
			Edema	Treatment Site No.03	
	2003		Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	0	
			Erythema	Treatment Site No.03	
2004	2004		Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	0	
			Edema	Treatment Site No.03	
	2005		Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	0	
			Erythema	Treatment Site No.03	
	2005		Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	0	
			Edema	Treatment Site No.03	

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date								
					16 SIRT	17 SIRT	18 SIRT	22 SIRT	29 SIRT	29 SIRT Pre	29 SIRT PostRx6	30 SIRT	31 SIRT
2	m	2001	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	m	2002	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
	m	2003	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
2	m	2004	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
	m	2005	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0	0
	m	2005	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1×10^{11} VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



			Day numbers relative to Start Date											
Group	Sex	Animal	Clinical Sign	Site	1	1	2	3	4	8	15	15	15	15
					SIRT Pre	SIRT PostRx6	SIRT	SIRT	SIRT	SIRT	SIRT	SIRT Pre	SIRT PostRx6	SIRT PostRx6
2	m	2006	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	.
			Erythema	Treatment Site No.02	0	0	0
			Erythema	Treatment Site No.03
	2007		Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	.
			Edema	Treatment Site No.02	0	0	0
			Edema	Treatment Site No.03
	2008		Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	.
			Erythema	Treatment Site No.02	0	0	0
			Erythema	Treatment Site No.03
2009	2009		Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	.
			Edema	Treatment Site No.02	0	0	0
			Edema	Treatment Site No.03
	2010		Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	.
			Erythema	Treatment Site No.02	0	0	0
			Erythema	Treatment Site No.03
	2010		Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	.
			Edema	Treatment Site No.02	0	0	0
			Edema	Treatment Site No.03

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date								
					16 SIRT	17 SIRT	18 SIRT	22 SIRT	29 SIRT	29 SIRT Pre	29 SIRT PostRx6	30 SIRT	31 SIRT
2	m	2006	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
		2007	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
	2008	2007	Edema	Treatment Site No.03	0	0	0	0
			Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
		2008	Erythema	Treatment Site No.03	0	0	0	0
			Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
		2009	Edema	Treatment Site No.03	0	0	0	0
			Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
	2010	2009	Erythema	Treatment Site No.03	0	0	0	0
			Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
		2010	Edema	Treatment Site No.03	0	0	0	0
			Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
		2010	Erythema	Treatment Site No.03	0	0	0	0
			Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1×10^{11} VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date									
					1 SIRT Pre	1 SIRT PostRx6	2 SIRT	3 SIRT	4 SIRT	8 SIRT	15 SIRT	15 SIRT Pre	15 SIRT PostRx6	
1	f	1501	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1502			Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1503			Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1504			Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1505			Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
			Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date								
					16 SIRT	17 SIRT	18 SIRT	22 SIRT	29 SIRT	29 SIRT Pre	29 SIRT PostRx6	30 SIRT	31 SIRT
1	f	1501	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	f	1502	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
	f	1503	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
1	f	1504	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
	f	1505	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0	0
	f	1505	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1×10^{11} VP

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period

[REDACTED]

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date									
					1 SIRT Pre	1 SIRT PostRx6	2 SIRT	3 SIRT	4 SIRT	8 SIRT	15 SIRT	15 SIRT Pre	15 SIRT PostRx6	
1	f	1506	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
	f	1507	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1	m	1508	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
	m	1509	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	
1	m	1510	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	
			Erythema	Treatment Site No.03	
	m	1511	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	
			Edema	Treatment Site No.03	

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period

[REDACTED]

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date								
					16 SIRT	17 SIRT	18 SIRT	22 SIRT	29 SIRT	29 SIRT Pre	29 SIRT PostRx6	30 SIRT	31 SIRT
1	f	1506	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	f	1507	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0
	f	1508	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
1	f	1509	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0
	f	1510	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	f	1510	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1×10^{11} VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



			Day numbers relative to Start Date											
Group	Sex	Animal	Clinical Sign	Site	1	1	2	3	4	8	15	15	15	
					SIRT Pre	SIRT PostRx6	SIRT	SIRT	SIRT	SIRT	SIRT	SIRT Pre	SIRT PostRx6	
2	f	2501	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	0	
			Erythema	Treatment Site No.03	
	f	2502	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	0	
			Edema	Treatment Site No.03	
2503	f	2503	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	0	
			Erythema	Treatment Site No.03	
	f	2504	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	0	
			Edema	Treatment Site No.03	
2505	f	2505	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Erythema	Treatment Site No.02	0	0	0	
			Erythema	Treatment Site No.03	
	f	2505	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.	
			Edema	Treatment Site No.02	0	0	0	
			Edema	Treatment Site No.03	

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date								
					16 SIRT	17 SIRT	18 SIRT	22 SIRT	29 SIRT	29 SIRT Pre	29 SIRT PostRx6	30 SIRT	31 SIRT
2	f	2501	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	f	2502	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0
	f	2503	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
2	f	2504	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0
	f	2505	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	f	2505	Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1×10^{11} VP

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period

[REDACTED]

			Day numbers relative to Start Date										
Group	Sex	Animal	Clinical Sign	Site	1 SIRT Pre	1 SIRT PostRx6	2 SIRT	3 SIRT	4 SIRT	8 SIRT	15 SIRT	15 SIRT Pre	15 SIRT PostRx6
2	f	2506	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.
			Erythema	Treatment Site No.02	0	0	0
			Erythema	Treatment Site No.03
	f	2507	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.
			Edema	Treatment Site No.02	0	0	0
			Edema	Treatment Site No.03
2508	f	2507	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.
			Erythema	Treatment Site No.02	0	0	0
			Erythema	Treatment Site No.03
	f	2508	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.
			Edema	Treatment Site No.02	0	0	0
			Edema	Treatment Site No.03
2509	f	2508	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.
			Erythema	Treatment Site No.02	0	0	0
			Erythema	Treatment Site No.03
	f	2509	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.
			Edema	Treatment Site No.02	0	0	0
			Edema	Treatment Site No.03
2510	f	2509	Erythema	Treatment Site No.01	0	0	0	0	0	0	0	.	.
			Erythema	Treatment Site No.02	0	0	0
			Erythema	Treatment Site No.03
	f	2510	Edema	Treatment Site No.01	0	0	0	0	0	0	0	.	.
			Edema	Treatment Site No.02	0	0	0
			Edema	Treatment Site No.03

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 5

Individual Dermal Scoring Pretreatment and Dosing Period



Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date								
					16 SIRT	17 SIRT	18 SIRT	22 SIRT	29 SIRT	29 SIRT Pre	29 SIRT PostRx6	30 SIRT	31 SIRT
2	f	2506	Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
	2507		Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
	2508		Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0
2509	2509		Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0
	2510		Erythema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Erythema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Erythema	Treatment Site No.03	0	0	0	0	0
	2510		Edema	Treatment Site No.01	.	.	.	0	0	.	.	.	0
			Edema	Treatment Site No.02	0	0	0	0	0	.	.	.	0
			Edema	Treatment Site No.03	0	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1×10^{11} VP

Appendix 5Individual Dermal Scoring Recovery Period
[REDACTED]

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	31	32	36	39	43	50
					SIRT						
1	m	1006	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
	m	1007	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
	m	1008	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
1	m	1008	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
	m	1009	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
	m	1010	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
	m	1010	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
	m	1010	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Appendix 5Individual Dermal Scoring Recovery Period
[REDACTED]

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	31	32	36	39	43	50
					SIRT						
2	m	2006	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
		2007	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
	2008	2007	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
		2008	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
2009	2008	2007	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
		2008	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
	2009	2008	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
		2009	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
2010	2009	2008	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
		2009	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Appendix 5Individual Dermal Scoring Recovery Period
[REDACTED]

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date							
					30 SIRT	31 SIRT	32 SIRT	36 SIRT	39 SIRT	43 SIRT	50 SIRT	
1	f	1506	Erythema	Treatment Site No.01	.	0	.	0	0	0	0	
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0	
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0	
			Edema	Treatment Site No.01	.	0	.	0	0	0	0	
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	
			Edema	Treatment Site No.03	0	0	0	0	0	0	0	
			1507	Erythema	Treatment Site No.01	.	0	.	0	0	0	
				Erythema	Treatment Site No.02	.	0	.	0	0	0	
				Erythema	Treatment Site No.03	0	0	0	0	0	0	
1508			Edema	Treatment Site No.01	.	0	.	0	0	0	0	
			Edema	Treatment Site No.02	.	0	.	0	0	0	0	
			Edema	Treatment Site No.03	0	0	0	0	0	0	0	
1509			1509	Erythema	Treatment Site No.01	.	0	.	0	0	0	
				Erythema	Treatment Site No.02	.	0	.	0	0	0	
				Erythema	Treatment Site No.03	0	0	0	0	0	0	
				Edema	Treatment Site No.01	.	0	.	0	0	0	
				Edema	Treatment Site No.02	.	0	.	0	0	0	
				Edema	Treatment Site No.03	0	0	0	0	0	0	
1510			1510	Erythema	Treatment Site No.01	.	0	.	0	0	0	
				Erythema	Treatment Site No.02	.	0	.	0	0	0	
				Erythema	Treatment Site No.03	0	0	0	0	0	0	
				Edema	Treatment Site No.01	.	0	.	0	0	0	
				Edema	Treatment Site No.02	.	0	.	0	0	0	
				Edema	Treatment Site No.03	0	0	0	0	0	0	

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Appendix 5Individual Dermal Scoring Recovery Period
[REDACTED]

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	30	31	32	36	39	43	50
					SIRT						
2	f	2506	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
	f	2507	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
	f	2508	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
2	f	2508	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
	f	2509	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
	f	2509	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0
2	f	2510	Erythema	Treatment Site No.01	.	0	.	0	0	0	0
			Erythema	Treatment Site No.02	.	0	.	0	0	0	0
			Erythema	Treatment Site No.03	0	0	0	0	0	0	0
	f	2510	Edema	Treatment Site No.01	.	0	.	0	0	0	0
			Edema	Treatment Site No.02	.	0	.	0	0	0	0
			Edema	Treatment Site No.03	0	0	0	0	0	0	0

Severity Codes: 0 = Grade 0

Group 1 - 0

Group 2 - 1x10^11 VP

Appendix 6

Individual Body Weights (g)

Explanation Page

Abbreviation	Description	Abbreviation	Description
AVS	Aberrant value suppressed/excluded	X	Excluded from mean
--	Animal deceased or collection not scheduled to be performed unless otherwise listed below		

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

At set up of the electronic protocol for data capture a module was selected that only allowed for the body weight of the animals to be recorded in kilograms. The use of this unit in the selected module restricts body weights to be recorded to one decimal place, for example, 2.3 kg. The study protocol indicated that body weights should be recorded in grams, and this is what was completed by the animal technical group.

At study reporting, the units in the group mean and individual table headers state grams as this can be manually adjusted. However, all in-life body weights in the raw data indicates that the units are kilograms.

Appendix 6
Individual Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Animal No.	Day					
		-7	1	2	3	4	8
1M	1001	2336	2465	2479	2510	2497	2582
	1002	2588	2838	2896	2869	2923	3040
	1003	2077	2212	2271	2270	2293	2390
	1004	2580	2777	2789	2812	2854	2939
	1005	2230	2375	2406	2417	2450	2509
	1006	2294	2397	2394	2405	2453	2501
	1007	2461	2561	2571	2571	2595	2675
	1008	2092	2217	2212	2249	2252	2345
	1009	2409	2504	2543	2545	2567	2623
	1010	2174	2277	2264	2304	2307	2405
2M	2001	2029	2168	2191	2196	2216	2295
	2002	2502	2688	2577	2695	2694	2820
	2003	1946	2076	1989	2139	2166	2266
	2004	2471	2560	2584	2616	2637	2766
	2005	2076	2211	2231	2267	2295	2350
	2006	1989	2144	2158	2177	2208	2258
	2007	2340	2447	2490	2535	2537	2624
	2008	2699	2813	2855	2868	2919	2982
	2009	2359	2476	2513	2486	2537	2640
	2010	2230	2374	2328	2396	2421	2483



Appendix 6
Individual Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Sex	Group / Animal No.	Day					
		15	16	17	18	22	25
1M	1001	2710	2708	2707	2737	2796	2804
	1002	3210	3259	3239	3296	3372	3422
	1003	2514	2554	2554	2559	2637	2688
	1004	3114	3123	3146	3179	3272	3339
	1005	2636	2664	2719	2715	2728	2765
	1006	2701	2735	2730	2715	2784	2853
	1007	2805	2848	2872	2894	2955	2963
	1008	2484	2503	2519	2528	2622	2642
	1009	2748	2769	2773	2790	2832	2882
	1010	2494	2547	2558	2535	2583	2611
2M	2001	2372	2368	2378	2398	2463	2484
	2002	2941	2947	2938	2951	3028	3073
	2003	2393	2331	2378	2445	2480	2556
	2004	2905	2904	2931	3012	3049	3040
	2005	2485	2492	2493	2544	2625	2620
	2006	2344	2360	2371	2397	2431	2470
	2007	2743	2751	2711	2730	2771	2824
	2008	3162	3147	3155	3196	3221	3293
	2009	2742	2779	2780	2813	2885	2883
	2010	2617	2559	2597	2648	2727	2766



Appendix 6
Individual Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Animal No.	Day		
		30	31	Change 1 - 31
1M	1001	2810	2838	373
	1002	3502	3525	687
	1003	2679	2727	515
	1004	3432	3454	677
	1005	2825	2850	475
	1006	2900	3022	625
	1007	3076	3027	466
	1008	2726	2708	491
	1009	2943	2948	444
	1010	2713	2665	388
2M	2001	2374	2349	181
	2002	3076	3094	406
	2003	2596	2585	509
	2004	3118	3102	542
	2005	2661	2666	455
	2006	2503	2520	376
	2007	2820	2866	419
	2008	3334	3371	558
	2009	2909	2895	419
	2010	2753	2828	454

Appendix 6
Individual Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Animal No.	Day					
		-7	1	2	3	4	8
1F	1501	2317	2520	2546	2549	2610	2698
	1502	2190	2363	2384	2404	2400	2501
	1503	2286	2437	2405	2422	2466	2482
	1504	2259	2436	2460	2496	2541	2622
	1505	2216	2331	2355	2408	2410	2490
	1506	2158	2281	2286	2326	2376	2471
	1507	2200	2358	2374	2384	2392	2494
	1508	2154	2320	2310	2328	2373	2459
	1509	2303	2463	2430	2486	2509	2598
	1510	2320	2498	2513	2554	2611	2674
2F	2501	2367	2495	2440	2521	2558	2604
	2502	2220	2386	2367	2374	2428	2496
	2503	2248	2462	2431	2496	2528	2590
	2504	2304	2445	2441	2437	2523	2616
	2505	2315	2455	2437	2484	2526	2614
	2506	2387	2575	2577	2699	2684	2783
	2507	2299	2410	2361	2437	2462	2540
	2508	2412	2589	2586	2662	2667	2769
	2509	2444	2637	2588	2645	2710	2827
	2510	2291	2439	2405	2449	2501	2603

[REDACTED]

Appendix 6
Individual Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Animal No.	Day					
		15	16	17	18	22	25
1F	1501	2871	2926	2917	2962	3048	3138
	1502	2730	2765	2763	2824	2849	2917
	1503	2701	2700	2711	2757	2814	2895
	1504	2733	2750	2929	2981	3002	2902
	1505	2750	2767	2778	2773	2911	3001
	1506	2670	2639	2650	2644	2772	2831
	1507	2616	2639	2678	2682	2775	2834
	1508	2619	2608	2638	2615	2698	2822
	1509	2774	2792	2820	2750	2884	2864
	1510	2909	2854	2955	2961	3073	3123
2F	2501	2816	2782	2826	2879	2973	3021
	2502	2714	2731	2750	2759	2868	2963
	2503	2733	2763	2753	2790	2910	2951
	2504	2795	2807	2773	2864	2980	3082
	2505	2793	2805	2799	2839	2966	3006
	2506	2946	2963	3009	2969	3128	3125
	2507	2687	2732	2707	2742	2900	2886
	2508	2953	3021	2980	3031	3117	3137
	2509	3052	3015	3029	3066	3190	3263
	2510	2783	2760	2809	2833	2926	2971



Appendix 6
Individual Body Weights (g) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Animal No.	Day 30	Day 31	Change 1 - 31
1F	1501	3229	3256	736
	1502	2871	2927	564
	1503	2965	2985	548
	1504	3001	3093	657
	1505	3059	3123	792
	1506	2843	2890	609
	1507	2875	2947	589
	1508	2873	2907	587
	1509	2891	2975	512
	1510	3146	3176	678
2F	2501	3046	3120	625
	2502	3013	3014	628
	2503	3023	3093	631
	2504	3174	3155	710
	2505	3074	3107	652
	2506	3181	3219	644
	2507	2973	3008	598
	2508	3172	3167	578
	2509	3299	3319	682
	2510	3045	3065	626

Appendix 6
Individual Body Weights (g) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	Group / Animal No.	Day						
		30	31	32	36	39	43	46
1M	1006	2900	3022	2903	2923	2945	3007	3097
	1007	3076	3027	3070	3161	3183	3204	3277
	1008	2726	2708	2745	2763	2826	2809	2870
	1009	2943	2948	2934	2975	2975	3025	3073
	1010	2713	2665	2673	2729	2687	2709	2785
2M	2006	2503	2520	2529	2566	2606	2678	2714
	2007	2820	2866	2857	2929	2939	3011	3068
	2008	3334	3371	3409	3372	3466	3510	3492
	2009	2909	2895	2936	2991	3021	3077	3093
	2010	2753	2828	2809	2892	2909	2950	2952

Appendix 6
Individual Body Weights (g) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day 50	Day 52	Change 31 - 52
1M	1006	3050	3135	113
	1007	3325	3358	331
	1008	2859	2873	165
	1009	3091	3135	187
	1010	2734	2815	150
2M	2006	2750	2774	254
	2007	3120	3160	294
	2008	3525	3524	153
	2009	3118	3139	244
	2010	2982	3030	202

Appendix 6
Individual Body Weights (g) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	Group / Animal No.	Day						
		30	31	32	36	39	43	46
1F	1506	2843	2890	2893	3006	3119	3086	3077
	1507	2875	2947	2988	2944	3012	3077	3016
	1508	2873	2907	2882	2795	2744	2777	2823
	1509	2891	2975	2940	2988	3131	3155	3171
	1510	3146	3176	3170	3140	3305	3322	3341
2F	2506	3181	3219	3242	3293	3304	3432	3470
	2507	2973	3008	3052	3199	3144	3244	3123
	2508	3172	3167	3208	3299	3293	3452	3453
	2509	3299	3319	3406	3406	3429	3650	3511
	2510	3045	3065	3062	3179	3142	3194	3201

Appendix 6
Individual Body Weights (g) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day		
		50	52	Change 31 - 52
1F	1506	3109	3153	263
	1507	3055	3040	93
	1508	2858	2938	31
	1509	3195	3187	212
	1510	3437	3444	268
2F	2506	3516	3575	356
	2507	3111	3122	114
	2508	3509	3551	384
	2509	3593	3624	305
	2510	3115	3188	123

Appendix 7
Individual Food Consumption (g/animal/day)
Explanation Page

Abbreviation	Description	Abbreviation	Description
AFE	Animal found with no food during measurement interval, excluded	NC	Not calculable
AFNF	Animal found with no food during measurement interval	OA	Omitted activity
ANH	Animal found with no hopper during measurement interval	POWF	Powdered food
ANIC	Animal not in cage or in incorrect cage during measurement	REHO	Animal rehoused during measurement interval
ANW	Animal found with no water access during measurement intervals	REPL	Animal replaced during measurement interval
ANWB	Animal found with no water bottle during measurement interval	SPIL	Spilled food (by animal)
AVS	Suspected aberrant value	TERR	Technical error
AWE	Animal found with no water in bottle during measurement interval, excluded	UPTD	Unable to perform due to technical difficulty
FSG	Food supplementation given during interval, included in feed weight	WETF	Wet or contaminated food (in container)
FSNC	Food supplementation given during interval, value not calculable	X	Excluded from mean/statistical analysis
--	Animal deceased, collection not scheduled to be performed or unable to calculate		

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

Appendix 7
Individual Food Consumption (g/animal/day) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Animal No.	Day (From/To)					
		-7/1	1/2	2/3	3/4	4/8	8/11
1M	1001	87.1	121.0	123.0	120.0	123.5	120.3
	1002	111.0	160.0	155.0	143.0	157.5	184.0
	1003	103.3	127.0	113.0	108.0	120.0	110.7
	1004	147.6	140.0	146.0	148.0	156.0	156.7
	1005	105.0	98.0	111.0	99.0	110.5	105.7
	1006	114.4	108.0	116.0	111.0	122.0	130.3
	1007	101.1	108.0	116.0	115.0	117.5	130.3
	1008	93.3	88.0	108.0	91.0	100.5	115.0
	1009	105.0	111.0	123.0	109.0	112.8	119.3
	1010	97.3	103.0	109.0	92.0	105.5	106.7
2M	2001	99.9	106.0	102.0	103.0	100.8	96.0
	2002	142.7	72.0	127.0	130.0	119.8	156.7
	2003	99.4	61.0	114.0	121.0	120.0	130.7
	2004	138.6	134.0	134.0	133.0	146.8	152.3
	2005	99.6	107.0	110.0	108.0	108.8	109.7
	2006	108.4	110.0	108.0	120.0	111.0	114.7
	2007	99.4	87.0	100.0	89.0	101.8	121.7
	2008	98.3	153.0	144.0	139.0	148.0	152.0
	2009	108.0	118.0	111.0	121.0	120.0	122.0
	2010	116.6	76.0	114.0	127.0	117.0	131.3



Appendix 7
Individual Food Consumption (g/animal/day) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	Group / Animal No.	Day (From/To)					
		11/15	15/16	16/17	17/18	18/22	22/25
1M	1001	128.8	135.0	112.0	138.0	125.3	120.3
	1002	162.8	174.0	138.0	183.0	162.3	175.3
	1003	131.3	137.0	124.0	137.0	137.3	140.0
	1004	164.3	148.0	146.0	177.0	168.5	171.0
	1005	108.0	114.0	114.0	119.0	99.3	108.0
	1006	140.3	126.0	115.0	105.0	122.0	128.7
	1007	130.8	138.0	131.0	132.0	125.8	111.7
	1008	114.8	110.0	110.0	109.0	116.8	120.7
	1009	121.3	119.0	106.0	125.0	117.8	116.7
	1010	100.5	102.0	100.0	131.0	99.3	103.3
2M	2001	105.5	91.0	102.0	107.0	116.5	110.0
	2002	150.3	123.0	131.0	124.0	144.3	144.0
	2003	122.8	67.0	105.0	133.0	126.5	126.0
	2004	154.0	144.0	149.0	149.0	148.8	141.0
	2005	109.5	113.0	103.0	123.0	107.8	112.3
	2006	118.3	92.0	103.0	114.0	118.8	118.0
	2007	107.0	98.0	95.0	84.0	112.0	134.7
	2008	152.8	121.0	123.0	141.0	150.3	138.3
	2009	128.8	126.0	129.0	126.0	118.0	131.3
	2010	128.5	62.0	106.0	113.0	127.8	135.3

[REDACTED]

Appendix 7
Individual Food Consumption (g/animal/day) Pretreatment and Dosing Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Animal No.	Day (From/To)		
		25/29	29/30	30/31
1M	1001	142.8	120.0	110.0
	1002	174.8	147.0	141.0
	1003	143.5	121.0	116.0
	1004	177.3	160.0	162.0
	1005	129.8	86.0	105.0
	1006	141.3	119.0	113.0
	1007	131.3	133.0	112.0
	1008	125.0	113.0	92.0
	1009	129.8	131.0	112.0
	1010	115.3	108.0	69.0
2M	2001	118.0	33.0	31.0
	2002	140.5	107.0	106.0
	2003	128.5	126.0	114.0
	2004	149.0	158.0	134.0
	2005	116.3	115.0	97.0
	2006	126.5	107.0	107.0
	2007	132.0	102.0	109.0
	2008	158.5	134.0	137.0
	2009	128.5	127.0	95.0
	2010	135.5	108.0	116.0

Appendix 7
Individual Food Consumption (g/animal/day) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day (From/To)					
		30/31	31/32	32/36	36/39	39/43	43/46
1M	1006	113.0	96.0	103.3	119.3	136.3	134.7
	1007	112.0	125.0	124.0	137.3	132.8	143.0
	1008	92.0	121.0	113.5	106.7	103.5	100.7
	1009	112.0	110.0	120.3	115.0	121.8	136.0
	1010	69.0	113.0	101.8	93.3	86.3	85.0
2M	2006	107.0	115.0	112.5	118.3	121.3	132.3
	2007	109.0	134.0	117.0	112.3	120.0	148.0
	2008	137.0	172.0	133.5	155.7	162.3	157.0
	2009	95.0	142.0	127.5	129.7	123.0	135.0
	2010	116.0	128.0	121.3	112.7	115.5	119.3

Appendix 7
Individual Food Consumption (g/animal/day) Recovery Period

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Animal No.	Day (From/To)	
		46/50	50/52
1M	1006	133.0	136.0
	1007	141.8	136.0
	1008	99.5	104.0
	1009	133.0	130.5
	1010	93.8	103.5
2M	2006	131.3	122.5
	2007	148.8	148.5
	2008	145.3	141.5
	2009	128.8	115.0
	2010	119.0	111.5

Appendix 8
Individual Ophthalmoscopy Findings
Explanation Page

Abbreviation	Description	Abbreviation	Description
Abs	Absence	Inc	Increased
Alt Ref	Altered Reflection	Irreg	Irregular Reflectivity
Ant	Anterior	Mac	Macula
Cap	Capsule	Multi	Multifocal
Ch	Chamber	Myd	Mydriatic
Chor	Choroid	Op	Opacity
Conj	Conjunctiva	Pers	Persistent
Cont	Control	Pers Pup	Persistent Pupillary
Cort	Cortex	Pig	Pigmented/Pigmentation
C/NJ	Cortical/Nuclear Junction	Post	Posterior
Depig	Depigmentation	Refl	Reflectivity
Detach	Detachment	Rej	Rejected
Diff	Diffuse	Ret	Retina
Disch	Discharge	Rupt	Rupture
Dru	Drusen	Subcap	Subcapsular
Foll	Follicular	Subconj	Subconjunctiva
Fov	Fovea	Sut	Suture
Hemo	Hemorrhage	Vac	Vacuole
Hyper	HyperPigmentation	Var Rx	Variation from dosing
Hyperpl	Hyperplasia	Vasc	Vascularization
Hypo	HypoPigmentation	V	Visualize
Incomp Dil	Incomplete Dilation	Visu	Visualized
OD	Right Eye	OS	Left Eye
OU	Both Eyes		
.	No abnormality detected, animal not examined or animal deceased.		
*	Comment present		

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

Only animals and time points with at least one positive ocular findings are presented in this appendix.

Appendix 8Individual Ophthalmoscopy Findings
[REDACTED]

Day numbers relative to Start Date					
Group	Sex	Animal	Clinical Sign	Site	-2 30 51
1	m	1005	Cornea, Opacity, Diffuse	Left Inferior	7 2 .
		1006	Nictitans, Hyperemia	Right	. 2 .
		1007	Cornea, Erosion	Left Inferior	. 2 .
		1008	Cornea, Erosion	Right Superior	. . 7
		1009	Cornea, Erosion	Left	. 2 7
		1010	Cornea, Erosion	Left	. 2 .
			Cornea, Erosion	Right Superior	. 2 .

Severity Codes: X = Present; 2 = 2 Slight; 7 = 7 Small / -

Group 1 - 0

Group 2 - 1x10¹¹ VP

Appendix 8Individual Ophthalmoscopy Findings
[REDACTED]

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	-2	30	51
2	m	2003	Lens Op, Cortex, Ant, Multi	Left	.	7	.
			Lens Op, Cortex, Ant, Multi	Right	.	7	.
		2005	Lens Op, Cortex, Post, Focal	Left Central	7	7	.
			Lens Op, Cortex, Post, Focal	Right Central	7	7	.
		2006	Lens Op, Nucleus, Focal	Left	.	7	7
			Lens Op, Nucleus, Focal	Right	.	7	.
		2007	Cornea, Erosion	Right	.	2	.
		2008	Cornea, Erosion	Right Superior	.	.	7
			Vitreous, Op, Multifocal	Right	7	.	.
		2009	Cornea, Erosion	Left	.	2	2
		2010	Cornea, Erosion	Right	.	.	2
			Cornea, Erosion	Right Central	.	2	.

Severity Codes: X = Present; 2 = 2 Slight; 7 = 7 Small / -

Group 1 - 0

Group 2 - 1x10^11 VP

Appendix 8Individual Ophthalmoscopy Findings
[REDACTED]

					Day numbers relative to Start Date		
Group	Sex	Animal	Clinical Sign	Site	-2	30	51
1	f	1501	Cornea, Erosion	Right Inferior	.	2	.
		1502	Cornea, Erosion	Left	.	2	.
		1503	Cornea, Opacity, Multifocal	Left Superior	.	2	.
		1504	Vitreous, Op, Multifocal	Left	7	.	.
		1505	Cornea, Erosion	Left Superior	.	2	.
		1506	Cornea, Erosion	Right Nasal	.	2	.
		1507	Cornea, Erosion	Left	.	.	2
		1508	Cornea, Erosion	Right Central	.	2	.
		1509	Cornea, Erosion	Left	2	2	.
			Cornea, Erosion	Right	.	2	.

Severity Codes: X = Present; 2 = 2 Slight; 7 = 7 Small / -

Group 1 - 0

Group 2 - 1x10^11 VP

Appendix 8Individual Ophthalmoscopy Findings
[REDACTED]

				Day numbers relative to Start Date	-2	30	51
Group	Sex	Animal	Clinical Sign	Site			
2	f	2501	Cornea, Erosion	Right	2	2	.
		2502	Cornea, Erosion	Left Inferior	2	2	.
		2503	Optic Disc, Cupping	Left	X	X	.
			Optic Disc, Cupping	Right	X	X	.
		2506	Cornea, Erosion	Left Supero-Temporal	2	2	2
			Cornea, Erosion	Right Supero-Temporal	2	2	2
		2508	Lens Op, Cortex, Post, Multi	Left Central	7	7	7
			Vitreous, Op, Focal	Right	7	.	.
		2509	Cornea, Erosion	Left	.	.	2
			Cornea, Erosion	Right	.	.	2
2510			Retina, Vessels, Attenuation	Left	2	2	2
			Retina, Vessels, Attenuation	Right	2	2	2
			Lens Op, Nucleus, Focal	Left	.	.	7
			Lens Op, Nucleus, Focal	Right	.	.	7
			Vitreous, Hyaloid Remnant	Right	X	X	X

Severity Codes: X = Present; 2 = 2 Slight; 7 = 7 Small / -

Group 1 - 0

Group 2 - 1x10^11 VP

Appendix 9

Individual Body Temperature (°C)

Explanation Page

Abbreviation	Description	Abbreviation	Description
PreRx or pr	Predose	PostRx6 or p6	6 hours postdose
PostRx or p	Body temperature recorded on non-dosing days		
--	Animal deceased or collection not scheduled to be performed unless otherwise listed below		

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

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 9
Individual Body Temperature (°C)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day -7 pr	Day 1 p6	Day 2 p	Day 15 pr	Day 16 p6	Day 16 p
1M	1001	39.4	39.4	38.8	39.2	39.1	38.9
	1002	39.5	39.5	38.8	39.1	39.1	38.8
	1003	39.3	39.5	39.0	39.1	39.2	39.0
	1004	39.2	39.5	39.1	39.1	39.4	39.0
	1005	39.2	39.6	38.8	39.0	39.1	39.1
	1006	39.3	39.5	39.3	39.5	39.3	39.3
	1007	39.4	39.4	38.9	38.8	39.1	39.3
	1008	39.3	39.1	38.9	39.1	39.3	39.2
	1009	39.3	39.2	39.3	39.0	39.2	38.8
	1010	39.1	39.5	39.3	39.1	39.4	39.2
2M	2001	39.1	39.5	38.8	39.0	39.1	39.1
	2002	39.2	39.2	39.1	39.9	39.1	39.6
	2003	39.2	39.6	39.0	39.5	39.1	39.7
	2004	39.2	39.3	39.3	39.3	39.1	39.4
	2005	39.2	39.1	39.3	39.0	39.2	39.9
	2006	39.2	39.8	39.3	39.1	39.3	39.6
	2007	38.6	39.6	38.9	39.0	39.0	39.9
	2008	39.1	39.4	39.3	39.6	39.4	39.7
	2009	39.2	39.1	39.3	39.5	38.9	39.1
	2010	39.3	39.3	38.9	39.2	39.1	39.5

Appendix 9
Individual Body Temperature (°C)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day 29 pr	Day 30 p6	Day 30 p	Day 31 p	Day 52 p
1M	1001	39.1	39.0	39.1	39.3	--
	1002	39.2	39.1	39.1	39.0	--
	1003	39.3	39.2	39.6	39.4	--
	1004	39.4	38.9	39.2	39.1	--
	1005	39.3	38.9	39.8	38.9	--
	1006	39.3	39.1	39.4	39.3	39.3
	1007	39.4	39.1	39.3	39.1	39.0
	1008	39.4	39.0	39.0	39.1	38.9
	1009	39.3	38.9	39.2	38.9	39.0
	1010	39.1	38.9	39.1	38.9	38.9
2M	2001	39.1	39.0	38.5	38.8	--
	2002	39.1	39.9	39.0	39.2	--
	2003	39.2	39.4	39.1	39.2	--
	2004	39.1	39.0	39.2	39.1	--
	2005	39.1	39.1	39.0	39.1	--
	2006	39.3	38.9	39.2	39.0	39.3
	2007	39.0	39.3	38.6	38.9	39.0
	2008	39.1	39.3	39.1	39.4	39.0
	2009	39.1	38.9	39.0	38.9	39.2
	2010	39.5	39.3	39.0	39.7	39.2

Appendix 9
Individual Body Temperature (°C)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day -7 pr	Day 1 p6	Day 2 p	Day 15 pr	Day 16 p6	Day 16 p
1F	1501	39.4	39.5	39.3	39.1	39.7	39.2
	1502	39.4	39.6	39.4	39.2	39.5	39.7
	1503	39.4	39.5	39.0	39.2	39.4	39.0
	1504	39.5	39.6	38.9	38.9	39.7	39.5
	1505	39.3	39.2	38.9	38.9	39.4	39.2
	1506	39.5	39.6	39.3	39.1	39.1	39.7
	1507	39.4	39.5	39.3	39.2	39.9	39.7
	1508	39.1	39.5	39.0	39.0	39.1	39.6
	1509	39.5	39.5	39.1	39.0	39.4	39.3
	1510	39.4	39.6	39.4	39.1	39.6	39.7
2F	2501	39.0	39.2	38.8	39.2	39.3	39.1
	2502	39.7	39.7	39.2	39.7	39.3	39.5
	2503	39.1	39.2	38.8	39.2	39.1	39.4
	2504	39.3	39.1	39.2	39.1	39.4	39.7
	2505	39.3	39.4	39.2	39.2	39.4	39.7
	2506	39.2	39.1	39.0	39.3	39.1	39.9
	2507	39.4	39.8	39.2	39.4	39.4	40.0
	2508	39.1	39.4	39.0	39.3	39.3	39.4
	2509	39.2	39.1	38.9	39.7	39.3	39.2
	2510	39.1	39.1	39.1	39.5	39.5	39.0

Appendix 9
Individual Body Temperature (°C)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day 29		Day 30		Day 31		Day 52	
		pr	p6	p	p	p	p	p	p
1F	1501	39.4	39.5	40.1	39.4	--	--	--	--
	1502	39.4	39.4	39.5	39.4	--	--	--	--
	1503	39.2	39.2	39.8	39.6	--	--	--	--
	1504	39.3	39.2	40.0	39.3	--	--	--	--
	1505	39.3	39.1	39.2	39.0	--	--	--	--
	1506	39.2	39.1	39.5	39.7	39.0	39.0	39.0	39.0
	1507	39.4	39.2	39.5	39.5	39.1	39.1	39.1	39.1
	1508	39.4	39.1	39.5	39.2	39.2	39.2	39.2	39.2
	1509	39.2	39.4	39.2	39.5	39.3	39.3	39.3	39.3
	1510	39.6	39.3	39.4	39.6	39.4	39.4	39.4	39.4
2F	2501	39.3	39.1	39.3	39.4	--	--	--	--
	2502	39.3	39.1	38.8	39.1	--	--	--	--
	2503	39.3	39.2	38.8	39.2	--	--	--	--
	2504	39.2	39.1	38.9	39.4	--	--	--	--
	2505	39.8	39.4	39.5	39.5	--	--	--	--
	2506	39.3	39.2	38.9	39.6	39.2	39.2	39.2	39.2
	2507	39.4	39.1	39.6	39.4	39.1	39.1	39.1	39.1
	2508	39.4	39.1	39.2	39.0	39.0	39.0	39.0	39.0
	2509	39.3	39.0	38.9	39.3	38.9	38.9	38.9	38.9
	2510	39.1	39.1	39.0	39.1	39.2	39.2	39.2	39.2

Appendix 10
Individual Haematology, Coagulation and Blood Cell Morphology Values
Explanation Pages

ADVIA 2120i Analyser

Analysed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Erythrocytes Distribution Width	RDW	%	Calculated
Haematocrit	HCT	L/L	Calculated
Haemoglobin	HGB	g/dL	Colorimetric
Mean Corpuscular Haemoglobin	MCH	pg	Calculated
Mean Corpuscular Haemoglobin Concentration	MCHC	g/dL	Calculated
Mean Corpuscular Volume	MCV	fL	Calculated
Mean Platelet Volume	MPV	fL	Calculated
Platelet Count	PLT	$\times 10^9/L$	Light scatter
Red Blood Cell Count	RBC	$\times 10^{12}/L$	Light scatter
Reticulocytes	RETIC	$\times 10^9/L$	Calculated
Reticulocytes Percent	RETIC	%	Light scatter
White Blood Cell Count	WBC	$\times 10^9/L$	Light scatter
White Blood Cell Differential Count			
Neutrophils Percent	NEUT	%	Light scatter
Lymphocytes Percent	LYMPH	%	Light scatter
Monocytes Percent	MONO	%	Light scatter
Eosinophils Percent	EOS	%	Light scatter
Basophils Percent	BASO	%	Light scatter
Large Unstained Cells Percent	LUC	%	Light scatter
Neutrophils	NEUT	$\times 10^9/L$	Calculated
Lymphocytes	LYMPH	$\times 10^9/L$	Calculated
Monocytes	MONO	$\times 10^9/L$	Calculated
Eosinophils	EOS	$\times 10^9/L$	Calculated
Basophils	BASO	$\times 10^9/L$	Calculated
Large Unstained Cells	LUC	$\times 10^9/L$	Calculated
Myeloperoxidase Index	MPXI	%	Calculated staining intensity of Neutrophils relative to the archetype.
PCT	PCT	%	Calculated
Platelet Distribution Width	PDW	%	Calculated
Mean Platelet Component	MPC	g/dL	Calculated
Hemoglobin Concentration Distribution Width	HDW	g/dL	Calculated
Erythrocyte Sedimentation Rate	ESR	mm/h	Modified Westergren method

Siemens HEMA-TEK 2000 Automated Slide Stainer

Analysed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Blood Smear Stain	None		Modified Wright Stain

Appendix 10

Individual Haematology, Coagulation and Blood Cell Morphology Values

Manual and Visual Analysed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
- Red Blood Cell Morphology	RBC MORPH		
- White Blood Cell Morphology	WBC MORPH		
- Platelet Morphology	PLT MORPH		
Cell Morphology Parameters			
Units: 1+ (Minimal), 2+ (Mild), 3+ (Moderate), 4+ (Marked)			
- Cytoplasmic Basophilia Neutrophil	CYTO BASO NEUT	1+, 2+, 3+, 4+	Microscopic Examination
- Polychromasia	POLY	1+, 2+, 3+, 4+	Microscopic Examination
- Anisocytosis	ANISO	1+, 2+, 3+, 4+	Microscopic Examination
- Hypochromasia	HYPOCHROMIA	1+, 2+, 3+, 4+	Microscopic Examination
- Reactive Lymphocytes	REACTIVE LYMPH	1+, 2+, 3+, 4+	Microscopic Examination
- Megakaryocytes	MEGAK	1+, 2+, 3+, 4+	Microscopic Examination
- Smudge Cells	SMUDGE CELL	1+, 2+, 3+, 4+	Microscopic Examination
- Microcytes	MICROCYTES	1+, 2+, 3+, 4+	Microscopic Examination
- Macrocytes	MACROCYTES	1+, 2+, 3+, 4+	Microscopic Examination
- Poikilocytosis	POIK	1+, 2+, 3+, 4+	Microscopic Examination
- Rouleaux Formation	ROULEAUX	1+, 2+, 3+, 4+	Microscopic Examination
- Agglutination	AGGL	1+, 2+, 3+, 4+	Microscopic Examination
- Red Blood Cell Clumping	RBC Clumping	1+, 2+, 3+, 4+	Microscopic Examination
- Acanthocytes	ACAN	1+, 2+, 3+, 4+	Microscopic Examination
- Codocytes	TARGET CELLS	1+, 2+, 3+, 4+	Microscopic Examination
- Dacryocytes	DACR	1+, 2+, 3+, 4+	Microscopic Examination
- Platelet Clumps	PLATELET CLUMPS	1+, 2+, 3+, 4+	Microscopic Examination
- Eccentrocytes	ECCENTCY	1+, 2+, 3+, 4+	Microscopic Examination
- Schistocytes	SCHZ	1+, 2+, 3+, 4+	Microscopic Examination
- Spherocytes	SPHR	1+, 2+, 3+, 4+	Microscopic Examination
- Stomatocytes	STOM	1+, 2+, 3+, 4+	Microscopic Examination
- Howell Jolly Bodies	HJB	1+, 2+, 3+, 4+	Microscopic Examination
- Basophilic Stippling	BASO STIP RBC	1+, 2+, 3+, 4+	Microscopic Examination
- Echinocytes	ECHINO	1+, 2+, 3+, 4+	Microscopic Examination
- Vacuolated Neutrophils	NEUTVAC	1+, 2+, 3+, 4+	Microscopic Examination
- Vacuolated Lymphocytes	LYMVAC	1+, 2+, 3+, 4+	Microscopic Examination
- Döhle Bodies	DOHLE BODY	1+, 2+, 3+, 4+	Microscopic Examination
- Degenerated Cells	DEG CELL	1+, 2+, 3+, 4+	Microscopic Examination
- Ovalocytes	OVAL	1+, 2+, 3+, 4+	Microscopic Examination
- Large Platelets Alpha	LARGE PLATELETS	1+, 2+, 3+, 4+	Microscopic Examination
- Immature Neutrophils Morphology	IMM NEUT MORPH	1+, 2+, 3+, 4+	Microscopic Examination
- Heinz Bodies	HEINZ BODY	1+, 2+, 3+, 4+	Microscopic Examination
- Plasmodium	PLASMOD	1+, 2+, 3+, 4+	Microscopic Examination
- Kurloff Cell	KURL	1+, 2+, 3+, 4+	Microscopic Examination
- Burr Cells	BURR	1+, 2+, 3+, 4+	Microscopic Examination
- Neutrophils Band Form Morphology	NEUT BAND MORPH	1+, 2+, 3+, 4+	Microscopic Examination

Appendix 10**Individual Haematology, Coagulation and Blood Cell Morphology Values****Cell Morphology Parameters**

Units: 1+ (Minimal), 2+ (Mild), 3+ (Moderate), 4+ (Marked)

	Abbreviation	Units	Methodology
- Nuclear Swelling	NUC SWELL NEUT	1+, 2+, 3+, 4+	Microscopic Examination
- Toxic Granulation	TOXG	1+, 2+, 3+, 4+	Microscopic Examination

Parameter

	Abbreviation	Units	Methodology
Nucleated Red blood Cells/100 Leukocytes	RBCNUCLE	#/100WBC	Microscopic Examination
Heinz Bodies Percent	HEINZ BODY	%	Microscopic examination. Methyl violet in physiological saline
Reticulocyte Percent	RETIC	%	Microscopic enumeration, new methylene blue stain

Sysmex CS-2000i

Analysed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Activated Partial Thromboplastin Time	APTT	sec	Turbidimetric
Fibrinogen	FIB	mg/dL	Turbidimetric
Fibrinogen (SI)	FIB	g/L	Turbidimetric
Prothrombin Time	PT	sec	Turbidimetric
von Willebrand Factor AG	VWF AG	%	Immunoturbidimetric

**Plasma Appearance
(Reported as SAMQ PLASMA)**

Analysed Parameter Descriptions

Parameter	Abbreviation	Degree is graded as	Methodology
Normal sample	N	Normal	Manual and visual
Haemolysed sample	H	+ = mild ++ = moderate +++ = marked	Manual and visual
Lipaemic sample	L	+ = mild ++ = moderate +++ = marked	Manual and visual
Icterus sample	I	+ = mild ++ = moderate +++ = marked	Manual and visual
Atypical sample	A	Color is identified	Manual and visual

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

Appendix 10

Individual Haematology, Coagulation and Blood Cell Morphology Values

Clinical Pathology Data Flags

Abbreviation	Description
--	No sample or no result. The exception is Urine Microscopic, Red and White Blood Cell Morphology and Platelet Morphology where it denotes an abnormal finding in one or more parameters
ADQ	Adequate
AVS	Suspected aberrant value
BE0	Volume below 0.1mL
CLOT	Sample clotted
COM	Contaminated with organic material
COME	See comment value excluded
COMI	See comment value included
COMM	Comment added
DEC	Decreased
Exc	Exclude
GFC	Gross fecal contamination present
INC	Increased
INV	Invalid result
IRPS	Presence of abundant plasmodium species
ISH	Result invalid due to severe haemolysis
ISL	Result invalid due to severe lipaemia
L100	Less than 100 cells used to perform differential
LLOQ	Less than lower limit of quantification
MDIFF	Manual differential
NA	Not applicable
NAF	No abnormal findings
NC	Not calculable
NCD	No clot detected
NRBC	WBC corrected for presence of nucleated RBC
NSCH	Not scheduled to be performed
OA	Omitted activity
OOS	Sample analysed outside of established stability, results for information only
QNS	Quantity not sufficient
RSV	Refer to source values
S	Spillage
SAMU	Large number of smudge cells
SNC	Sample not collected
SNR	Sample not received
SVGS	Sample volume greater than specified
SVLS	Sample volume less than specified
TERR	Technical error (explanation required)
TNP	Test not performed
TNR	Test not reported
UNCR	Results are not reproducible
UNEX	Unscheduled data excluded from statistics
UPTD	Unable to perform due to technical difficulty
UTC	Unable to collect
UTD	Unable to determine
UTDH	Unable to determine due to marked haemolysis
UTDL	Unable to determine due to marked lipaemia

Appendix 10
Individual Haematology, Coagulation and Blood Cell Morphology Values

Clinical Pathology Data Flags

Abbreviation	Description
UTDM	Unable to determine results, not confirmed by microscopy
UTDR	Unable to determine results not reproducible
VARR	Assigned value above reportable range
VBRR	Assigned value below reportable range
VNC	Value not calculable
X	Excluded from mean

Note: This is a comprehensive list of clinical pathology data flags. All of the data flags listed may not be applicable to this report.

Additional Abbreviations

Time Point	Description
REP1	Repeat sample
Un1	Diagnostic sample collected for welfare reasons (noted below if applicable) or sample collected from unscheduled decedent.

Additional Samples

Time Point (Day of Collection)	Animal No.	Explanation
Males		
Pretreatment (Day -2)	1007, 2005	Original coagulation samples clotted.
	1008, 1010, 2004	Original haematology and coagulation samples clotted.
	2007	Original haematology samples clotted.
Females		
Pretreatment (Day -2)	1502, 1507	Original coagulation samples clotted.
	1505, 1510, 2510	Original haematology and coagulation samples clotted.

Appendix 11
Individual Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Animal		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
Sex	No.							
1M	1001	5.38	1.05	3.69	0.03	0.15	0.46	0.01
	1002	5.26	1.20	3.42	0.04	0.17	0.41	0.03
	1003	5.98	0.83	4.43	0.04	0.20	0.47	0.01
	1004	5.50	1.15	3.76	0.07	0.12	0.39	0.01
	1005	6.90	2.41	3.84	0.06	0.10	0.46	0.02
	1006	5.33	0.92	3.79	0.07	0.11	0.40	0.05
	1007	5.08	0.80	3.72	0.05	0.07	0.42	0.02
	1008	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	1009	6.47	1.28	4.54	0.05	0.14	0.45	0.02
	1010	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
2M	2001	5.51	1.16	3.79	0.05	0.13	0.36	0.02
	2002	4.88	1.25	2.93	0.06	0.11	0.51	0.02
	2003	5.36	1.44	3.13	0.12	0.09	0.57	0.02
	2004	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	2005	4.63	0.75	3.28	0.05	0.11	0.43	0.01
	2006	5.66	1.49	3.63	0.08	0.11	0.34	0.01
	2007	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	2008	5.05	1.29	3.11	0.13	0.11	0.40	0.01
	2009	7.40	1.02	5.36	0.24	0.21	0.55	0.02
	2010	4.81	0.59	3.75	0.11	0.10	0.25	0.01

Appendix 11
Individual Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Animal	Sex	No.	RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1M	1001	6.50	13.2	0.406	62.5	20.3	32.4	12.8	
	1002	6.17	12.6	0.393	63.8	20.5	32.1	12.1	
	1003	6.37	12.8	0.390	61.2	20.1	32.8	13.3	
	1004	6.05	13.6	0.420	69.4	22.5	32.4	12.8	
	1005	6.42	12.8	0.408	63.6	19.9	31.3	13.0	
	1006	5.89	12.9	0.390	66.3	21.9	33.0	12.0	
	1007	7.05	14.3	0.448	63.5	20.3	32.0	13.0	
	1008	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	
	1009	6.56	12.7	0.387	59.0	19.4	32.8	13.1	
	1010	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	
2M	2001	6.37	13.1	0.402	63.0	20.6	32.7	13.2	
	2002	6.42	13.9	0.423	65.8	21.6	32.8	13.1	
	2003	6.35	13.0	0.402	63.3	20.5	32.4	12.6	
	2004	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	
	2005	6.66	13.9	0.425	63.8	20.9	32.8	13.1	
	2006	6.28	13.1	0.406	64.6	20.9	32.3	13.4	
	2007	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	
	2008	7.03	15.0	0.457	65.0	21.3	32.7	13.4	
	2009	6.15	13.2	0.400	65.1	21.5	33.0	12.4	
	2010	6.45	13.1	0.404	62.6	20.3	32.4	13.6	

Appendix 11
Individual Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L	SAMQ PLASMA
1M	1001	232	206.7	11.9	12.2	2.59	N	
	1002	337	106.9	12.1	13.6	2.21	N	
	1003	374	172.1	12.0	13.5	2.13	N	
	1004	377	86.3	13.5	12.6	2.65	N	
	1005	257	105.0	11.9	13.8	2.39	N	
	1006	219	113.1	12.9	12.7	2.10	N	
	1007	--UTDM	111.4	--CLOT	--CLOT	--CLOT	--CLOT	
	1008	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	
	1009	289	120.5	11.1	12.9	1.89	N	
	1010	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	
2M	2001	331	141.2	12.4	11.4	2.21	N	
	2002	232	108.0	12.0	13.3	2.30	N	
	2003	290	85.4	11.8	12.4	2.71	N	
	2004	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	
	2005	151	143.8	--CLOT	--CLOT	--CLOT	--CLOT	
	2006	394	151.8	11.7	11.1	3.35	N	
	2007	--CLOT	--CLOT	14.7	10.9	1.20	N	
	2008	236	92.2	11.6	11.5	3.53	N	
	2009	264	121.8	11.9	12.8	2.26	N	
	2010	152	147.9	16.8	12.0	1.75	N	

Appendix 11

Individual Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1×10^{11} vp

Appendix 11

Individual Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1×10^{11} vp

Appendix 11

Individual Haematology and Coagulation Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1×10^{11} vp

Appendix 11
Individual Haematology and Coagulation Values Pretreatment Repeat Samples (Day -2)

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Sex	Group / Animal No.	WBC 10 ⁹ /L		NEUT 10 ⁹ /L		LYMPH 10 ⁹ /L		MONO 10 ⁹ /L		EOS 10 ⁹ /L		BASO 10 ⁹ /L		LUC 10 ⁹ /L	
1M	1007	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	1008	5.09XExc	1.35XExc	2.86XExc	0.24XExc	0.26XExc	0.36XExc	0.02XExc							
	1010	6.07XExc	1.39XExc	4.04XExc	0.19XExc	0.08XExc	0.33XExc	0.02XExc							
2M	2004	6.89XExc	1.37XExc	4.54XExc	0.16XExc	0.17XExc	0.60XExc	0.05XExc							
	2005	--	--	--	--	--	--	--							
	2007	7.89XExc	1.54XExc	5.25XExc	0.17XExc	0.11XExc	0.79XExc	0.03XExc							

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 11
Individual Haematology and Coagulation Values Pretreatment Repeat Samples (Day -2)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal Sex	No.	RBC 10^12/L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1M	1007	--	--	--	--	--	--	--
	1008	5.79XExc	12.3XExc	0.380XExc	65.6XExc	21.3XExc	32.4XExc	13.3XExc
	1010	5.92XExc	12.5XExc	0.389XExc	65.8XExc	21.0XExc	32.0XExc	13.4XExc
2M	2004	5.61XExc	12.1XExc	0.378XExc	67.3XExc	21.5XExc	32.0XExc	14.6XExc
	2005	--	--	--	--	--	--	--
	2007	5.98XExc	12.9XExc	0.400XExc	66.9XExc	21.6XExc	32.3XExc	13.0XExc

Appendix 11
Individual Haematology and Coagulation Values Pretreatment Repeat Samples (Day -2)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L	SAMQ PLASMA
1M	1007	--	--	--	--CLOT	--CLOT	--CLOT	--CLOT
	1008	318XExc	192.1XExc	12.1XExc	10.9XExc	1.86XExc	N	
	1010	247XExc	189.0XExc	10.9XExc	11.5XExc	2.17XExc	N	
2M	2004	433XExc	236.8XExc	10.6XExc	14.2XExc	2.21XExc	N	
	2005	--	--	11.8XExc	13.4XExc	2.35XExc	N	
	2007	267XExc	235.6XExc	--	--	--	--	

Appendix 11
Individual Haematology and Coagulation Values Pretreatment Repeat Samples (Day -2)

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Sex	Group / Animal No.	Animal							
		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L	
1F	1502	--	--	--	--	--	--	--	
	1505	6.44XExc	1.48XExc	3.92XExc	0.22XExc	0.10XExc	0.69XExc	0.03XExc	
	1507	--	--	--	--	--	--	--	
	1510	4.95XExc	1.50XExc	2.65XExc	0.12XExc	0.22XExc	0.30XExc	0.17XExc	
2F	2510	5.66XExc	1.77XExc	3.00XExc	0.06XExc	0.13XExc	0.67XExc	0.02XExc	

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 11
Individual Haematology and Coagulation Values Pretreatment Repeat Samples (Day -2)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	RBC 10^12/L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1F	1502	--	--	--	--	--	--	--
	1505	6.01XExc	12.3XExc	0.388XExc	64.5XExc	20.4XExc	31.6XExc	14.1XExc
	1507	--	--	--	--	--	--	--
	1510	5.87XExc	12.1XExc	0.371XExc	63.2XExc	20.6XExc	32.6XExc	13.6XExc
2F	2510	5.99XExc	12.1XExc	0.370XExc	61.8XExc	20.2XExc	32.7XExc	13.4XExc

Appendix 11
Individual Haematology and Coagulation Values Pretreatment Repeat Samples (Day -2)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L	SAMQ PLASMA
1F	1502	--	--	11.8XExc	13.5XExc	2.65XExc	N
	1505	357XExc	206.6XExc	12.2XExc	13.1XExc	1.94XExc	N
	1507	--	--	11.0XExc	15.0XExc	2.35XExc	N
	1510	210XExc	181.6XExc	13.5XExc	13.6XExc	1.42XExc	N
2F	2510	288XExc	210.1XExc	11.7XExc	13.9XExc	2.11XExc	N

Appendix 11
Individual Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
Sex	No.							
1M	1001	5.56	1.02	4.01	0.05	0.10	0.38	0.01
	1002	5.08	1.39	3.10	0.04	0.15	0.38	0.01
	1003	6.24	0.85	4.44	0.17	0.25	0.52	0.02
	1004	5.67	1.11	4.00	0.16	0.07	0.32	0.01
	1005	5.28	1.00	3.73	0.04	0.09	0.40	0.02
	1006	5.27	0.76	3.91	0.06	0.08	0.43	0.03
	1007	5.57	0.75	4.11	0.04	0.08	0.56	0.03
	1008	4.70	0.63	3.74	0.03	0.07	0.22	0.02
	1009	6.09	1.28	4.22	0.03	0.14	0.42	0.01
	1010	5.48	0.90	4.12	0.07	0.08	0.30	0.02
2M	2001	4.87	0.71	3.79	0.07	0.06	0.23	0.01
	2002	4.93	1.23	2.74	0.54	0.09	0.29	0.05
	2003	4.99	0.68	3.54	0.23	0.08	0.45	0.01
	2004	5.91	1.07	4.00	0.28	0.12	0.42	0.03
	2005	5.02	0.64	3.84	0.08	0.08	0.37	0.01
	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	2007	4.20	0.56	3.21	0.03	0.06	0.33	0.01
	2008	4.91	1.42	2.97	0.11	0.06	0.34	0.01
	2009	6.28	0.72	4.74	0.23	0.11	0.43	0.04
	2010	4.84	0.63	3.74	0.08	0.08	0.29	0.01

Appendix 11
Individual Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1M	1001	5.94	12.2	0.377	63.5	20.5	32.2	13.6
	1002	5.84	11.9	0.375	64.2	20.5	31.8	13.2
	1003	6.33	12.7	0.395	62.4	20.1	32.3	14.6
	1004	5.62	12.4	0.390	69.4	22.1	31.8	14.0
	1005	5.76	11.6	0.365	63.5	20.2	31.8	14.7
	1006	5.64	12.2	0.376	66.8	21.6	32.3	14.0
	1007	6.39	13.0	0.402	62.9	20.4	32.4	14.3
	1008	5.63	12.0	0.371	65.8	21.3	32.3	14.1
	1009	6.13	12.1	0.366	59.8	19.8	33.1	14.8
	1010	6.00	12.6	0.400	66.7	21.0	31.4	13.8
2M	2001	5.88	12.1	0.374	63.5	20.6	32.5	14.5
	2002	5.72	12.5	0.378	66.1	21.8	33.0	14.0
	2003	5.69	11.1	0.357	62.8	19.6	31.2	13.3
	2004	5.25	11.5	0.354	67.4	21.8	32.4	14.6
	2005	6.03	12.5	0.388	64.3	20.8	32.3	14.1
	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	2007	5.95	12.7	0.390	65.6	21.3	32.5	13.3
	2008	5.72	12.0	0.370	64.7	21.1	32.6	14.3
	2009	5.75	12.4	0.379	65.9	21.6	32.8	13.2
	2010	5.63	11.4	0.346	61.4	20.3	33.0	14.7

Appendix 11
Individual Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L	SAMQ PLASMA
1M	1001	271	310.3	11.8	12.4	2.47	N	
	1002	273	181.9	13.8	11.8	1.89	N	
	1003	308	335.1	11.7	13.1	2.28	N	
	1004	365	195.4	11.9	13.3	2.97	N	
	1005	273	257.5	11.7	14.1	2.51	N	
	1006	195	266.7	11.1	13.8	2.80	N	
	1007	159	207.9	11.6	12.8	2.47	N	
	1008	108	229.7	14.9	10.6	1.19	N	
	1009	272	257.2	10.5	12.6	2.02	N	
	1010	185	248.7	11.6	11.9	2.24	N	
2M	2001	375	246.2	10.9	12.6	4.43	N	
	2002	184	155.7	12.3	12.6	4.22	N	
	2003	260	144.6	12.4	11.6	4.48	N	
	2004	407	244.7	10.6	13.4	4.19	N	
	2005	193	244.6	11.1	11.9	5.12	N	
	2006	--CLOT	--CLOT	11.0	11.1	4.78	N	
	2007	160	217.8	10.8	12.7	4.16	N	
	2008	291	160.5	11.3	12.2	4.35	N	
	2009	218	213.8	11.0	11.9	4.94	N	
	2010	313	194.5	11.2	14.0	4.19	N	

Appendix 11
Individual Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
Sex	No.							
1F	1501	7.13	2.41	3.96	0.11	0.13	0.42	0.09
	1502	6.31	1.26	4.45	0.04	0.09	0.45	0.02
	1503	4.30	0.86	2.92	0.12	0.10	0.29	0.02
	1504	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	1505	7.89	1.93	4.92	0.14	0.14	0.74	0.03
	1506	5.30	1.03	3.61	0.05	0.10	0.48	0.02
	1507	5.28	1.08	3.68	0.05	0.07	0.38	0.02
	1508	5.54	1.67	3.40	0.05	0.09	0.32	0.02
	1509	6.39	1.25	4.53	0.05	0.11	0.41	0.03
	1510	4.89	1.04	3.36	0.11	0.07	0.28	0.03
2F	2501	7.52	1.72	4.37	0.51	0.13	0.74	0.05
	2502	4.82	1.19	3.10	0.11	0.08	0.28	0.05
	2503	4.93	2.07	2.17	0.15	0.10	0.44	--MDIFF
	2504	6.65	1.43	4.35	0.38	0.09	0.35	0.06
	2505	4.91	0.86	3.44	0.14	0.20	0.22	0.05
	2506	4.31	0.68	2.91	0.36	0.06	0.26	0.04
	2507	5.57	0.98	3.75	0.32	0.10	0.39	0.03
	2508	4.22	0.62	2.98	0.12	0.09	0.34	0.08
	2509	5.02	2.51	1.91	0.15	0.00	0.45	--MDIFF
	2510	5.35	0.90	3.62	0.17	0.07	0.57	0.02

Appendix 11
Individual Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1F	1501	5.59	12.0	0.377	67.4	21.4	31.8	14.0
	1502	5.99	12.0	0.376	62.7	20.0	31.8	13.2
	1503	5.76	12.2	0.383	66.6	21.2	31.8	13.3
	1504	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT	--CLOT
	1505	5.98	12.3	0.386	64.5	20.5	31.8	14.5
	1506	5.67	11.3	0.353	62.2	19.8	31.9	13.6
	1507	6.00	12.7	0.391	65.2	21.1	32.4	13.3
	1508	5.69	11.7	0.365	64.2	20.6	32.1	13.5
	1509	5.85	12.7	0.389	66.5	21.7	32.7	13.4
	1510	5.71	11.6	0.367	64.3	20.4	31.7	14.4
2F	2501	6.48	11.9	0.390	60.2	18.4	30.6	13.2
	2502	5.60	11.6	0.352	62.8	20.8	33.0	13.7
	2503	5.71	11.1	0.359	62.8	19.5	31.0	13.0
	2504	6.36	11.6	0.359	56.4	18.2	32.3	13.4
	2505	5.98	12.3	0.388	64.8	20.5	31.7	13.9
	2506	5.60	11.3	0.351	62.6	20.2	32.2	14.6
	2507	5.45	11.2	0.349	64.0	20.5	32.0	12.9
	2508	5.75	12.2	0.370	64.3	21.2	33.0	13.1
	2509	6.16	11.6	0.366	59.4	18.8	31.7	13.1
	2510	5.91	12.0	0.366	61.9	20.2	32.7	13.9

Appendix 11
Individual Haematology and Coagulation Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L	SAMQ PLASMA
Sex	No.						
1F	1501	235	189.6	11.3	15.0	2.08	N
	1502	287	190.9	11.8	14.2	2.21	N
	1503	246	295.9	11.9	11.1	2.80	N
	1504	--CLOT	--CLOT	12.6	12.1	1.91	N
	1505	337	265.0	12.2	12.4	2.02	N
	1506	393	218.9	12.4	13.4	2.08	N
	1507	288	240.6	11.9	14.7	2.14	N
	1508	347	192.3	12.1	13.1	1.99	N
	1509	329	203.1	12.4	12.4	2.17	N
	1510	289	226.8	12.1	14.3	1.45	N
2F	2501	216	169.2	12.3	13.5	4.31	N
	2502	161	157.3	10.4	12.7	3.69	N
	2503	208	246.2	12.1	12.4	4.08	N
	2504	316	191.9	11.9	13.0	4.78	N
	2505	123	212.8	11.6	12.0	4.43	N
	2506	309	214.0	11.7	13.8	3.88	N
	2507	408	241.6	11.2	12.0	4.10	N
	2508	150	173.7	12.0	13.0	4.31	N
	2509	395	162.2	11.7	13.0	4.16	N
	2510	271	190.3	11.4	13.6	3.88	N

Appendix 11
Individual Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	Group / Animal No.						
		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L
1M	1001	5.82	0.85	4.27	0.05	0.11	0.53
	1002	5.01	1.05	3.30	0.06	0.11	0.44
	1003	8.58	2.61	4.64	0.19	0.27	0.81
	1004	7.87	2.86	4.15	0.29	0.09	0.45
	1005	5.63	1.02	3.70	0.11	0.13	0.62
2M	2001	5.24	0.80	3.89	0.14	0.07	0.31
	2002	4.97	1.14	2.85	0.35	0.08	0.52
	2003	6.13	0.85	4.20	0.10	0.12	0.61
	2004	7.36	1.81	4.59	0.10	0.14	0.68
	2005	6.67	1.13	4.70	0.08	0.10	0.58

Appendix 11
Individual Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1M	1001	6.54	13.5	0.407	62.2	20.7	33.2	11.6
	1002	6.08	12.7	0.389	64.0	21.0	32.8	12.5
	1003	6.49	13.2	0.407	62.7	20.4	32.5	12.9
	1004	5.58	12.7	0.389	69.7	22.7	32.6	13.4
	1005	5.98	12.4	0.383	64.0	20.8	32.5	12.4
2M	2001	6.35	13.4	0.403	63.5	21.1	33.3	12.2
	2002	6.15	13.3	0.412	67.0	21.6	32.2	13.2
	2003	5.98	12.3	0.386	64.5	20.5	31.8	13.5
	2004	5.58	12.7	0.377	67.5	22.8	33.8	13.1
	2005	6.14	13.2	0.400	65.2	21.5	33.0	12.6

Appendix 11
Individual Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L	SAMQ PLASMA
1M	1001	319	190.9	10.5	11.4	2.49	N	
	1002	318	155.3	11.4	12.3	1.80	N	
	1003	296	190.8	10.7	13.3	2.13	N	
	1004	362	149.7	10.4	12.8	3.53	N	
	1005	256	140.4	10.7	13.0	2.39	N	
2M	2001	472	139.1	10.1	10.8	5.08	N	
	2002	282	152.7	10.0	12.6	3.95	N	
	2003	428	142.9	10.2	12.4	4.46	N	
	2004	455	152.2	9.8	12.5	3.63	N	
	2005	264	162.0	10.3	11.4	4.46	N	

Appendix 11
Individual Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
Sex	No.							
1F	1501	7.98	2.71	4.53	0.12	0.15	0.43	0.04
	1502	5.51	2.09	2.76	0.11	0.11	0.44	--MDIFF
	1503	4.64	1.19	2.92	0.07	0.08	0.36	0.02
	1504	7.44	1.57	4.81	0.14	0.16	0.73	0.03
	1505	6.09	1.55	3.81	0.10	0.12	0.48	0.02
2F	2501	9.26	2.61	5.33	0.26	0.13	0.84	0.08
	2502	4.32	0.66	3.04	0.17	0.07	0.36	0.02
	2503	6.56	1.36	3.97	0.26	0.17	0.74	0.06
	2504	7.11	2.20	4.19	0.21	0.07	0.43	--MDIFF
	2505	7.07	1.41	4.85	0.21	0.10	0.41	0.10

Appendix 11
Individual Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1F	1501	5.49	12.0	0.378	68.8	21.9	31.8	13.3
	1502	6.56	13.7	0.425	64.9	20.9	32.2	12.2
	1503	5.79	12.5	0.388	67.1	21.6	32.2	12.3
	1504	5.53	11.9	0.361	65.2	21.6	33.1	12.0
	1505	5.85	12.5	0.388	66.3	21.4	32.3	13.1
2F	2501	6.42	12.2	0.383	59.7	19.0	31.8	13.5
	2502	5.87	12.2	0.371	63.3	20.8	32.9	12.8
	2503	5.78	11.7	0.363	62.8	20.3	32.3	12.1
	2504	6.40	12.3	0.375	58.6	19.2	32.8	12.8
	2505	5.75	12.0	0.383	66.6	20.9	31.3	13.1

Appendix 11
Individual Haematology and Coagulation Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L	SAMQ PLASMA
Sex	No.						
1F	1501	242	162.0	10.2	13.9	1.99	N
	1502	375	147.7	10.3	14.4	2.13	N
	1503	306	241.8	10.9	11.7	2.83	N
	1504	277	150.6	10.7	13.5	1.67	N
	1505	319	197.7	15.0	11.3	1.04	N
2F	2501	323	168.8	10.8	13.3	3.11	N
	2502	262	121.3	10.1	12.5	3.27	N
	2503	331	182.6	10.6	13.0	3.53	N
	2504	430	178.0	11.2	14.0	2.26	N
	2505	323	217.2	9.9	13.7	3.73	N

Appendix 11
Individual Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	Group / Animal No.							
		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
1M	1006	5.90	0.95	4.38	0.06	0.08	0.42	0.01
	1007	6.58	1.28	4.34	0.06	0.13	0.73	0.03
	1008	7.76	1.32	5.67	0.07	0.11	0.58	0.02
	1009	6.66	1.45	4.48	0.06	0.19	0.46	0.02
	1010	7.13	0.93	5.66	0.05	0.12	0.35	0.02
2M	2006	4.94	0.86	3.58	0.06	0.10	0.33	0.01
	2007	4.22	0.55	3.27	0.03	0.05	0.31	0.00
	2008	4.22	1.20	2.44	0.04	0.08	0.45	0.01
	2009	8.38	1.60	5.86	0.08	0.19	0.63	0.02
	2010	5.56	0.68	4.31	0.04	0.12	0.40	0.01

Appendix 11
Individual Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1M	1006	6.22	13.6	0.417	67.0	21.9	32.7	12.5
	1007	6.77	14.1	0.444	65.6	20.8	31.7	13.9
	1008	6.29	13.6	0.419	66.7	21.7	32.5	12.6
	1009	6.94	14.1	0.428	61.6	20.3	32.9	12.6
	1010	6.50	13.9	0.440	67.6	21.4	31.7	12.0
2M	2006	6.63	14.2	0.429	64.7	21.5	33.2	13.5
	2007	6.48	13.8	0.432	66.7	21.3	32.0	12.4
	2008	6.08	13.4	0.405	66.6	22.1	33.1	13.6
	2009	6.15	13.4	0.404	65.7	21.9	33.3	12.8
	2010	6.56	13.3	0.407	62.1	20.3	32.7	13.5

Appendix 11
Individual Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L	SAMQ PLASMA
1M	1006	279	179.3	10.9	12.9	2.44	N	
	1007	315	180.8	11.6	12.4	1.99	N	
	1008	328	158.8	10.7	12.0	1.85	N	
	1009	287	163.7	10.1	12.6	2.18	N	
	1010	168	107.0	10.7	10.8	1.80	N	
2M	2006	386	148.1	11.5	11.3	2.08	N	
	2007	219	166.5	10.4	12.9	2.08	N	
	2008	340	121.2	11.9	12.2	2.32	N	
	2009	273	162.4	11.0	11.9	1.88	N	
	2010	267	140.3	12.4	13.5	1.78	N	

Appendix 11
Individual Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		WBC 10 ⁹ /L	NEUT 10 ⁹ /L	LYMPH 10 ⁹ /L	MONO 10 ⁹ /L	EOS 10 ⁹ /L	BASO 10 ⁹ /L	LUC 10 ⁹ /L
Sex	No.							
1F	1506	6.03	1.13	4.03	0.04	0.13	0.68	0.02
	1507	4.74	0.87	3.23	0.04	0.12	0.48	0.01
	1508	5.20	1.20	3.34	0.05	0.15	0.45	0.01
	1509	6.01	1.07	4.10	0.11	0.16	0.56	0.01
	1510	5.05	1.17	3.33	0.04	0.11	0.39	0.02
2F	2506	5.31	1.37	3.30	0.05	0.13	0.46	0.00
	2507	5.55	1.28	3.47	0.07	0.13	0.58	0.02
	2508	5.20	0.92	3.65	0.03	0.13	0.45	0.02
	2509	6.02	1.44	3.85	0.05	0.12	0.54	0.02
	2510	6.95	2.74	3.12	0.13	0.13	0.78	0.05

Appendix 11
Individual Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		RBC 10 ¹² /L	HGB g/dL	HCT L/L	MCV fL	MCH pg	MCHC g/dL	RDW %
1F	1506	6.54	13.0	0.411	62.8	19.9	31.7	12.1
	1507	6.52	13.5	0.409	62.8	20.6	32.9	11.8
	1508	6.53	13.3	0.406	62.2	20.4	32.8	11.2
	1509	6.36	13.8	0.423	66.5	21.7	32.6	11.7
	1510	6.22	13.2	0.399	64.2	21.2	33.1	12.1
2F	2506	6.73	13.2	0.420	62.3	19.6	31.5	13.6
	2507	6.63	13.4	0.416	62.7	20.2	32.1	12.4
	2508	6.64	13.8	0.423	63.8	20.7	32.5	12.5
	2509	6.85	12.7	0.401	58.6	18.5	31.6	13.6
	2510	6.91	13.9	0.427	61.7	20.1	32.6	12.9

Appendix 11
Individual Haematology and Coagulation Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		PLT 10 ⁹ /L	RETIC 10 ⁹ /L	PT sec	APTT sec	FIB g/L	SAMQ PLASMA
Sex	No.						
1F	1506	375	128.0	13.0	15.2	1.59	N
	1507	298	122.4	10.8	16.8	1.96	N
	1508	225	58.7	11.9	15.2	1.65	N
	1509	368	114.2	11.2	13.6	1.91	N
	1510	388	127.3	11.4	17.1	1.29	N
2F	2506	315	139.4	12.4	14.2	1.65	N
	2507	303	81.5	11.6	13.3	2.08	N
	2508	295	134.1	12.4	15.6	1.83	N
	2509	367	128.2	11.6	13.8	1.83	N
	2510	290	133.0	10.5	13.6	2.94	N

Appendix 12
Individual Blood Cell Morphology Values

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day	ANISO	POLY	ECHINO	RBCNUCLE #/100 WBC	PLT MORPH
1M	1007	-5	1+	1+	1+	--	--
2M	2003	31	1+	1+	2+	--	NAF
	2004	31	1+	1+	1+	--	NAF
	2006	52	1+	1+	--	1	--

Appendix 12
Individual Blood Cell Morphology Values

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day	PLATELET CLUMPS	WBC MORPH
1M	1007	-5	4+	NAF
2M	2003	31	--	NAF
	2004	31	--	NAF
	2006	52	2+	NAF

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 12
Individual Blood Cell Morphology Values

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day	ANISO	POLY	ECHINO	RBCNUCLE #/100 WBC	PLT MORPH
1F	1502	31	1+	1+	3+	--	--
	1508	-5	2+	1+	--	--	--
2F	2501	31	--	1+	1+	--	NAF
	2502	3	1+	1+	2+	--	--
	31		1+	1+	1+	--	NAF
2503	3		1+	1+	2+	--	NAF
	31		1+	1+	--	--	--
2504	31		1+	1+	1+	--	--
2505	31		--	1+	2+	--	NAF
2508	-5		2+	1+	1+	--	--
2509	3		1+	--	3+	--	NAF
2510	3		1+	1+	3+	2	NAF

Appendix 12
Individual Blood Cell Morphology Values

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day	PLATELET CLUMPS	WBC MORPH
1F	1502	31	2+	NAF
	1508	-5	1+	NAF
2F	2501	31	--	NAF
	2502	3	3+	NAF
	31		--	NAF
	2503	3	--	NAF
	31		3+	NAF
	2504	31	2+	NAF
2505	31		--	NAF
2508	-5		4+	NAF
2509	3		--	NAF
2510	3		--	NAF



Appendix 13
Individual Clinical Chemistry and C-Reactive Protein Values
Explanation Pages

P Module 800

Analysed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
3-Hydroxybutyrate	3-HB	µmol/L	Enzymatic colorimetric
5-Nucleotidase	5-NT	U/L	Enzymatic colorimetric
Alanine Aminotransferase	ALT	U/L	ALT IFCC UV
Albumin	ALB	g/L	Brom cresol green colorimetric
Albumin Rabbit	RALB	g/L	Brom cresol green colorimetric
Alkaline Phosphatase	ALP	U/L	ALP IFCC liquid colorimetric
Amylase	AMYL	U/L	Enzymatic colorimetric
Ammonia	AMM	µg/dL	Enzymatic kinetic
Aspartate Aminotransferase	AST	U/L	AST IFCC UV
Bile Acids	BILEAC	µmol/L	Enzymatic colorimetric
Bile Acids Plasma	BILEAC-P	µmol/L	Enzymatic colorimetric
Bicarbonate	CO2	mmol/L	PEPC enzymatic colorimetric method
Calcium	CA	mmol/L	NM-BAPTA
Chloride	CL	mmol/L	Indirect measurement (Ion selective electrode)
Cholesterol	CHOL	mmol/L	CHOD-PAP enzymatic colorimetric
C3c	C3C	mg/dL	Immunoturbidimetric
C4	C4	mg/dL	Immunoturbidimetric
Creatine Kinase	CK	U/L	CK IFCC UV
CK MB Isoenzyme	CK MB	U/L	Immunological colorimetric.
Creatinine	CREAT	µmol/L	Jaffe kinetic colorimetric. Rate-blanked and compensated
C-Reactive Protein	CRP	mg/dL	Immunoturbidimetric
D-Dimer	DDIM	µg/mL	Immunoturbidimetric
Direct Bilirubin	DBIL	µmol/L	Diazo Method
Gamma-Glutamyl Transferase	GGT	U/L	Nitro-Anilide, Glycylglycine; enzymatic colorimetric
Ferritin	FERR	ng/mL	Immunoturbidimetric
Fructosamine	FRUC	µmol/L	Colorimetric
Glucose	GLUC	mmol/L	Hexokinase UV
Glutamate Dehydrogenase	GLDH	U/L	GLDH UV
Glycosylated Haemoglobin Percent	GLY HGB	%	Turbidimetric inhibition immunoassay
Haptoglobin	HAPTO	g/L	Colorimetric
HDL Cholesterol	HDL	mmol/L	Enzymatic colorimetric
Immunoglobulin A	IGA	mg/dL	Immunoturbidimetric
Immunoglobulin G	IGG	mg/dL	Immunoturbidimetric
Immunoglobulin M	IGM	mg/dL	Immunoturbidimetric
Inorganic Phosphate	PHOS	mmol/L	Molybdate -endpoint
Iron	FE	µmol/L	Colorimetric
Lactate	LACT	mmol/L	Enzymatic colorimetric
Lactate Dehydrogenase	LDH	U/L	LDH IFCC UV
Lipase	LIPASE	U/L	Enzymatic colorimetric
Magnesium	MG	mmol/L	Colorimetric endpoint method.
Non-Esterified Fatty Acids	NEFA	mmol/L	Enzymatic colorimetric
Potassium	K	mmol/L	Indirect measurement (Ion selective electrode)
Sodium	NA	mmol/L	Indirect measurement (Ion selective electrode)
Sorbitol Dehydrogenase	SDH	U/L	Enzymatic colorimetric

Appendix 13

Individual Clinical Chemistry and C-Reactive Protein Values

P Module 800

Analysed Parameter Descriptions

Total Bilirubin	TBIL	µmol/L	DPD colorimetric
Total Ketone Bodies	TOTAL KETONE BODIES	µmol/L	Cyclic enzymatic
Total Protein	TPROT	g/L	Biuret colorimetric
Triglycerides	TRIG	mmol/L	GPO-PAP enzymatic colorimetric
Urea	UREA	mmol/L	Urease kinetic UV
Uric Acid	URIC ACID	µmol/L	Enzymatic colorimetric

Immunoassay

Analysed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Adiponectin (HMW)	ADPNCTN	ng/mL	Mouse specific ELISA
Insulin	INSULIN	µg/L	Demeditec rat specific ELISA
Insulin	INSULIN	µg/L	Shibayagi Dog specific ELISA
Insulin-like Growth Factor-1	IGF-1	µg/L	R&D Quantakine mouse/rat specific ELISA
Somatotrophin;Growth Hormone	GH SOMATRO	µg/L	Demeditec mouse/rat specific ELISA
Thyroid Stimulating Hormone	TSH	ng/mL	Demeditec rat specific ELISA
Corticosterone	CRTRONE	ng/mL	Mouse/rat specific ELISA
C-Peptide (ng/mL)	CPEPTIDE	ng/mL	Mouse specific ELISA
C-Reactive Protein	CRP	mg/L	Tridelta canine CRP ELISA
C-Reactive Protein	CRP	mg/L	Life Diagnostic rat CRP ELISA
C-Reactive Protein	CRP	mg/L	Life Diagnostic rabbit CRP ELISA
Myoglobin	MGB	ng/mL	ELISA
Osteocalcin ng/mL	OSTEOCALCIN	ng/mL	Rat specific ELISA
Aldosterone	ALDSTRN	µg/L	ELISA
Bb Fragment of Factor B	BB	mg/L	ELISA
Complement Component C3a	C3A	ng/mL	ELISA
Complement Component C4d	C4d	µg/mL	ELISA
Soluble Terminal Component C5 through C9 complex	SC5b-9	ng/mL	ELISA
50% Complement Haemolytic Activity	CH50	CH50 U Eq/mL	ELISA

Meso Scale Discovery Sector Imager

Analysed Parameter Descriptions

Parameter	Abbreviation	Units	Methodology
Alpha-2 Macroglobulin	A2M	mg/L	Electrochemiluminescent
Alpha-1 Acid Glycoprotein SI	AGPSI	mg/L	Electrochemiluminescent

Appendix 13

Individual Clinical Chemistry and C-Reactive Protein Values

i-STAT 1

Parameter	Analysed Parameter Descriptions		
	Abbreviation	Units	Methodology
Blood pH	pH		i-STAT
Bicarbonate for Blood Gas	HCO3	mmol/L	i-STAT
Partial Pressure Carbon Dioxide	PCO2	mmHg	i-STAT
Carbon Dioxide, Total	TOTAL CO2	mmol/L	i-STAT
Partial Pressure Oxygen	PO2	mmHg	i-STAT
Oxygen Saturation	O2SAT	%	i-STAT
Lactate	LACT	mmol/L	i-STAT
Base Excess	Base Excess	mmol/L	i-STAT
Ionised Calcium	ION CA	mmol/L	i-STAT

Calculations

Parameter	Parameter Descriptions		
	Abbreviation	Units	Methodology
Albumin/Globulin ratio	A/G	None	Albumin / Globulin
Globulin	GLOB	g/L	Total Protein – Albumin
Indirect Bilirubin	IBIL	µmol/L	Total Bilirubin – Direct Bilirubin
Urea Nitrogen	UREAN	mg/dL	Urea*2.801

Serum and Plasma Appearance (Reported as SAMQ SERUM)

Parameter	Abbreviation	Analysed Parameter Descriptions	
		Degree is graded as	Methodology
Normal sample	N	Normal	Manual and visual
Haemolysed sample	H	+ = mild ++ = moderate +++ = marked	Manual and visual
Lipaemic sample	L	+ = mild ++ = moderate +++ = marked	Manual and visual
Icterus sample	I	+ = mild ++ = moderate +++ = marked	Manual and visual
Atypical sample	A	Color is identified	Manual and visual

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

Appendix 13

Individual Clinical Chemistry and C-Reactive Protein Values

Clinical Pathology Data Flags

Abbreviation	Description
--	No sample or no result. The exception is Urine Microscopic, Red and White Blood Cell Morphology and Platelet Morphology where it denotes an abnormal finding in one or more parameters
ADQ	Adequate
AVS	Suspected aberrant value
BE0	Volume below 0.1mL
CLOT	Sample clotted
COM	Contaminated with organic material
COME	See comment value excluded
COMI	See comment value included
COMM	Comment added
DEC	Decreased
Exc	Exclude
GFC	Gross fecal contamination present
INC	Increased
INV	Invalid result
IRPS	Presence of abundant plasmodium species
ISH	Result invalid due to severe haemolysis
ISL	Result invalid due to severe lipaemia
L100	Less than 100 cells used to perform differential
LLOQ	Less than lower limit of quantification
MDIFF	Manual differential
NA	Not applicable
NAF	No abnormal findings
NC	Not calculable
NCD	No clot detected
NRBC	WBC corrected for presence of nucleated RBC
NSCH	Not scheduled to be performed
OA	Omitted activity
OOS	Sample analysed outside of established stability, results for information only
QNS	Quantity not sufficient
RSV	Refer to source values
S	Spillage
SAMU	Large number of smudge cells
SNC	Sample not collected
SNR	Sample not received
SVGS	Sample volume greater than specified
SVLS	Sample volume less than specified
TERR	Technical error (explanation required)
TNP	Test not performed
TNR	Test not reported
UNCR	Results are not reproducible
UNEX	Unscheduled data excluded from statistics
UPTD	Unable to perform due to technical difficulty
UTC	Unable to collect
UTD	Unable to determine
UTDH	Unable to determine due to marked haemolysis

Appendix 13
Individual Clinical Chemistry and C-Reactive Protein Values

Clinical Pathology Data Flags

Abbreviation	Description
UTDL	Unable to determine due to marked lipaemia
UTDM	Unable to determine results, not confirmed by microscopy
UTDR	Unable to determine results not reproducible
VARR	Assigned value above reportable range
VBRR	Assigned value below reportable range
VNC	Value not calculable
X	Excluded from mean

Note: This is a comprehensive list of clinical pathology data flags. All of the data flags listed may not be applicable to this report.

Assigned values denoted with the data flags VARR or VBRR have been used for statistical/group mean analysis where appropriate.

Appendix 14
Individual Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1M	1001	17	35	195	6	387	1.3VBRR	5.6
	1002	10	23	262	8	570	1.3VBRR	5.0
	1003	10	28	157	8	483	1.3VBRR	4.5
	1004	15	29	334	4	827	1.3VBRR	6.9
	1005	17	19	167	6	397	1.3VBRR	6.4
	1006	14	35	246	7	704	1.3VBRR	6.0
	1007	17	32	198	7	1949	1.3VBRR	5.3
	1008	18	30	288	9	410	1.3VBRR	3.7
	1009	15	40	184	11	401	1.3VBRR	6.2
	1010	12	31	186	10	606	1.3VBRR	6.6
2M	2001	13	31	295	9	704	1.3VBRR	3.7
	2002	11	15	314	6	436	1.3VBRR	5.8
	2003	11	22	217	6	342	1.3VBRR	5.1
	2004	19	30	252	9	475	1.3VBRR	4.6
	2005	15	41	172	5	442	1.3VBRR	4.2
	2006	10	37	176	7	595	1.3VBRR	5.6
	2007	13	36	346	8	1059	1.3VBRR	5.2
	2008	21	64	312	6	702	1.3VBRR	5.8
	2009	11	39	192	12	602	1.3VBRR	4.2
	2010	19	50	210	9	617	1.3VBRR	7.1

Appendix 14
Individual Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Animal		Sex	No.	CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1M	1001		73	8.25	0.6	1.35	56	44	12	
	1002		58	8.19	0.9	0.89	56	43	12	
	1003		59	8.15	0.8	1.24	56	42	13	
	1004		55	8.03	0.4	1.06	62	46	16	
	1005		63	8.17	1.0	2.21	60	45	15	
	1006		51	7.77	1.1	1.74	58	44	14	
	1007		70	8.35	1.1	1.74	60	46	14	
	1008		76	8.50	0.9	1.70	57	45	12	
	1009		59	7.22	1.0	1.31	57	45	12	
	1010		56	7.62	0.9	1.51	58	47	11	
2M	2001		62	8.01	1.3	2.20	58	44	14	
	2002		58	8.86	0.5	1.15	60	47	12	
	2003		73	8.94	0.8	1.45	61	46	15	
	2004		58	8.50	1.0	1.32	57	47	11	
	2005		65	9.36	0.9	1.36	54	43	11	
	2006		54	8.48	1.0	1.84	57	43	14	
	2007		67	8.33	0.9	1.10	56	44	12	
	2008		100	9.25	1.0	1.36	67	49	18	
	2009		51	8.80	1.0	1.45	57	44	13	
	2010		69	7.79	1.7	5.96	65	50	15	

Appendix 14
Individual Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1M	1001	3.7	3.73	2.16	143	4.6	97	
	1002	3.5	3.87	2.06	143	4.5	98	
	1003	3.1	3.77	2.03	142	4.8	100	
	1004	2.8	4.05	2.16	142	4.8	96	
	1005	3.1	3.94	2.04	142	4.6	97	
	1006	3.2	3.82	1.95	140	5.0	98	
	1007	3.3	4.00	2.02	142	4.8	96	
	1008	3.9	3.88	2.11	143	4.2	92	
	1009	3.7	3.95	1.95	144	4.8	100	
	1010	4.3	3.96	1.89	142	4.7	101	
2M	2001	3.2	3.72	1.98	142	4.6	99	
	2002	3.8	3.98	2.16	141	5.1	98	
	2003	3.0	3.72	2.44	141	4.7	96	
	2004	4.4	3.82	2.29	142	4.7	100	
	2005	3.8	3.66	2.34	141	4.8	97	
	2006	3.0	3.92	2.14	144	4.9	97	
	2007	3.6	3.81	2.15	143	5.4	97	
	2008	2.7	4.00	2.28	146	5.2	96	
	2009	3.5	3.82	2.16	141	4.6	95	
	2010	3.3	4.15	2.09	141	5.6	91	

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 14
Individual Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1F	1501	16	35	220	11	607	1.3VBRR	4.6	
	1502	14	41	312	10	551	1.3VBRR	3.9	
	1503	13	28	232	10	416	1.3VBRR	6.8	
	1504	18	34	241	7	581	1.3VBRR	4.8	
	1505	11	24	186	7	427	1.3VBRR	5.7	
	1506	12	27	204	9	419	1.3VBRR	5.2	
	1507	14	23	222	8	388	1.3VBRR	4.9	
	1508	15	42	257	10	563	1.3VBRR	3.5	
	1509	11	23	270	8	591	1.3VBRR	5.0	
	1510	11	17	258	7	413	1.3VBRR	5.1	
2F	2501	14	31	231	10	673	1.3VBRR	5.1	
	2502	14	34	242	8	853	1.3VBRR	4.2	
	2503	9	28	199	9	353	1.3VBRR	6.1	
	2504	11	28	234	9	488	1.3VBRR	4.7	
	2505	12	36	340	7	3533	1.3VBRR	5.8	
	2506	14	33	242	8	621	1.3VBRR	5.1	
	2507	10	33	227	7	358	1.3VBRR	5.3	
	2508	11	18	171	10	624	1.3VBRR	4.5	
	2509	12	25	291	9	599	1.3VBRR	4.6	
	2510	9	31	236	7	854	1.3VBRR	5.2	

Appendix 14
Individual Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		Sex	No.	CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1F	1501		72	7.54	1.3	0.96	54	42	12	
	1502		67	8.22	1.6	1.72	58	43	15	
	1503		66	8.43	1.1	1.31	56	44	12	
	1504		67	9.14	1.5	1.58	57	43	14	
	1505		71	9.28	1.2	1.18	56	44	12	
	1506		80	8.54	1.6	3.90	57	44	13	
	1507		80	8.78	1.1	1.17	56	43	13	
	1508		68	8.13	1.3	1.42	60	47	13	
	1509		72	8.67	1.5	1.06	53	41	12	
	1510		67	8.85	0.9	0.92	51	42	9	
2F	2501		84	9.01	1.5	1.23	58	45	13	
	2502		74	8.64	1.4	0.85	51	40	10	
	2503		73	8.06	0.9	1.09	55	43	12	
	2504		65	8.93	1.8	1.43	58	45	14	
	2505		69	9.52	1.3	1.05	61	46	14	
	2506		64	9.98	1.3	1.23	57	44	14	
	2507		79	9.71	1.1	1.60	60	45	15	
	2508		69	9.14	1.4	0.92	53	41	12	
	2509		79	7.89	1.4	1.09	58	44	14	
	2510		66	9.21	1.6	1.31	56	44	12	

Appendix 14
Individual Clinical Chemistry Values Pretreatment

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1F	1501	3.4	3.78	2.21	140	5.0	99	
	1502	3.0	3.85	1.93	142	4.4	99	
	1503	3.6	4.06	1.95	141	4.7	98	
	1504	3.0	3.85	2.10	141	4.7	97	
	1505	3.6	4.09	1.89	141	4.9	98	
	1506	3.4	3.84	1.93	140	4.6	95	
	1507	3.3	3.87	2.05	141	3.7	96	
	1508	3.8	3.90	1.97	141	4.3	94	
	1509	3.4	3.83	1.88	141	4.3	95	
	1510	4.6	3.86	2.14	140	4.8	98	
2F	2501	3.6	3.83	2.08	143	4.6	97	
	2502	3.9	3.77	2.00	143	4.8	100	
	2503	3.7	3.82	2.42	143	5.2	96	
	2504	3.2	3.90	2.20	141	4.5	95	
	2505	3.2	4.13	2.23	140	4.5	95	
	2506	3.2	3.86	2.21	140	4.7	93	
	2507	3.0	3.70	2.35	142	4.6	97	
	2508	3.4	3.69	2.14	139	4.4	97	
	2509	3.1	4.01	2.44	140	5.2	91	
	2510	3.7	3.96	2.25	140	5.2	96	

Appendix 14
Individual Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1M	1001	16	32	161	6	460	1.3VBRR	5.9
	1002	8	24	211	9	500	1.3VBRR	5.3
	1003	9	23	135	10	553	1.3VBRR	5.1
	1004	11	29	278	5	645	1.3VBRR	7.0
	1005	12	17	170	5	467	1.3VBRR	5.4
	1006	7	27	210	8	591	1.3VBRR	4.7
	1007	14	32	181	5	1146	1.3VBRR	6.0
	1008	12	26	215	9	524	1.3VBRR	4.7
	1009	9	30	167	12	441	1.3VBRR	5.7
	1010	7	28	168	10	732	1.3VBRR	6.5
2M	2001	11	30	186	9	833	1.3VBRR	5.5
	2002	10	17	196	7	690	1.3VBRR	5.7
	2003	11	23	151	5	757	1.3VBRR	5.9
	2004	17	38	161	10	944	1.3VBRR	5.2
	2005	13	39	145	6	1071	1.3VBRR	4.3
	2006	11	38	139	7	698	1.3VBRR	5.3
	2007	11	31	228	8	768	1.3VBRR	4.7
	2008	19	46	215	7	1516	1.3VBRR	6.1
	2009	14	42	147	14	532	1.3VBRR	4.3
	2010	13	35	175	9	1147	1.3VBRR	4.6

Appendix 14
Individual Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		Sex	No.	CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1M	1001		67	8.36	0.4	1.03	54	42	11	
	1002		62	8.52	0.9	1.43	54	43	12	
	1003		64	7.65	0.9	1.06	53	43	11	
	1004		54	7.53	0.4	1.60	58	46	12	
	1005		61	7.50	0.7	1.67	56	44	12	
	1006		55	7.82	0.9	1.44	58	43	15	
	1007		63	8.59	0.9	2.20	57	45	12	
	1008		65	8.86	0.7	1.32	55	45	11	
	1009		60	7.43	1.0	1.88	55	44	12	
	1010		65	7.60	0.6	0.95	57	46	11	
2M	2001		57	8.04	1.2	1.72	60	44	15	
	2002		55	8.76	0.4	0.84	60	45	16	
	2003		68	9.46	0.6	0.85	58	43	15	
	2004		61	8.46	1.1	1.05	59	44	15	
	2005		63	8.53	0.9	1.93	57	42	15	
	2006		57	8.17	1.1	1.84	57	42	15	
	2007		72	8.53	0.8	1.36	58	43	15	
	2008		77	8.34	0.9	1.76	60	44	16	
	2009		61	8.69	1.0	1.52	60	44	15	
	2010		65	9.13	1.1	3.81	59	45	14	

Appendix 14
Individual Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1M	1001	3.7	3.78	1.83	142	5.0	99	
	1002	3.7	3.86	1.79	141	4.5	99	
	1003	4.0	3.72	2.18	141	4.8	100	
	1004	3.7	3.89	2.01	143	4.7	98	
	1005	3.6	3.57	1.99	142	4.4	98	
	1006	2.9	3.86	1.93	144	4.5	101	
	1007	3.8	3.92	2.01	145	4.9	97	
	1008	4.1	3.76	2.06	146	4.9	96	
	1009	3.7	3.87	1.91	143	4.5	100	
	1010	4.0	3.80	1.83	142	4.6	100	
2M	2001	2.9	3.82	2.07	142	4.7	97	
	2002	2.8	3.70	1.84	142	4.9	96	
	2003	2.9	3.69	2.10	142	4.3	94	
	2004	3.0	3.70	2.01	141	4.6	97	
	2005	2.9	3.70	2.05	140	4.5	96	
	2006	2.8	3.74	2.12	144	4.3	95	
	2007	2.8	3.73	2.12	144	5.0	97	
	2008	2.8	3.82	2.14	140	5.1	95	
	2009	2.9	3.83	2.01	142	5.1	99	
	2010	3.3	3.81	1.84	142	5.4	94	

Appendix 14
Individual Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
1F	1501	20	48	219	10	1730	1.3VBRR	5.6
	1502	10	34	289	11	861	1.3VBRR	5.2
	1503	8	29	218	10	763	1.3VBRR	5.0
	1504	12	31	231	7	875	1.3VBRR	5.9
	1505	6	27	185	8	413	1.3VBRR	5.5
	1506	8	29	173	8	1578	1.3VBRR	5.8
	1507	12	24	219	9	435	1.3VBRR	6.2
	1508	10	39	215	10	681	1.3VBRR	4.5
	1509	7	24	248	8	704	1.3VBRR	6.4
	1510	6	21	252	8	375	1.3VBRR	6.5
2F	2501	10	31	191	11	803	1.3VBRR	5.7
	2502	13	34	216	8	1190	1.3VBRR	4.3
	2503	8	25	161	9	620	1.3VBRR	5.8
	2504	12	33	189	8	829	1.3VBRR	5.3
	2505	21	36	254	7	1016	1.3VBRR	6.2
	2506	10	34	217	8	1044	1.3VBRR	5.7
	2507	11	37	185	7	587	1.3VBRR	5.6
	2508	18	19	149	8	1648	1.3VBRR	5.8
	2509	12	26	221	10	981	1.3VBRR	5.2
	2510	12	30	185	9	1166	1.3VBRR	5.3

Appendix 14
Individual Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		Sex	No.	CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1F	1501		80	8.69	1.4	0.65	56	44	12	
	1502		68	8.51	1.4	0.93	57	43	13	
	1503		63	7.80	1.3	1.26	56	43	13	
	1504		70	8.57	1.3	1.11	54	42	12	
	1505		75	8.54	1.3	0.80	56	44	12	
	1506		78	8.10	1.4	2.77	55	44	11	
	1507		79	8.68	1.2	1.20	57	45	12	
	1508		68	8.95	1.3	1.23	56	44	12	
	1509		65	8.56	1.5	1.05	55	44	10	
	1510		63	8.77	1.1	0.87	52	41	10	
2F	2501		75	9.15	1.8	1.27	59	46	14	
	2502		80	9.17	1.4	1.33	52	39	13	
	2503		75	8.57	1.1	0.95	56	41	15	
	2504		65	8.34	1.6	1.30	59	43	16	
	2505		84	10.32	1.5	1.89	58	44	13	
	2506		57	9.01	1.5	1.09	56	42	14	
	2507		70	9.32	1.2	1.34	59	43	15	
	2508		72	9.06	1.4	0.61	54	41	13	
	2509		73	8.83	1.5	1.20	58	44	14	
	2510		71	9.99	1.8	1.12	57	43	14	

Appendix 14
Individual Clinical Chemistry Values Day 3

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1F	1501	3.7	3.74	2.30	144	5.0	100	
	1502	3.2	3.85	1.86	142	4.4	96	
	1503	3.4	3.68	1.81	142	4.0	100	
	1504	3.4	3.57	2.23	141	5.4	99	
	1505	3.8	3.80	2.04	142	4.6	98	
	1506	3.8	3.74	1.85	141	4.4	95	
	1507	3.6	3.81	1.93	141	4.4	98	
	1508	3.8	3.83	2.00	142	4.5	95	
	1509	4.2	3.90	2.06	142	4.3	98	
	1510	4.0	3.74	1.87	141	4.6	99	
2F	2501	3.3	3.91	2.12	144	4.8	98	
	2502	2.9	3.62	1.77	142	4.3	100	
	2503	2.8	3.73	2.26	144	4.7	97	
	2504	2.7	3.90	1.96	141	4.5	96	
	2505	3.3	3.79	1.82	141	4.3	96	
	2506	3.0	3.75	2.07	141	4.9	98	
	2507	2.8	3.77	1.81	141	4.3	98	
	2508	3.2	3.77	2.33	140	4.9	97	
	2509	3.1	3.97	1.55	141	4.7	97	
	2510	3.0	3.91	2.27	142	4.8	97	

Appendix 14
Individual Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
Sex	No.							
1M	1001	16	42	129	5	438	1.3VBRR	7.5
	1002	8	31	189	5	1016	1.3VBRR	6.0
	1003	6	27	118	8	489	1.3VBRR	5.4
	1004	10	34	178	5	829	1.3VBRR	6.2
	1005	11	19	127	6	623	1.3VBRR	6.0
2M	2001	11	45	129	6	1610	1.3VBRR	5.4
	2002	10	25	143	7	956	1.3VBRR	6.2
	2003	8	26	115	4	377	1.3VBRR	6.6
	2004	13	39	162	7	783	1.3VBRR	4.9
	2005	12	57	94	6	740	1.3VBRR	4.6

Appendix 14
Individual Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		Sex	No.	CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1M	1001	72		8.32	0.4	2.01	60	47	12	
	1002	65		8.22	0.7	1.05	57	46	12	
	1003	62		7.95	0.5	1.50	56	44	12	
	1004	58		8.34	0.3	0.97	61	47	15	
	1005	65		8.16	0.6	2.47	57	45	12	
2M	2001	72		8.41	1.0	1.22	63	45	18	
	2002	60		8.67	0.3	1.14	61	45	16	
	2003	64		8.72	0.5	0.86	61	45	16	
	2004	61		9.03	0.8	0.95	62	46	16	
	2005	66		8.41	0.6	0.99	57	43	14	

Appendix 14
Individual Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1M	1001	3.8	3.88	1.68	150	5.1	103	
	1002	3.9	3.76	1.76	148	4.7	104	
	1003	3.8	3.72	1.52	147	5.0	106	
	1004	3.1	3.93	1.74	148	5.3	102	
	1005	3.7	3.72	1.72	148	5.0	104	
2M	2001	2.5	3.64	1.54	139	4.5	97	
	2002	2.9	3.68	1.46	144	5.1	101	
	2003	2.9	3.70	1.79	148	4.8	100	
	2004	3.0	3.68	1.57	148	4.4	105	
	2005	3.0	3.59	1.68	148	4.9	107	

Appendix 14
Individual Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
Sex	No.							
1F	1501	23	52	168	10	2278	1.3VBRR	7.2
	1502	12	41	222	10	2618	1.3VBRR	6.7
	1503	21	48	199	9	2821	1.3VBRR	6.8
	1504	10	40	159	9	3413	1.3VBRR	5.9
	1505	11	32	149	10	376	1.3VBRR	7.5
2F	2501	18	48	144	10	3189	1.3VBRR	7.2
	2502	11	43	162	8	1620	1.3VBRR	7.1
	2503	7	35	112	7	731	1.3VBRR	8.5
	2504	10	37	154	7	609	1.3VBRR	6.4
	2505	12	40	188	11	924	1.3VBRR	7.8

Appendix 14
Individual Clinical Chemistry Values Day 31

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		Sex	No.	CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1F	1501	87		8.05	1.3	0.63	56	44	13	
	1502	71		8.08	1.8	1.03	58	45	13	
	1503	78		7.55	1.2	0.95	58	45	13	
	1504	71		8.82	1.3	0.59	55	42	12	
	1505	88		8.77	1.5	0.65	58	46	12	
2F	2501	94		8.71	1.6	1.23	60	45	14	
	2502	77		9.08	1.4	0.61	57	42	15	
	2503	82		8.10	1.1	1.02	54	41	14	
	2504	66		8.23	1.6	0.98	56	42	14	
	2505	82		8.44	1.2	1.23	62	46	17	

**Appendix 14
Individual Clinical Chemistry Values Day 31**

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1F	1501	3.4	3.62	2.04	146	4.9	104	
	1502	3.5	3.93	1.41	141	4.9	102	
	1503	3.5	3.71	1.50	141	4.0	99	
	1504	3.4	3.62	1.59	137	4.2	101	
	1505	3.8	3.85	1.68	146	5.2	103	
2F	2501	3.1	3.84	1.71	143	5.1	102	
	2502	2.8	3.68	1.37	142	4.3	100	
	2503	2.9	3.56	1.64	145	4.4	103	
	2504	3.0	3.84	1.48	137	4.4	97	
	2505	2.7	3.84	1.50	148	4.6	106	

Appendix 14
Individual Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
Sex	No.							
1M	1006	10	38	145	5	1093	1.3VBRR	6.1
	1007	11	42	117	7	784	1.3VBRR	6.9
	1008	11	33	142	6	460	1.3VBRR	6.2
	1009	16	44	117	9	448	1.3VBRR	8.4
	1010	13	35	115	8	540	1.3VBRR	8.2
2M	2006	21	63	115	4	505	1.3VBRR	7.9
	2007	12	38	125	5	867	1.3VBRR	8.2
	2008	23	96	129	6	861	1.3VBRR	7.7
	2009	11	42	99	8	634	1.3VBRR	5.8
	2010	16	44	131	7	664	1.3VBRR	6.5

Appendix 14
Individual Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		Sex	No.	CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1M	1006	62		7.40	0.5	1.53	60	46	15	
	1007	71		7.27	0.6	1.60	60	47	12	
	1008	77		9.09	0.4	1.51	59	46	13	
	1009	68		7.51	0.7	3.00	62	49	13	
	1010	78		7.61	0.6	1.28	59	47	12	
2M	2006	74		7.63	0.9	4.74	62	47	15	
	2007	71		8.05	0.4	1.06	60	46	14	
	2008	78		7.48	0.6	2.47	60	46	15	
	2009	63		8.38	0.5	1.94	57	45	12	
	2010	76		8.27	0.8	3.73	59	46	13	

**Appendix 14
Individual Clinical Chemistry Values Day 52**

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	No.	Group / Animal					
		A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1M	1006	3.1	3.80	1.39	144	4.5	102
	1007	3.9	3.93	1.46	145	4.5	99
	1008	3.6	3.80	1.53	143	4.4	98
	1009	3.9	4.03	1.63	142	4.7	99
	1010	3.9	3.80	1.47	144	4.4	103
2M	2006	3.2	3.92	1.66	142	4.5	98
	2007	3.2	3.97	1.44	140	5.2	98
	2008	3.1	3.82	1.44	147	4.7	106
	2009	3.7	3.74	1.45	147	4.3	103
	2010	3.6	3.85	1.49	146	4.8	102

Appendix 14
Individual Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		AST U/L	ALT U/L	ALP U/L	GGT U/L	CK U/L	TBIL umol/L	UREA mmol/L
Sex	No.							
1F	1506	11	46	129	7	802	1.3VBRR	8.5
	1507	13	29	118	11	484	1.3VBRR	8.8
	1508	10	39	137	7	914	1.3VBRR	6.9
	1509	10	28	130	8	1444	1.3VBRR	8.1
	1510	11	26	159	4	482	1.3VBRR	9.1
2F	2506	13	50	123	7	695	1.3VBRR	7.0
	2507	12	54	119	7	1010	1.3VBRR	7.9
	2508	11	29	76	8	2199	1.3VBRR	7.4
	2509	12	41	117	7	682	1.3VBRR	7.8
	2510	14	41	106	10	1057	1.3VBRR	8.4

Appendix 14
Individual Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		Sex	No.	CREAT umol/L	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L	TPROT g/L	ALB g/L	GLOB g/L
1F	1506		82	7.19	1.0	1.53	57	45	12	
	1507		92	7.58	1.1	0.91	58	44	14	
	1508		78	8.85	0.8	0.86	52	41	11	
	1509		83	8.82	1.2	0.65	54	42	12	
	1510		79	8.39	0.7	1.46	54	42	12	
2F	2506		64	7.35	1.7	0.97	57	43	15	
	2507		87	8.16	1.1	0.63	59	44	15	
	2508		82	8.53	0.9	0.48	53	42	11	
	2509		91	7.87	1.0	0.65	60	45	14	
	2510		96	8.23	1.3	0.85	57	43	14	

Appendix 14
Individual Clinical Chemistry Values Day 52

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal	Sex	No.	A/G	CA mmol/L	PHOS mmol/L	NA mmol/L	K mmol/L	CL mmol/L
1F	1506	3.8	3.92	1.26	140	4.2	98	
	1507	3.1	3.63	1.23	141	4.1	102	
	1508	3.8	3.79	1.23	142	4.1	100	
	1509	3.6	3.66	1.30	141	3.8	101	
	1510	3.6	3.78	1.30	139	4.2	102	
2F	2506	2.9	3.87	1.28	148	4.5	107	
	2507	2.9	3.66	1.42	140	4.2	102	
	2508	3.9	3.66	1.25	141	4.3	103	
	2509	3.2	3.90	1.15	142	4.3	104	
	2510	3.1	3.75	1.25	141	4.3	103	

Appendix 15
Individual C-Reactive Protein Values (mg/L)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day -5	Day 2	Day 7	Day 30	Day 52
1M	1001	0.39	0.31	0.36	1.10	--
	1002	1.04	1.29	2.02	2.08	--
	1003	0.24	0.18	0.19	0.34	--
	1004	3.84	6.53	4.96	12.00	--
	1005	2.26	0.80	1.02	2.81	--
	1006	1.60	1.29	1.59	2.45	2.72
	1007	4.81	1.15	1.86	1.36	1.56
	1008	1.86	0.92	1.17	2.16	1.13
	1009	0.73	0.39	0.42	0.93	3.80
	1010	0.23	0.19	0.21	0.20	0.19
2M	2001	1.36	121.00	1.40	158.70	--
	2002	3.90	197.10	2.80	109.20	--
	2003	1.24	63.20	3.62	73.20	--
	2004	0.21	58.70	0.71	67.90	--
	2005	0.19	31.80	0.12	23.00	--
	2006	8.76	136.50	1.90	131.00	4.31
	2007	0.45	38.90	0.81	38.60	1.77
	2008	5.42	44.30	1.43	53.80	0.89
	2009	1.00	92.10	1.50	96.30	1.65
	2010	12.70	74.60	2.24	98.50	1.88

Appendix 15
Individual C-Reactive Protein Values (mg/L)

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Day -5	Day 2	Day 7	Day 30	Day 52
1F	1501	2.69	6.38	4.83	25.95	--
	1502	2.61	6.17	6.59	11.90	--
	1503	1.59	29.45	1.92	3.25	--
	1504	3.10	4.31	8.45	3.81	--
	1505	10.60	10.40	5.56	9.17	--
	1506	10.60	13.80	11.80	14.40	7.27
	1507	1.69	2.25	23.80	5.82	0.91
	1508	3.52	2.83	2.63	2.37	1.60
	1509	5.06	2.79	3.37	4.06	2.43
	1510	4.63	5.42	5.87	10.80	5.30
2F	2501	3.00	57.10	3.67	41.20	--
	2502	2.89	52.60	4.04	40.90	--
	2503	1.24	41.50	2.77	51.90	--
	2504	5.21	74.40	7.63	53.80	--
	2505	5.46	199.40	30.15	137.00	--
	2506	9.29	91.50	11.60	64.40	11.40
	2507	3.53	60.00	2.53	44.30	1.95
	2508	1.48	40.00	4.10	41.30	4.26
	2509	9.89	232.00	10.50	134.00	3.43
	2510	3.29	130.00	5.63	133.00	25.20

Appendix 16

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Study Report [REDACTED]

Title:	An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study [REDACTED] [REDACTED] Vaccine in NZW Rabbits with a 21- Day Recovery Period: vaccine induced immunogenicity readout
Responsible Scientist:	[REDACTED]
Report Author:	[REDACTED]
Report Date:	05-FEB-2018
Study Phase Plan:	[REDACTED]
Charles River Laboratories [REDACTED]	[REDACTED]
Study number:	[REDACTED]
Study location:	[REDACTED]
Study start and completion data:	01-NOV-2017 until 05-DEC-2017

Appendix 16

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

AIM:	To evaluate the immunogenicity of [REDACTED] administered in a prime-boost-boost regimen in New Zealand White (NZW) rabbits dosed with 10^{11} vp [REDACTED] via the intramuscular route at day 1, 15 and 29 as part of toxicology study [REDACTED]
MAIN CONCLUSIONS:	[REDACTED] vaccine formulation induced [REDACTED] antibody responses in NZW rabbits, as measured by ELISA in serum isolated at day 14, following a single administration, and day 31 (main and recovery animals) or day 52 (recovery animals only), after 3 immunizations. No [REDACTED] response was detected in animals that received 0.9% (w/v) sodium chloride solution control. Note: Sample An1009, control and An2009, [REDACTED] treated measured at day 52 are expected to have been switched during serum sampling or processing.

[REDACTED]	[REDACTED]	PAGE : 2 of 16
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Appendix 16

[REDACTED]	[REDACTED]

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Appendix 16

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

1 BACKGROUND

[REDACTED] ([REDACTED]) is a member of the [REDACTED] family, which also includes [REDACTED], [REDACTED] and [REDACTED] virus.

In 2015 there was a large outbreak of [REDACTED] in [REDACTED]. Despite its relatively mild impact on healthy adults, [REDACTED] can result in severe birth defects when pregnant women are infected. Currently there is no [REDACTED] vaccine available, but several preclinical vaccine candidates based on the [REDACTED], [REDACTED] and [REDACTED] showed promising results in mice and non-human primates (NHP). We demonstrated immunogenicity and protective efficacy of [REDACTED]

[REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] in mice and NHPs.

[REDACTED] induced strong cellular and humoral immune responses in mice and NHPs. In mice, the humoral and cellular responses were maintained at least up to 12 weeks. Humoral responses were characterized by [REDACTED] while cellular responses were characterized by [REDACTED] and [REDACTED]. More importantly, a single immunization with a very low dose of [REDACTED] protected mice from [REDACTED] challenge [REDACTED]. In NHP, a single immunization with a full human dose of [REDACTED] completely protected against viremia induced by [REDACTED] challenge [REDACTED]. Together these data provided the rationale to move [REDACTED] candidate vaccine forward to clinical testing. Therefore, a toxicology study was performed that assessed potential toxicity and local tolerance of a prime-boost-boost immunization of [REDACTED] vaccine when administered to New Zealand White (NZW) rabbits. In addition, the reversibility, persistence or delayed occurrence of any adverse effects of the vaccine regimen during a 21-day recovery period following the last injection was assessed. The results of the toxicological assessments are described in the study report of study [REDACTED]. The current study report captures the immunogenicity readouts that were performed as part of the toxicology study.

Appendix 16

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

2 OBJECTIVE

The aim of this study phase was to evaluate [REDACTED] responses induced by [REDACTED] vaccine formulations in rabbits.

3 EXPERIMENTAL DESIGN

New Zealand White (NZW) rabbits were dosed at day 1, 15 and 29 with [REDACTED] via the i.m route as part of toxicology study [REDACTED] (Table 1). To evaluate the immunogenicity, serum was isolated pretreatment (referred to as day 1) and at day 14 (all animals), day 31 (all animals) and day 52 (recovery animals). The presence of [REDACTED] was determined using an ELISA-based analytical method according to the procedure described in appendix 2 and summarized in the method section in paragraph 4. This part of the study was not conducted in compliance with GLP, using a non-qualified Env-ELISA assay. However, the data were analyzed, tabulated and reported using local SOPs and quality control procedures. Serum was provided from the Test Facility and stored at -20 °C until analysis.

Table 1: Experimental design

Group No.	Treatment	Dosage	Animal Numbers			
			Main Study		Recovery Study	
			Males	Females	Males	Females

Appendix 16

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		[REDACTED]

Group No.	Treatment	Dosage	Animal Numbers			
			Main Study		Recovery Study	
			Males	Females	Males	Females
1	Control	n.a.	1001-1005	1501-1505	1006-1010	1506-1510
2	[REDACTED] Batch Number: [REDACTED] ml	[REDACTED]	2001-2005	2501-2505	2006-2010	2506-2510

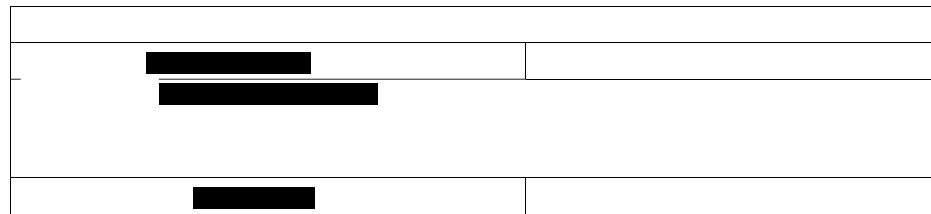
Control: [REDACTED]

Immunization: [REDACTED] and control item were administered by intramuscular injection (1 ml) on days 1, 15 and 29. Serum was isolated for immunology readout at pretreatment (referred to as day 1), days 14, 31 and 52.

4 METHODS**4.1 [REDACTED] (ELISA)**

IgG antibodies to [REDACTED] were measured by ELISA as described in Appendix 2: [REDACTED]. In brief, 96-well plates were coated overnight with [REDACTED]. On the next day, the plates were washed and blocked for 1 hr with 2% BSA. Serially diluted serum samples and a serial dilution of [REDACTED] (Rabbit) as standard were added. Plates were incubated for 1 hr at RT. After washing, [REDACTED] were detected by [REDACTED] (60 min at RT) followed by a washing step and luminescence readout with LumiGlow substrate for 30 min. The relative potency of a sample was calculated as the ratio of the IC50 of the sample over the standard on the same plate. The IC50 values of the samples and standard on a plate were derived from a 4-parameter logistic curve fit per sample or standard with a common upper and lower asymptote and a common slope across samples and standard. The reported [REDACTED] antibody titers were defined as the log10 of the (relative potency × 1000).

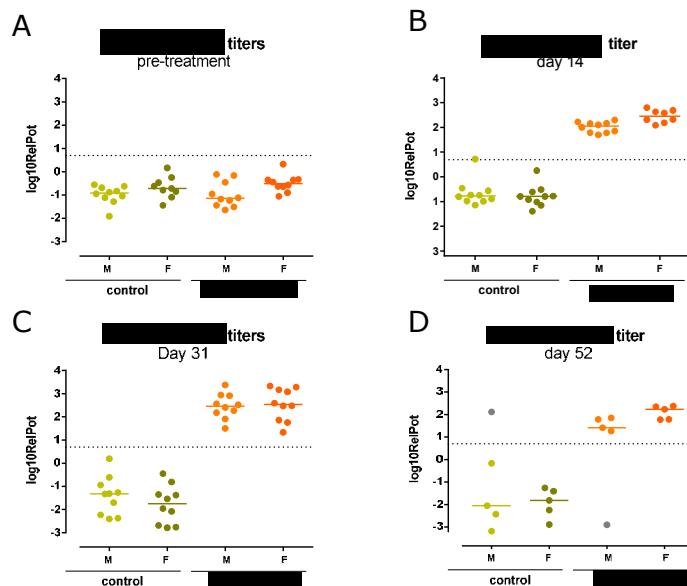
Appendix 16



5 RESULTS

5.1 [REDACTED] responses measured by ELISA

All male and female rabbits that received [REDACTED] developed [REDACTED] responses as measured at day 14 (after a single administration) and day 31 or day 52 (Figure 1B-D) where the rabbits had received 3 administrations. In contrast, animals that received only 0.9% (w/v) sodium chloride solution (control) or samples taken pretreatment did not exhibit [REDACTED] antibody titers (Figure 1A-D). A tabulated summary of all reportable data is displayed in appendix 3.



Appendix 16

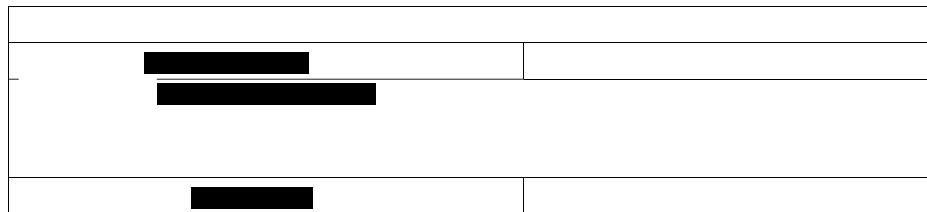


Figure 1: [REDACTED] responses in Rabbits. Male (M) or female (F) (n=5 per group) were dosed 3-times i m at day 1, 15 and 29 with [REDACTED] or with control (0.9% (w/v) sodium chloride solution). Serum was isolated and tested for Env-specific antibody responses in an ELISA based assay, pretreatment (A) or at day 14 (B), day 31 (C) and day 52 (D). The mean responses (log₁₀ relative potency titers) per group are indicated with a horizontal line. Dashed line indicates background level defined as mean+3-times the standard deviation of the response in the animal pre-treatment (0.699 on log₁₀-scale). Note: Sample An1507 (Control) at pre-treatment and sample An2502 and An2503 [REDACTED] from day 14 were excluded from analysis due to high deviation between duplicated measurements. Samples indicated in gray (An1009, control and An2009, [REDACTED] treated) measured at day 52 are expected to have been switched during serum sampling or processing. Repeated measurements of these samples confirmed the [REDACTED] data. (reference: N470-089A) Furthermore, samples from both animals showed the expected responses when analyzed on day 14 and day 31, namely, [REDACTED] [REDACTED] immunized).

6 CONCLUSION

[REDACTED] vaccine formulation induced [REDACTED] antibody responses in NZW rabbits, as measured by ELISA in serum isolated at day 14, following a single administration, and day 31 (main and recovery animals) or day 52 (recovery animals only) following 3 immunizations. No [REDACTED] antibody response was detected in animals that received 0.9% (w/v) sodium chloride solution control.

Note Samples indicated in gray in Figure 1 (An1009, control and An2009, [REDACTED] treated) measured at day 52 are expected to have been switched during serum sampling or processing.

Appendix 16

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

7 DATA STORAGE

Table 1: Raw Data storage

Experiment	Lab notebook reference to first page	Data storage Science data	Lab notebook reference to last page
[REDACTED] day 14 and pretreatment, serum from males	N470-080	[REDACTED]	N470-081
[REDACTED] day 14 and pretreatment, serum from females	N470-081A	[REDACTED]	N470-082
[REDACTED] day 31 (main animals)	N470-084A	[REDACTED]	N470-085
[REDACTED] day 31 + 52 (recovery animals)	N470-086	[REDACTED]	N470-087
[REDACTED] day 52 repeat suspected switched samples	N470-089A	[REDACTED]	N470-090

Appendix 16



8 REVIEW AND APPROVAL

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

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[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

9 APPENDICES

Appendix 1: Abbreviations

Ad	Adenoviral vector
ELISA	Enzyme Linked Immunosorbant Assay
[REDACTED]	[REDACTED]
i.m	Intramuscular
n.a	Not applicable
M	Membrane protein
pr	Peptide precursor
vp	Viral particles
[REDACTED]	[REDACTED]

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Appendix 2: Protocol [REDACTED] [REDACTED]

[REDACTED] protein

Day 0

Dilute to **1 µg/ml** in 1x PBS pH 7.4 and add 100 µl to all wells of 96-well white plate. Incubate O/N @ 4 °C.

Lot#s

Day 1

- Wash with PBS/0.05% Tween-20 (PBST) using the plate washer. Program "ELISA"
- Add 180 µl/well Block buffer (PBS pH 7.4 + 2% BSA). Incubate 1 h @ RT (use wet tissues in umlaufende luftung box for all incubations)
 - In the meantime:
 - STD (1000ug/ml): Dilute the standard **to 6 µg/ml** (final dilution 2µg/ml).
 - Dilute serum samples 8.3x in predilution plate: 132ul Block buffer + 18ul serum. Divide the predilution over 2 wells (duplo's).
- Wash with PBST using the plate washer. Program "ELISA"
- Add 100µl Block buffer in all wells.
- Transfer 50 µl of the standard or serum samples to the plate (all wells of column 1) according to the plate layout.
- Make a 3-fold dilution using 50µl from column 1 to column 2 to column 3 etc, up to column 11. Then discard this 50µl from column 11 so there will remain 100µl in each well. Column 12 will not contain serum/Ab. Incubate 1 h @ RT.
- Wash with PBST using the plate washer. Program "ELISA"
- Add 100µl per well of a [REDACTED] in all wells of the plate (dilute in Block buffer) and incubate 1 h @ RT.
- For Lumiglow development:
 - Add the lumiglow buffers together 1:1
 - Wash with PBST using the plate washer. Program "ELISA"
 - Add 50ul lumiglow per well and incubate for 30minutes at RT in the dark
 - After incubation read the plates for luminescence at the BioTek Synergy Neo.
 - Filterset 11 below, 41 above

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[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Table 3: Required reagents and disposals for [REDACTED] Elisa

Reagent	Manufacturer	Cat#
White Microplate, Lumitrac	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
PBS pH 7.4	[REDACTED]	[REDACTED]
PBS pH 7.4 10x	[REDACTED]	[REDACTED]
Tween20	[REDACTED]	[REDACTED]
BSA	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Lumiglow Sub A	[REDACTED]	[REDACTED]
Lumiglow Sub B	[REDACTED]	[REDACTED]

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Appendix 3: Overview Reportable Data individual animals

Animal ID	Type	Sex	Treatment	Env-Specific antibody titers (Log10)			
				Day 1	Day 14	Day 31	Day 52
An1001	main	Male	Control	-1,04116425	-0,743826973	-1,3312777	n.a
An1002	main	Male	Control	-1,28664724	-0,980675115	-0,6148804	n.a
An1003	main	Male	Control	-0,95025007	-0,804760665	-2,3759985	n.a
An1004	main	Male	Control	-0,62273811	0,715534872	-2,2311236	n.a
An1005	main	Male	Control	-0,55421597	-0,460210876	-2,4013452	n.a
An1006	Recovery	Male	Control	-0,8301848	-0,990214529	-1,2645524	-3,187694375
An1007	Recovery	Male	Control	-1,91118867	-0,896863104	-1,3180954	-2,431758814
An1008	Recovery	Male	Control	-1,10998403	-1,144167587	-1,7033582	-2,055523606
An1009	Recovery	Male	Control	-0,87432065	-0,564897897	0,19157923	2,121258223
An1010	Recovery	Male	Control	-0,68494827	-0,73241339	-0,9423147	-0,163576642
An1501	main	Female	Control	0,164418385	-0,791654702	-2,082192	n.a
An1502	main	Female	Control	-0,24277503	-0,512534376	-2,757086	n.a
An1503	main	Female	Control	-0,84565489	-1,39211148	-2,6877867	n.a
An1504	main	Female	Control	-0,46578588	-1,015419683	-1,9561473	n.a
An1505	main	Female	Control	-1,09215615	-1,154645133	-2,784247	n.a
An1506	Recovery	Female	Control	-0,61516155	0,25114815	-1,3529277	-2,243510245
An1507	Recovery	Female	Control	excluded	-0,918047914	-0,8143483	-1,819910744
An1508	Recovery	Female	Control	-1,44510245	-0,792290394	-1,5407919	-2,889934
An1509	Recovery	Female	Control	-0,71355852	-0,609411596	-1,3797153	-1,403697373
An1510	Recovery	Female	Control	-0,79073348	-0,777021224	-0,4545303	-1,258600618
An2001	main	Male	[REDACTED]	-1,51386624	2,099437117	1,90489091	n.a
An2002	main	Male	[REDACTED]	-1,64355702	1,700511373	1,49956377	n.a
An2003	main	Male	[REDACTED]	-0,45385638	2,222237199	2,17814073	n.a
An2004	main	Male	[REDACTED]	-0,16137382	1,776705265	2,40287173	n.a
An2005	main	Male	[REDACTED]	-1,44329922	2,166552479	2,26787748	n.a
An2006	Recovery	Male	[REDACTED]	-0,11680113	1,854128259	3,36890984	1,78437408
An2007	Recovery	Male	[REDACTED]	-1,11817076	1,788354328	2,51824467	1,269429396
An2008	Recovery	Male	[REDACTED]	-0,96153676	2,156729511	2,9363407	1,853591194
An2009	Recovery	Male	[REDACTED]	-1,23319739	2,29523397	2,5601288	-2,900377667
An2010	Recovery	Male	[REDACTED]	-1,17451325	2,004816172	2,91051184	1,412285004
An2501	main	Female	[REDACTED]	-0,62845174	2,627119901	2,4701738	n.a
An2502	main	Female	[REDACTED]	-0,33314916	excluded	2,47456769	n.a
An2503	main	Female	[REDACTED]	-0,57110879	excluded	1,33030004	n.a
An2504	main	Female	[REDACTED]	-0,63607704	2,800534803	1,85686748	n.a
An2505	main	Female	[REDACTED]	0,32351865	2,084499103	1,75167857	n.a
An2506	Recovery	Female	[REDACTED]	-0,4492649	2,687497866	3,16311201	2,238087504
An2507	Recovery	Female	[REDACTED]	-0,9019505	2,309838864	3,32777228	2,35364369
An2508	Recovery	Female	[REDACTED]	-0,35136975	2,183013937	3,27940883	1,791456395
An2509	Recovery	Female	[REDACTED]	-0,35196004	2,578489179	3,07823649	2,381285094
An2510	Recovery	Female	[REDACTED]	-1,05510597	2,323218527	2,59048828	1,772737809

END OF DOCUMENT

	PAGE : 14 of 16
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Appendix 16

Document Revision History			
Version Number	Section	Description of Change	Justification of Change
1.0	All	This is the first issuance of this document	New document

Appendix 16

APPROVAL PAGE

Approver Name	Justification	Date
[REDACTED]	Subject Matter Expert	09-Feb-2018 06:07:15 EST
[REDACTED]	Department Approval	09-Feb-2018 10:37:45 EST
[REDACTED]	Author Approval	21-Feb-2018 04:32:16 EST

[REDACTED]	[REDACTED]	PAGE : 16 of 16
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Appendix 17
Individual Organ Weights**Explanation Page**

Abbreviation	Description	Abbreviation	Description
AVS	Aberrant value suppressed/excluded from mean/statistical calculations	Exc	Excluded from relative, mean/statistical calculations
MPE	Macroscopic pathology – excluded from mean/statistical calculations	MPI	Macroscopic pathology – included in mean/statistical calculations
OA	Omitted activity	ONP	Organ not present for weighing
OPOP	Only one of the paired organs present for weighing	X	Excluded (applied with one of the exclusion flags)
LYMPH	Medial iliac		
NODE			

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

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 18
Individual Absolute Organ Weights Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Body Weight kg	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	1001	2.8	10.098	2.309	0.331	0.030	1.102	0.323
	1002	3.5	10.125	2.309	0.278	0.029	0.536	0.453
	1003	2.7	10.316	2.250	0.248	0.029	0.661	0.378
	1004	3.4	10.189	2.249	0.240	0.043	0.696	0.498
	1005	2.9	9.829	2.046	0.421	0.056	0.290	0.348
2M	2001	2.3	8.752	1.834	0.260	0.043	0.839	0.332
	2002	3.1	8.711	1.396	0.206	0.039	0.847	0.345
	2003	2.6	9.767	2.111	0.298	0.031	0.645	0.246
	2004	3.1	9.994	2.326	0.262	0.030	0.914	0.316
	2005	2.7	9.718	1.638	0.299	0.038	0.575	0.265

Appendix 18
Individual Absolute Organ Weights Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	Group / Animal No.								
		HEART g	KIDNEY g	LIVER g	LYMPH NODE g	SPLEEN g	TESTIS g	THYMUS g	
1M	1001	8.571	15.331	115.287	0.017	1.226	6.314	4.302	
	1002	11.831	23.051	130.181	0.005	1.775	4.612	5.389	
	1003	8.506	19.209	122.664	0.015	0.791	4.035	4.252	
	1004	8.952	21.599	142.969	0.045	1.244	4.633	4.998	
	1005	7.846	17.099	113.249	0.066	1.069	3.840	2.823	
2M	2001	6.717	15.791	71.745	0.147	0.935	3.514	2.290	
	2002	8.258	18.264	106.761	0.102	1.147	3.893	4.630	
	2003	6.639	17.486	117.563	0.310	1.054	3.825	2.429	
	2004	8.475	19.628	105.314	0.329	1.966	4.162	3.466	
	2005	7.078	16.275	95.774	0.262	1.238	2.677	3.347	

Appendix 18
Individual Absolute Organ Weights Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Body Weight kg	BRAIN g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND THYROID g	HEART g	KIDNEY g
1F	1501	3.2	10.787	0.181	0.028	0.302	8.662	15.677
	1502	2.9	9.917	0.191	0.034	0.266	7.757	16.376
	1503	3.0	10.606	0.256	0.048	0.345	7.662	17.525
	1504	3.1	10.026	0.308	0.037	0.290	8.491	17.261
	1505	3.1	10.292	0.170	0.044	0.354	7.150	14.499
2F	2501	3.1	9.469	0.279	0.025	0.243	7.785	14.305
	2502	3.0	9.922	0.244	0.031	0.340	7.182	14.281
	2503	3.0	10.817	0.313	0.029	0.318	9.153	14.750
	2504	3.1	9.709	0.221	0.032	0.285	7.608	14.981
	2505	3.1	9.741	0.312	0.032	0.295	8.037	15.221

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 18
Individual Absolute Organ Weights Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	Group / Animal No.	LIVER	LYMPH NODE	OVARY	SPLEEN	THYMUS
		g	g	g	g	g
1F	1501	124.946	0.011	0.213	0.879	4.217
	1502	110.795	0.029	0.433	1.600	2.990
	1503	109.725	0.054	0.324	2.455	2.948
	1504	108.107	0.053	0.372	1.597	4.793
	1505	124.925	0.042	0.269	1.576	3.280
2F	2501	115.121	0.156	0.311	2.200	2.194
	2502	93.052	0.749	0.271	1.949	4.179
	2503	109.687	0.298	0.363	2.729	3.235
	2504	99.164	0.484	0.482	2.313	3.446
	2505	123.819	0.272	0.360	1.914	3.876

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 18
Individual Absolute Organ Weights Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Body Weight kg	BRAIN g	EPIDIDYMIS g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND PROSTATE g	GLAND THYROID g
1M	1006	3.1	9.240	2.570	0.297	0.017	0.641	0.270
	1007	3.3	10.182	2.649	0.228	0.018	0.785	0.230
	1008	2.9	9.976	2.166	0.257	0.018	0.514	0.293
	1009	3.1	10.171	2.275	0.241	0.034	0.553	0.334
	1010	2.8	9.009	1.878	0.373	0.030XAVS	0.903	0.297
2M	2006	2.8	9.301	2.029	0.231	0.016	0.640	0.203
	2007	3.2	9.559	3.072	0.338	0.025	1.701	0.294
	2008	3.5	10.331	2.910	0.406	0.055	1.117	0.430
	2009	3.1	9.909	2.434	0.281	0.049	0.840	0.299
	2010	3.1	9.752	2.703	0.302	0.024	1.163	0.442

Appendix 18
Individual Absolute Organ Weights Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Sex	Group / Animal No.								
		HEART g	KIDNEY g	LIVER g	LYMPH NODE g	SPLEEN g	TESTIS g	THYMUS g	
1M	1006	9.074	18.203	119.561	0.058	1.177	5.113	3.692	
	1007	9.706	16.935	110.499	0.011	0.941	5.991	3.519	
	1008	7.330	16.481	97.429	0.012	0.828	4.692	2.752	
	1009	8.812	16.553	114.581	0.024	1.025	5.154	5.064	
	1010	6.550	16.119	110.842	0.012	1.225	5.048	1.861	
2M	2006	8.444	17.691	117.768	0.083	1.392	4.575	3.768	
	2007	8.952	17.204	142.941	0.031	1.886	5.494	3.666	
	2008	9.641	18.068	134.622	0.024	1.198	6.090	4.008	
	2009	8.831	20.746	124.591	0.032	1.658	5.168	2.583	
	2010	7.855	17.149	119.496	0.028	0.702	4.894	3.216	

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 18
Individual Absolute Organ Weights Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	Body Weight kg	BRAIN g	GLAND ADRENAL g	GLAND PITUITARY g	GLAND THYROID g	HEART g	KIDNEY g
1F	1506	3.1	10.120	0.258	0.030	0.325	7.974	15.080
	1507	3.0	9.673	0.260	0.036	0.308	8.354	12.794XOPOP
	1508	3.0	10.601	0.302	0.045	0.378	8.306	17.295
	1509	3.2	10.423	0.344	0.032	0.437	8.627	15.615
	1510	3.5	10.850	0.274	0.037	0.273	8.198	16.651
2F	2506	3.6	9.196	0.332	0.026	0.245	9.115	20.485
	2507	3.1	10.156	0.272	0.050	0.199XAVS	8.749	14.518
	2508	3.5	9.080	0.224	0.032	0.299	9.018	14.750
	2509	3.6	10.065	0.210	0.036	0.349	8.198	13.549
	2510	3.1	9.766	0.284	0.038	0.364	8.173	14.973

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 18
Individual Absolute Organ Weights Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Sex	Group / Animal No.	LIVER	LYMPH NODE	OVARY	SPLEEN	THYMUS
		g	g	g	g	g
1F	1506	118.217	0.022	0.292	1.144	2.652
	1507	97.009	0.011	0.553	1.828	3.184
	1508	95.822	0.060	0.525	1.005	3.140
	1509	82.788	0.042	0.330	1.358	3.253
	1510	126.055	0.047	0.838	1.516	4.411
2F	2506	132.465	0.007	0.328	1.394	3.462
	2507	91.968	0.041	0.570	1.868	3.470
	2508	97.531	0.025	0.412	1.584	3.323
	2509	96.159	0.020	0.369	1.894	3.084
	2510	87.578	0.028	0.694	1.490	2.708

Appendix 19
Individual Organ Weights Relative to Body Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1001	0.3606	0.0825	0.0118	0.0011	0.0394	0.0115	0.3061
	1002	0.2893	0.0660	0.0079	0.0008	0.0153	0.0129	0.3380
	1003	0.3821	0.0833	0.0092	0.0011	0.0245	0.0140	0.3150
	1004	0.2997	0.0661	0.0071	0.0013	0.0205	0.0146	0.2633
	1005	0.3389	0.0706	0.0145	0.0019	0.0100	0.0120	0.2706
2M	2001	0.3805	0.0797	0.0113	0.0019	0.0365	0.0144	0.2920
	2002	0.2810	0.0450	0.0066	0.0013	0.0273	0.0111	0.2664
	2003	0.3757	0.0812	0.0115	0.0012	0.0248	0.0095	0.2553
	2004	0.3224	0.0750	0.0085	0.0010	0.0295	0.0102	0.2734
	2005	0.3599	0.0607	0.0111	0.0014	0.0213	0.0098	0.2621

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 19
Individual Organ Weights Relative to Body Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	Group / Animal No.	Organ Weights (% of body weight)					
		KIDNEY %	LIVER %	LYMPH NODE %	SPLEEN %	TESTIS %	THYMUS %
1M	1001	0.5475	4.1174	0.0006	0.0438	0.2255	0.1536
	1002	0.6586	3.7195	0.0001	0.0507	0.1318	0.1540
	1003	0.7114	4.5431	0.0006	0.0293	0.1494	0.1575
	1004	0.6353	4.2050	0.0013	0.0366	0.1363	0.1470
	1005	0.5896	3.9051	0.0023	0.0369	0.1324	0.0973
2M	2001	0.6866	3.1193	0.0064	0.0407	0.1528	0.0996
	2002	0.5892	3.4439	0.0033	0.0370	0.1256	0.1494
	2003	0.6725	4.5217	0.0119	0.0405	0.1471	0.0934
	2004	0.6332	3.3972	0.0106	0.0634	0.1343	0.1118
	2005	0.6028	3.5472	0.0097	0.0459	0.0991	0.1240

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 19
Individual Organ Weights Relative to Body Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	BRAIN %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND THYROID %	HEART %	KIDNEY %	LIVER %
1F	1501	0.3371	0.0057	0.0009	0.0094	0.2707	0.4899	3.9046
	1502	0.3420	0.0066	0.0012	0.0092	0.2675	0.5647	3.8205
	1503	0.3535	0.0085	0.0016	0.0115	0.2554	0.5842	3.6575
	1504	0.3234	0.0099	0.0012	0.0094	0.2739	0.5568	3.4873
	1505	0.3320	0.0055	0.0014	0.0114	0.2306	0.4677	4.0298
2F	2501	0.3055	0.0090	0.0008	0.0078	0.2511	0.4615	3.7136
	2502	0.3307	0.0081	0.0010	0.0113	0.2394	0.4760	3.1017
	2503	0.3606	0.0104	0.0010	0.0106	0.3051	0.4917	3.6562
	2504	0.3132	0.0071	0.0010	0.0092	0.2454	0.4833	3.1988
	2505	0.3142	0.0101	0.0010	0.0095	0.2593	0.4910	3.9942

Appendix 19
Individual Organ Weights Relative to Body Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Sex	Group / Animal No.				
		LYMPH NODE %	OVARY %	SPLEEN %	THYMUS %
1F	1501	0.0003	0.0067	0.0275	0.1318
	1502	0.0010	0.0149	0.0552	0.1031
	1503	0.0018	0.0108	0.0818	0.0983
	1504	0.0017	0.0120	0.0515	0.1546
	1505	0.0014	0.0087	0.0508	0.1058
2F	2501	0.0050	0.0100	0.0710	0.0708
	2502	0.0250	0.0090	0.0650	0.1393
	2503	0.0099	0.0121	0.0910	0.1078
	2504	0.0156	0.0155	0.0746	0.1112
	2505	0.0088	0.0116	0.0617	0.1250

Appendix 19
Individual Organ Weights Relative to Body Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	BRAIN %	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %
1M	1006	0.2981	0.0829	0.0096	0.0005	0.0207	0.0087	0.2927
	1007	0.3085	0.0803	0.0069	0.0005	0.0238	0.0070	0.2941
	1008	0.3440	0.0747	0.0089	0.0006	0.0177	0.0101	0.2528
	1009	0.3281	0.0734	0.0078	0.0011	0.0178	0.0108	0.2843
	1010	0.3218	0.0671	0.0133	--AVS	0.0323	0.0106	0.2339
2M	2006	0.3322	0.0725	0.0083	0.0006	0.0229	0.0073	0.3016
	2007	0.2987	0.0960	0.0106	0.0008	0.0532	0.0092	0.2798
	2008	0.2952	0.0831	0.0116	0.0016	0.0319	0.0123	0.2755
	2009	0.3196	0.0785	0.0091	0.0016	0.0271	0.0096	0.2849
	2010	0.3146	0.0872	0.0097	0.0008	0.0375	0.0143	0.2534

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 19
Individual Organ Weights Relative to Body Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Sex	Group / Animal No.	Organ Weights (% of body weight)					
		KIDNEY %	LIVER %	LYMPH NODE %	SPLEEN %	TESTIS %	THYMUS %
1M	1006	0.5872	3.8568	0.0019	0.0380	0.1649	0.1191
	1007	0.5132	3.3485	0.0003	0.0285	0.1815	0.1066
	1008	0.5683	3.3596	0.0004	0.0286	0.1618	0.0949
	1009	0.5340	3.6962	0.0008	0.0331	0.1663	0.1634
	1010	0.5757	3.9586	0.0004	0.0438	0.1803	0.0665
2M	2006	0.6318	4.2060	0.0030	0.0497	0.1634	0.1346
	2007	0.5376	4.4669	0.0010	0.0589	0.1717	0.1146
	2008	0.5162	3.8463	0.0007	0.0342	0.1740	0.1145
	2009	0.6692	4.0191	0.0010	0.0535	0.1667	0.0833
	2010	0.5532	3.8547	0.0009	0.0226	0.1579	0.1037

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 19
Individual Organ Weights Relative to Body Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	BRAIN %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND THYROID %	HEART %	KIDNEY %	LIVER %
1F	1506	0.3265	0.0083	0.0010	0.0105	0.2572	0.4865	3.8135
	1507	0.3224	0.0087	0.0012	0.0103	0.2785	--OPOP	3.2336
	1508	0.3534	0.0101	0.0015	0.0126	0.2769	0.5765	3.1941
	1509	0.3257	0.0108	0.0010	0.0137	0.2696	0.4880	2.5871
	1510	0.3100	0.0078	0.0011	0.0078	0.2342	0.4757	3.6016
2F	2506	0.2554	0.0092	0.0007	0.0068	0.2532	0.5690	3.6796
	2507	0.3276	0.0088	0.0016	--AVS	0.2822	0.4683	2.9667
	2508	0.2594	0.0064	0.0009	0.0085	0.2577	0.4214	2.7866
	2509	0.2796	0.0058	0.0010	0.0097	0.2277	0.3764	2.6711
	2510	0.3150	0.0092	0.0012	0.0117	0.2636	0.4830	2.8251

Appendix 19
Individual Organ Weights Relative to Body Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Sex	Group / Animal No.				
		LYMPH NODE %	OVARY %	SPLEEN %	THYMUS %
1F	1506	0.0007	0.0094	0.0369	0.0855
	1507	0.0004	0.0184	0.0609	0.1061
	1508	0.0020	0.0175	0.0335	0.1047
	1509	0.0013	0.0103	0.0424	0.1017
	1510	0.0013	0.0239	0.0433	0.1260
2F	2506	0.0002	0.0091	0.0387	0.0962
	2507	0.0013	0.0184	0.0603	0.1119
	2508	0.0007	0.0118	0.0453	0.0949
	2509	0.0006	0.0103	0.0526	0.0857
	2510	0.0009	0.0224	0.0481	0.0874

Appendix 20
Individual Organ Weights Relative to Brain Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1001	22.8659	3.2779	0.2971	10.9131	3.1987	84.8782	151.8221
	1002	22.8049	2.7457	0.2864	5.2938	4.4741	116.8494	227.6642
	1003	21.8108	2.4040	0.2811	6.4075	3.6642	82.4544	186.2059
	1004	22.0728	2.3555	0.4220	6.8309	4.8876	87.8595	211.9835
	1005	20.8160	4.2832	0.5697	2.9505	3.5405	79.8250	173.9648
2M	2001	20.9552	2.9707	0.4913	9.5864	3.7934	76.7482	180.4273
	2002	16.0257	2.3648	0.4477	9.7233	3.9605	94.7997	209.6659
	2003	21.6136	3.0511	0.3174	6.6039	2.5187	67.9738	179.0314
	2004	23.2740	2.6216	0.3002	9.1455	3.1619	84.8009	196.3978
	2005	16.8553	3.0768	0.3910	5.9169	2.7269	72.8339	167.4727

Appendix 20
Individual Organ Weights Relative to Brain Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Animal	Sex	No.	LIVER %	LYMPH NODE %	SPLEEN %	TESTIS %	THYMUS %
1M	1001	1141.6815	0.1684	12.1410	62.5272	42.6025	
	1002	1285.7383	0.0494	17.5309	45.5506	53.2247	
	1003	1189.0655	0.1454	7.6677	39.1140	41.2175	
	1004	1403.1701	0.4417	12.2092	45.4706	49.0529	
	1005	1152.1925	0.6715	10.8760	39.0681	28.7211	
2M	2001	819.7555	1.6796	10.6833	40.1508	26.1654	
	2002	1225.5883	1.1709	13.1673	44.6906	53.1512	
	2003	1203.6756	3.1740	10.7914	39.1625	24.8695	
	2004	1053.7723	3.2920	19.6718	41.6450	34.6808	
	2005	985.5320	2.6960	12.7392	27.5468	34.4412	

Appendix 20
Individual Organ Weights Relative to Brain Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Sex	Animal No.	GLAND ADRENAL %	GLAND PITUITARY %	GLAND THYROID %	HEART %	KIDNEY %	LIVER %	LYMPH NODE %
1F	1501	1.6779	0.2596	2.7997	80.3004	145.3323	1158.3017	0.1020
	1502	1.9260	0.3428	2.6823	78.2192	165.1306	1117.2230	0.2924
	1503	2.4137	0.4526	3.2529	72.2421	165.2367	1034.5559	0.5091
	1504	3.0720	0.3690	2.8925	84.6898	172.1624	1078.2665	0.5286
	1505	1.6518	0.4275	3.4396	69.4714	140.8764	1213.8068	0.4081
2F	2501	2.9465	0.2640	2.5663	82.2157	151.0719	1215.7672	1.6475
	2502	2.4592	0.3124	3.4267	72.3846	143.9327	937.8351	7.5489
	2503	2.8936	0.2681	2.9398	84.6168	136.3594	1014.0242	2.7549
	2504	2.2762	0.3296	2.9354	78.3603	154.3001	1021.3616	4.9851
	2505	3.2030	0.3285	3.0284	82.5069	156.2571	1271.1118	2.7923

Appendix 20
Individual Organ Weights Relative to Brain Weight Main Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Animal		OVARY %	SPLEEN %	THYMUS %
Sex	No.			
1F	1501	1.9746	8.1487	39.0934
	1502	4.3662	16.1339	30.1502
	1503	3.0549	23.1473	27.7956
	1504	3.7104	15.9286	47.8057
	1505	2.6137	15.3129	31.8694
2F	2501	3.2844	23.2337	23.1703
	2502	2.7313	19.6432	42.1185
	2503	3.3558	25.2288	29.9066
	2504	4.9645	23.8233	35.4928
	2505	3.6957	19.6489	39.7906

Appendix 20
Individual Organ Weights Relative to Brain Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	EPIDIDYMIS %	GLAND ADRENAL %	GLAND PITUITARY %	GLAND PROSTATE %	GLAND THYROID %	HEART %	KIDNEY %
1M	1006	27.8139	3.2143	0.1840	6.9372	2.9221	98.2035	197.0022
	1007	26.0165	2.2392	0.1768	7.7097	2.2589	95.3251	166.3229
	1008	21.7121	2.5762	0.1804	5.1524	2.9370	73.4763	165.2065
	1009	22.3675	2.3695	0.3343	5.4370	3.2838	86.6385	162.7470
	1010	20.8458	4.1403	--AVS	10.0233	3.2967	72.7051	178.9211
2M	2006	21.8149	2.4836	0.1720	6.8810	2.1826	90.7859	190.2054
	2007	32.1373	3.5359	0.2615	17.7947	3.0756	93.6500	179.9770
	2008	28.1677	3.9299	0.5324	10.8121	4.1622	93.3211	174.8911
	2009	24.5635	2.8358	0.4945	8.4771	3.0175	89.1210	209.3652
	2010	27.7174	3.0968	0.2461	11.9258	4.5324	80.5476	175.8511

Appendix 20
Individual Organ Weights Relative to Brain Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Animal Sex	No.	LIVER %	LYMPH NODE %	SPLEEN %	TESTIS %	THYMUS %
1M	1006	1293.9502	0.6277	12.7381	55.3355	39.9567
	1007	1085.2387	0.1080	9.2418	58.8391	34.5610
	1008	976.6339	0.1203	8.2999	47.0329	27.5862
	1009	1126.5461	0.2360	10.0777	50.6735	49.7886
	1010	1230.3474	0.1332	13.5975	56.0329	20.6571
2M	2006	1266.1864	0.8924	14.9661	49.1883	40.5118
	2007	1495.3552	0.3243	19.7301	57.4746	38.3513
	2008	1303.0878	0.2323	11.5962	58.9488	38.7959
	2009	1257.3519	0.3229	16.7323	52.1546	26.0672
	2010	1225.3486	0.2871	7.1985	50.1846	32.9779

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 20
Individual Organ Weights Relative to Brain Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10^11 vp

Group / Sex	Animal No.	GLAND ADRENAL %	GLAND PITUITARY %	GLAND THYROID %	HEART %	KIDNEY %	LIVER %	LYMPH NODE %
1F	1506	2.5494	0.2964	3.2115	78.7945	149.0119	1168.1522	0.2174
	1507	2.6879	0.3722	3.1841	86.3641	--OPOP	1002.8843	0.1137
	1508	2.8488	0.4245	3.5657	78.3511	163.1450	903.8959	0.5660
	1509	3.3004	0.3070	4.1927	82.7689	149.8129	794.2819	0.4030
	1510	2.5253	0.3410	2.5161	75.5576	153.4654	1161.7972	0.4332
2F	2506	3.6103	0.2827	2.6642	99.1192	222.7599	1440.4632	0.0761
	2507	2.6782	0.4923	--AVS	86.1461	142.9500	905.5534	0.4037
	2508	2.4670	0.3524	3.2930	99.3172	162.4449	1074.1300	0.2753
	2509	2.0864	0.3577	3.4675	81.4506	134.6150	955.3800	0.1987
	2510	2.9080	0.3891	3.7272	83.6883	153.3176	896.7643	0.2867

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 20
Individual Organ Weights Relative to Brain Weight Recovery Study

Group 1 - Control

Group 2 - [REDACTED] 1x10¹¹ vp

Group / Animal Sex	No.	OVARY %	SPLEEN %	THYMUS %
1F	1506	2.8854	11.3043	26.2055
	1507	5.7169	18.8980	32.9164
	1508	4.9524	9.4802	29.6198
	1509	3.1661	13.0289	31.2098
	1510	7.7235	13.9724	40.6544
2F	2506	3.5668	15.1588	37.6468
	2507	5.6124	18.3931	34.1670
	2508	4.5374	17.4449	36.5969
	2509	3.6662	18.8177	30.6408
	2510	7.1063	15.2570	27.7289

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1001	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : left caudal lobe, 1mm diam, red (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GALLBLADDER : Postmortem Change Present

GALLBLADDER : Examined

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

KIDNEY : Mineralization; cortical, minimal

KIDNEY : Basophilia; cortical, minimal

LUNG : Congestion; agonal, mild [LUNG : Focus; dark : left caudal lobe, 1mm diam, red (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1002	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; mottled : all lobes (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GALLBLADDER : Postmortem Change Present

GALLBLADDER : Examined

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; mottled : all lobes (G)]

LYMPH NODE, ILIAC : One Of A Pair Available For Evaluation.

LYMPH NODE, ILIAC : Examined

URETER : One Of A Pair Available For Evaluation.

URETER : Examined

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1003	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; mottled : all lobes (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

GLAND, THYROID : One Of A Pair Available For Evaluation.

GLAND, THYROID : Examined

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; mottled : all lobes (G)]

LYMPH NODE, ILIAC : One Of A Pair Available For Evaluation.

LYMPH NODE, ILIAC : Examined

TESTIS : Atrophy; focal, minimal, seminiferous tubule

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GALLBLADDER - Postmortem Change Precludes Evaluation.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1004	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, THYROID : Discoloration; dark : red, both (TGL)

LUNG : Discoloration; mottled : all lobes (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LARGE INTESTINE, APPENDIX : Abscess; minimal : microabscess

LUNG : Congestion; agonal, marked [LUNG : Discoloration; mottled : all lobes (G)]

LYMPH NODE, ILIAC : One Of A Pair Available For Evaluation.

LYMPH NODE, ILIAC : Examined

NO CORRELATE : No correlating lesion [GLAND, THYROID : Discoloration; dark : red, both (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1005	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, PROSTATE : Small (TGL)

LUNG : Discoloration; mottled : all lobes (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

GLAND, PROSTATE : Immaturity [GLAND, PROSTATE : Small (G)]

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; mottled : all lobes (G)]

SITE, ADMINISTRATION, 3 : Inflammation, mononuclear cell; minimal, striated muscle

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

GALLBLADDER - Postmortem Change Precludes Evaluation.

GALT - Insufficient Tissue Available For Evaluation.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1006	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

LYMPH NODE, ILIAC : One Of A Pair Available For Evaluation.

LYMPH NODE, ILIAC : Examined

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

LARGE INTESTINE, COLON - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1007	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1008	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; mottled : All lobes. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, SEMINAL VESICLE : incomplete

KIDNEY : Basophilia; cortical, minimal

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; mottled : All lobes. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1009	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

LUNG : Congestion; agonal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1010	Group: 1	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, PITUITARY : Tissue Incomplete

LUNG : Discoloration; dark : All Lobes, Red (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

KIDNEY : Mineralization; cortical, minimal

KIDNEY : Basophilia; cortical, minimal

LUNG : Congestion; agonal, mild [LUNG : Discoloration; dark : All Lobes, Red (G)]

TESTIS : Atrophy; focal, mild, seminiferous tubule : with dilatation

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1501	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

SITE, ADMINISTRATION, 2 : Discoloration; dark : subcutis, red (TGL)

SITE, ADMINISTRATION, 3 : Discoloration; dark : subcutis, red (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

VAGINA : Infiltration, mixed cell; mild, in adjacent tissue

SITE, ADMINISTRATION, 3 : Ulceration; focal, mild, epidermis [SITE, ADMINISTRATION, 3 : Discoloration; dark : subcutis, red (G)]

SITE, ADMINISTRATION, 3 : Inflammation, mixed cell; mild, subcutaneous tissue

SITE, ADMINISTRATION, 3 : Hemorrhage; mild, subcutaneous tissue [SITE, ADMINISTRATION, 3 : Discoloration; dark : subcutis, red (G)]

NO CORRELATE : No correlating lesion [SITE, ADMINISTRATION, 2 : Discoloration; dark : subcutis, red (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY; MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

Appendix 21

None

[REDACTED] Individual Necropsy and Histopathological Findings

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1502	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; mottled : all lobes (TGL)

SITE, ADMINISTRATION, 2 : Discoloration; dark : subcutis, red (TGL)

SITE, ADMINISTRATION, 3 : Discoloration; dark : subcutis, red (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, LACRIMAL : One Of A Pair Available For Evaluation.

GLAND, LACRIMAL : Examined

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

KIDNEY : Mineralization; cortical, minimal

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; mottled : all lobes (G)]

LUNG : Cyst; alveolar, moderate : relates to cyst noted at trim

SITE, ADMINISTRATION, 2 : Hemorrhage; minimal, subcutaneous tissue [SITE, ADMINISTRATION, 2 :

Discoloration; dark : subcutis, red (G)]

SITE, ADMINISTRATION, 3 : Hemorrhage; mild, subcutaneous tissue [SITE, ADMINISTRATION, 3 : Discoloration; dark : subcutis, red (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY; MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE; APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1503	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, ILIAC : Discoloration; dark : left, dark (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

LYMPH NODE, ILIAC : Erythrocytosis; moderate, sinusoid : left [LYMPH NODE, ILIAC : Discoloration; dark : left, dark (G)]

LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, mild : with reduced number of germinal centers

THYMUS : Atrophy; cortical, minimal

SITE, ADMINISTRATION, 1 : Infiltration, mononuclear cell; focal, minimal, striated muscle

SITE, ADMINISTRATION, 3 : Inflammation, mononuclear cell; focal, minimal, striated muscle

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, MANDIBULAR; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1504	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, ILIAC : Discoloration; dark : left (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, ADRENAL : Hypertrophy; minimal, cortex : fasciculata/reticularis

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

LARGE INTESTINE, RECTUM : Infiltration, heterophilic; minimal, in adjacent tissue

LYMPH NODE, ILIAC : Erythrocytosis; moderate, sinusoid : left [LYMPH NODE, ILIAC : Discoloration; dark : left (G)]

SITE, ADMINISTRATION, 3 : Ulceration; focal, minimal, epidermis

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY; MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARYNX; LIVER; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1505	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; dark : all lobes (TGL)

OVIDUCT : Cyst; clear : left, 4mm diam (TGL)

TRACHEA : Fluid accumulation; dark : frothy, red

SITE, ADMINISTRATION, 2 : Discoloration; dark : subcutis, red (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

LUNG : Congestion; agonal, marked [LUNG : Discoloration; dark : all lobes (G)]

LYMPH NODE, ILIAC : One Of A Pair Available For Evaluation.

LYMPH NODE, ILIAC : Examined

OVIDUCT : Cyst; mild [OVIDUCT : Cyst; clear : left, 4mm diam (G)]

SITE, ADMINISTRATION, 2 : Hemorrhage; minimal, subcutaneous tissue [SITE, ADMINISTRATION, 2 :

Discoloration; dark : subcutis, red (G)]

SITE, ADMINISTRATION, 2 : Pigmented macrophage; minimal, subcutaneous tissue [SITE, ADMINISTRATION, 2 : Discoloration; dark : subcutis, red (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1506	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

TRACHEA : Fluid accumulation; pale : Frothy

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, ADRENAL : Cortex And One Medulla Available For Evaluation.

GLAND, ADRENAL : Examined

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

KIDNEY : Mineralization; cortical, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1507	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

KIDNEY : Left not present at necropsy

KIDNEY : One Of A Pair Available For Evaluation.

KIDNEY : Submitted

OVARY : Enlargement : left (TGL)

OVIDUCT : Cyst; clear : Left, few, up to 4mm diam. (TGL)

THYMUS : Discoloration; mottled : Left lobe. (TGL)

URETER : Left not present at necropsy

URETER : One Of A Pair Available For Evaluation.

URETER : Submitted

UTERUS : Abnormal appearance : Left horn not present at necropsy. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

KIDNEY : One Of A Pair Available For Evaluation.

KIDNEY : Examined

OVIDUCT : One Of A Pair Available For Evaluation.

OVIDUCT : Examined

OVIDUCT : Cyst; moderate [OVIDUCT : Cyst; clear : Left, few, up to 4mm diam. (G)]

URETER : One Of A Pair Available For Evaluation.

URETER : Examined

UTERUS : only one horn and one cervix

UTERUS : Congenital anomaly [UTERUS : Abnormal appearance : Left horn not present at necropsy. (G)]

NO CORRELATE : No correlating lesion [THYMUS : Discoloration; mottled : Left lobe. (G) | OVARY : Enlargement : left (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1508	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : Left caudal lobe, 1mm diam. (TGL)

SPLEEN : Abnormal appearance : second spleen weight, 0.627g (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

KIDNEY : Mineralization; cortical, minimal

KIDNEY : Basophilia; cortical, minimal

LIVER : Fatty change; hepatocellular, focal, minimal

NO CORRELATE : No correlating lesion [LUNG : Focus; dark : Left caudal lobe, 1mm diam. (G) | SPLEEN : Abnormal appearance : second spleen weight, 0.627g (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY; MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LUNG; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

MUSCLE, DIAPHRAGM - Lost During Necropsy.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1509	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; dark : Red, all lobes. (TGL)

LUNG : Abnormal consistency : Spongy, all lobes. (TGL)

LYMPH NODE, ILIAC : Discoloration; dark : Red, bilateral. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; dark : Red, all lobes. (G) | LUNG : Abnormal consistency : Spongy, all lobes. (G)]

LYMPH NODE, ILIAC : Erythrocytosis; minimal, sinusoid [LYMPH NODE, ILIAC : Discoloration; dark : Red, bilateral. (G)]

NERVE, OPTIC : One Of A Pair Available For Evaluation.

NERVE, OPTIC : Examined

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 1510	Group: 1	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 0	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; dark : All lobes. (TGL)

OVIDUCT : Cyst; clear : Left, few, up to 4mm diam. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Basophilia; cortical, minimal

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; dark : All lobes. (G)]

NERVE, OPTIC : One Of A Pair Available For Evaluation.

NERVE, OPTIC : Examined

NO CORRELATE : No correlating lesion [OVIDUCT : Cyst; clear : Left, few, up to 4mm diam. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY; MANDIBULAR; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2001	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; mottled : All lobes. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GALLBLADDER : Postmortem Change Present

GALLBLADDER : Examined

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; mottled : All lobes. (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : both

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

TESTIS : Atrophy; multifocal, mild, seminiferous tubule

SITE, ADMINISTRATION, 1 : Hemorrhage; minimal, subcutaneous tissue

SITE, ADMINISTRATION, 3 : Infiltration, mixed cell; minimal, fascia

SITE, ADMINISTRATION, 3 : Cellular debris; focal, minimal, epidermis : scab

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2002	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, SALIVARY, MANDIBULAR : Discoloration; dark : Red, left. (TGL)

GLAND, THYROID : Enlargement : Bilateral. (TGL)

SITE, ADMINISTRATION, 3 : Discoloration; dark : Red, subcutis. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GALLBLADDER : Postmortem Change Present

GALLBLADDER : Examined

GLAND, LACRIMAL : One Of A Pair Available For Evaluation.

GLAND, LACRIMAL : Examined

GLAND, SALIVARY, MANDIBULAR : Congestion; agonal, mild [GLAND, SALIVARY, MANDIBULAR : Discoloration; dark : Red, left. (G)]

KIDNEY : Mineralization; cortical, minimal

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : both

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, generalised : right

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

TESTIS : Atrophy; multifocal, mild, seminiferous tubule

SITE, ADMINISTRATION, 3 : Inflammation, mixed cell; moderate, striated muscle

SITE, ADMINISTRATION, 3 : Hemorrhage; mild, fascia [SITE, ADMINISTRATION, 3 : Discoloration; dark : Red, subcutis. (G)]

SITE, ADMINISTRATION, 3 : Necrosis; moderate, striated muscle

NO CORRELATE : No correlating lesion [GLAND, THYROID : Enlargement : Bilateral. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

GALT - Insufficient Tissue Available For Evaluation.

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2003	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, SEMINAL VESICLE : Small : Both horns, 7x2x2mm for both left and right horns. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

LUNG : Congestion; agonal, mild

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : both

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, moderate, generalised : left

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

TESTIS : Atrophy; focal, minimal, seminiferous tubule

SITE, ADMINISTRATION, 1 : Infiltration, mononuclear cell; minimal, fascia

SITE, ADMINISTRATION, 3 : Infiltration, mixed cell; minimal, subcutaneous tissue

NO CORRELATE : No correlating lesion [GLAND, SEMINAL VESICLE : Small : Both horns, 7x2x2mm for both left and right horns. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2004	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, LACRIMAL : One Of A Pair Available For Evaluation.

GLAND, LACRIMAL : Examined

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

KIDNEY : Mineralization; cortical, minimal

KIDNEY : Basophilia; cortical, minimal : with minimal dilatation

KIDNEY : Infiltration, mononuclear cell; cortical, minimal

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : both

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, generalised : right

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

SITE, ADMINISTRATION, 1 : Infiltration, mononuclear cell; minimal, fascia

SITE, ADMINISTRATION, 3 : Inflammation, mixed cell; mild, striated muscle

SITE, ADMINISTRATION, 3 : Infiltration, mixed cell; minimal, subcutaneous tissue

SITE, ADMINISTRATION, 3 : Necrosis; mild, striated muscle

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 2

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2005	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, PROSTATE : Small (TGL)

LUNG : Discoloration; mottled : All lobes. (TGL)

LUNG : Abnormal consistency : Spongy, all lobes. (TGL)

TRACHEA : Fluid accumulation : frothy, pink

SITE, ADMINISTRATION, 3 : Discoloration; dark : Red. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

GLAND, PROSTATE : Immaturity [GLAND, PROSTATE : Small (G)]

LUNG : Congestion; agonal, marked [LUNG : Discoloration; mottled : All lobes. (G) | LUNG : Abnormal consistency : Spongy, all lobes. (G)]

LYMPH NODE, ILIAC : One Of A Pair Available For Evaluation.

LYMPH NODE, ILIAC : Examined

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : right

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, moderate, generalised : right

SPLEEN : Increased cellularity; lymphoid, minimal, germinal center

SITE, ADMINISTRATION, 1 : Infiltration, mononuclear cell; minimal, fascia

SITE, ADMINISTRATION, 3 : Inflammation, mixed cell; moderate, striated muscle

SITE, ADMINISTRATION, 3 : Inflammation, mixed cell; mild, subcutaneous tissue [SITE, ADMINISTRATION, 3 : Discoloration; dark : Red. (G)]

SITE, ADMINISTRATION, 3 : Hemorrhage; mild, fascia [SITE, ADMINISTRATION, 3 : Discoloration; dark : Red. (G)]

SITE, ADMINISTRATION, 3 : Hemorrhage; mild, subcutaneous tissue [SITE, ADMINISTRATION, 3 : Discoloration; dark : Red. (G)]

SITE, ADMINISTRATION, 3 : Necrosis; moderate, striated muscle

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, MESENTERIC - Insufficient Tissue Available For Evaluation.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2006	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

GLAND, THYROID : One Of A Pair Available For Evaluation.

GLAND, THYROID : Examined

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, minimal, germinal center : left

SPLEEN : Increased cellularity; lymphoid, minimal, germinal center

TESTIS : Atrophy; focal, mild, seminiferous tubule : with dilatation

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2007	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10^11 VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, SEMINAL VESICLE : incomplete

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, minimal, germinal center : left

SPLEEN : Increased cellularity; lymphoid, minimal, germinal center

SITE, ADMINISTRATION, 1 : Infiltration, mononuclear cell; focal, minimal, striated muscle

SITE, ADMINISTRATION, 3 : Infiltration, mononuclear cell; focal, minimal, striated muscle

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2008	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, ILIAC : Discoloration; dark : right, red (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

GLAND, PITUITARY : Pars Distalis Available For Evaluation.

GLAND, PITUITARY : Examined

LYMPH NODE, ILIAC : Erythrocytosis; minimal, sinusoid [LYMPH NODE, ILIAC : Discoloration; dark : right, red (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : left

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, MANDIBULAR; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, MESENTERIC - Insufficient Tissue Available For Evaluation.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2009	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; mottled : all lobes (TGL)

LUNG : Abnormal consistency : spongy, all lobes (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

KIDNEY : Basophilia; cortical, minimal

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; mottled : all lobes (G) | LUNG : Abnormal consistency : spongy, all lobes (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : both

NERVE, OPTIC : One Of A Pair Available For Evaluation.

NERVE, OPTIC : Examined

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; TESTIS; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2010	Group: 2	Sex: Male
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin, except eyes and optic nerves submitted in Davidson's and testes in modified Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GALLBLADDER : Postmortem Change Present

GALLBLADDER : Examined

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

KIDNEY : Mineralization; cortical, minimal

KIDNEY : Basophilia; cortical, mild

SPLEEN : Increased cellularity; lymphoid, minimal, germinal center

TESTIS : Atrophy; multifocal, mild, seminiferous tubule : with dilatation

SITE, ADMINISTRATION, 1 : Infiltration, mononuclear cell; focal, minimal, striated muscle

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; EPIDIDYMIS; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, PROSTATE; GLAND, SALIVARY, MANDIBULAR; GLAND, SEMINAL VESICLE; GLAND, THYROID; HEART; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2501	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, ILIAC : Discoloration; dark : Red, right. (TGL)

SITE, ADMINISTRATION, 1 : Discoloration; dark : Red, intramuscular. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GALLBLADDER : Postmortem Change Present

GALLBLADDER : Examined

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

LUNG : Congestion; agonal, mild

LYMPH NODE, ILIAC : Erythrocytosis; mild, sinusoid [LYMPH NODE, ILIAC : Discoloration; dark : Red, right. (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : both

MUSCLE, SKELETAL : Infiltration, mononuclear cell; focal, minimal

SPLEEN : Increased cellularity; lymphoid, minimal, germinal center : with increased number

SITE, ADMINISTRATION, 2 : Degeneration/regeneration; focal, minimal, striated muscle

SITE, ADMINISTRATION, 2 : Infiltration, mononuclear cell; focal, mild, striated muscle : following fascial plane

SITE, ADMINISTRATION, 3 : Inflammation, mixed cell; mild, fascia

NO CORRELATE : No correlating lesion [SITE, ADMINISTRATION, 1 : Discoloration; dark : Red, intramuscular. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2502	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, ILIAC : Enlargement : Bilateral. (TGL)

SITE, ADMINISTRATION, 1 : Discoloration; dark : Red, subcutis. (TGL)

SITE, ADMINISTRATION, 3 : Discoloration; dark : Red, subcutis. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : examined with larynx

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : both [LYMPH NODE, ILIAC : Enlargement : Bilateral. (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, generalised : right, 'generalised' [LYMPH NODE, ILIAC : Enlargement : Bilateral. (G)]

NERVE, OPTIC : One Of A Pair Available For Evaluation.

NERVE, OPTIC : Examined

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

SITE, ADMINISTRATION, 1 : Infiltration, heterophilic; focal, minimal, subcutaneous tissue

SITE, ADMINISTRATION, 3 : Hemorrhage; mild, subcutaneous tissue : extending to fascia [SITE, ADMINISTRATION, 3 : Discoloration; dark : Red, subcutis. (G)]

SITE, ADMINISTRATION, 3 : Infiltration, mixed cell; mild, subcutaneous tissue : extending to fascia

SITE, ADMINISTRATION, 3 : Infiltration, mononuclear cell; focal, minimal, striated muscle

NO CORRELATE : No correlating lesion [SITE, ADMINISTRATION, 1 : Discoloration; dark : Red, subcutis. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2503	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; mottled : All lobes. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

LUNG : Congestion; agonal, moderate : with associated early autolysis [LUNG : Discoloration; mottled : All lobes. (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : right

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

SITE, ADMINISTRATION, 1 : Infiltration, mononuclear cell; focal, minimal, striated muscle

SITE, ADMINISTRATION, 1 : Hemorrhage; minimal, subcutaneous tissue

SITE, ADMINISTRATION, 3 : Infiltration, mixed cell; mild, fascia

SITE, ADMINISTRATION, 3 : Infiltration, mixed cell; multifocal, minimal, striated muscle

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY; MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2504	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Focus; dark : Red, all lobes, few, up to 2mm diam. (TGL)

MUSCLE, SKELETAL : Focus; dark : Red, 9x2mm. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LARYNX : ventral pouch not examined

LUNG : Congestion; agonal, mild [LUNG : Focus; dark : Red, all lobes, few, up to 2mm diam. (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : both

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, moderate, generalised : left

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

SPLEEN : Macrophage aggregation; focal, minimal

SITE, ADMINISTRATION, 1 : Infiltration, mononuclear cell; multifocal, mild, striated muscle

SITE, ADMINISTRATION, 3 : Infiltration, mixed cell; minimal, fascia

SITE, ADMINISTRATION, 3 : Infiltration, mononuclear cell; focal, minimal, striated muscle

NO CORRELATE : No correlating lesion [MUSCLE, SKELETAL : Focus; dark : Red, 9x2mm. (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2505	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Terminal Euthanasia	
	Day (Week) of Death 31 (5)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative.

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; mottled : All lobes. (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, LACRIMAL : One Of A Pair Available For Evaluation.

GLAND, LACRIMAL : Examined

LUNG : Congestion; agonal, mild [LUNG : Discoloration; mottled : All lobes. (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : both

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, moderate, generalised : both

LYMPH NODE, MESENTERIC : Decreased cellularity; lymphoid, mild

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

THYMUS : Atrophy; cortical, minimal

SITE, ADMINISTRATION, 1 : Infiltration, mononuclear cell; focal, minimal, striated muscle

SITE, ADMINISTRATION, 3 : Inflammation, mixed cell; multifocal, moderate, striated muscle

SITE, ADMINISTRATION, 3 : Hemorrhage; moderate, striated muscle

SITE, ADMINISTRATION, 3 : Necrosis; multifocal, moderate, striated muscle

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 2

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2506	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LYMPH NODE, MESENTERIC : Discoloration; dark : red (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

SPLEEN : Increased cellularity; lymphoid, minimal, germinal center

NO CORRELATE : No correlating lesion [LYMPH NODE, MESENTERIC : Discoloration; dark : red (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

LYMPH NODE, ILIAC - Insufficient Tissue Available For Evaluation.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2507	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, THYROID : Right thyroid incomplete, incomplete weight

LUNG : Abnormal consistency : Spongy, all lobes (TGL)

OVARY : weight verified

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

LUNG : Congestion; agonal, moderate [LUNG : Abnormal consistency : Spongy, all lobes (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : right

SPLEEN : Increased cellularity; lymphoid, minimal, germinal center

SITE, ADMINISTRATION, 2 : Degeneration/regeneration; focal, minimal, striated muscle

SITE, ADMINISTRATION, 2 : Infiltration, mononuclear cell; multifocal, mild, striated muscle

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2508	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10^11 VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

GLAND, PARATHYROID : One Of A Pair Available For Evaluation.

GLAND, PARATHYROID : Examined

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PARATHYROID; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LUNG; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACCULUS ROTUNDUS; SPINAL CORD; SPLEEN; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

None

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2509	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10^11 VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

GLAND, LACRIMAL : Discoloration; pale : bilateral, white (TGL)

LUNG : Discoloration; mottled : all lobes (TGL)

LYMPH NODE, ILIAC : Discoloration; dark : right, red (TGL)

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; mottled : all lobes (G)]

LYMPH NODE, ILIAC : Erythrocytosis; minimal, sinusoid [LYMPH NODE, ILIAC : Discoloration; dark : right, red (G)]

LYMPH NODE, ILIAC : Increased cellularity; lymphoid, mild, germinal center : left

NERVE, OPTIC : One Of A Pair Available For Evaluation.

NERVE, OPTIC : Examined

SPLEEN : Increased cellularity; lymphoid, mild, germinal center

NO CORRELATE : No correlating lesion [GLAND, LACRIMAL : Discoloration; pale : bilateral, white (G)]

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, LACRIMAL - Insufficient Tissue Available For Evaluation.

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Animal: 2510	Group: 2	Sex: Female
Species: Rabbit	Strain: New Zealand White	
	Dose: 1x10 ¹¹ VP	
	Removal Reason Recovery Euthanasia	
	Day (Week) of Death 52 (8)	

Gross Pathology Animal Details:

Comments: Tissues submitted in 10% neutral buffered formalin except eyes and optic nerves submitted in Davidson's fixative

Animal Notes: EUTHANASIA VIA ANESTHESIA AND EXSANGUINATION

Gross Pathology Observations:

LUNG : Discoloration; mottled : all lobes (TGL)

LUNG : Abnormal consistency : spongy, all lobes (TGL)

TRACHEA : Fluid accumulation; pale : frothy

Any remaining protocol required tissues, which have been examined, have no visible lesions

Gross Pathology - The following Tissues were Not Examined:

None

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

LUNG : Congestion; agonal, moderate [LUNG : Discoloration; mottled : all lobes (G) | LUNG : Abnormal consistency : spongy, all lobes (G)]

SPLEEN : Increased cellularity; lymphoid, minimal, germinal center

Histo Pathology - The following Tissues were Within Normal Limits:

ARTERY, AORTA; BONE, FEMUR; BONE, STERNUM; BONE MARROW; BRAIN; CERVIX; ESOPHAGUS; EYE; GALLBLADDER; GALT; GLAND, ADRENAL; GLAND, LACRIMAL; GLAND, MAMMARY; GLAND, PITUITARY; GLAND, SALIVARY, MANDIBULAR; GLAND, THYROID; HEART; KIDNEY; LARGE INTESTINE, APPENDIX; LARGE INTESTINE, CECUM; LARGE INTESTINE, COLON; LARGE INTESTINE, RECTUM; LARYNX; LIVER; LYMPH NODE, ILIAC; LYMPH NODE, MANDIBULAR; LYMPH NODE, MESENTERIC; MUSCLE, DIAPHRAGM; MUSCLE, SKELETAL; NERVE, OPTIC; NERVE, SCIATIC; OVARY; OVIDUCT; PANCREAS; SKIN; SMALL INTESTINE, DUODENUM; SMALL INTESTINE, ILEUM; SMALL INTESTINE, JEJUNUM; SMALL INTESTINE, SACculus ROTUNDUS; SPINAL CORD; STOMACH; THYMUS; TONGUE; TRACHEA; URETER; URINARY BLADDER; UTERUS; VAGINA; SITE, ADMINISTRATION, 1; SITE, ADMINISTRATION, 2; SITE, ADMINISTRATION, 3

Histo Pathology - The following Tissues were Not Examined:

GLAND, PARATHYROID - Not Present In Section.

Appendix 21

[REDACTED] Individual Necropsy and Histopathological Findings

Key Page

Codes

(TGL) = Trackable Gross Lesion, (MPF) = Major Pathological Finding, (?) = Questionable, (E) = Excluded, (C) = Clinical Observation, (M) = Mass, (G) = Gross Pathology, (H) = Histo Pathology

Sponsor Reference No. [REDACTED]

Test Facility Study No. [REDACTED]

Appendix 22



FINAL REPORT

Study Phase: Pathology

Test Facility Study No. [REDACTED]

Sponsor Reference No. [REDACTED]

Charles River Laboratories [REDACTED]
[REDACTED]
[REDACTED]

EH33 2NE
UK

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Appendix 22

1. SUMMARY

Intramuscular administration to New Zealand White rabbits of [REDACTED] on 3 occasions (Days 1, 15 and 29) was well tolerated.

At Day 31: microscopic findings associated with administration of [REDACTED] were limited to the local inflammatory effects at the administration sites, and the expected immune response in the draining lymph node and spleen. The findings were as follows; inflammation and/or inflammatory cell infiltration, necrosis or haemorrhage in the striated muscle or fascia/subcutaneous tissue particularly at the Day 29 administration site. There was increased lymphoid cellularity of the germinal center in the iliac lymph node and the spleen; and also increased generalised lymphoid cellularity in the iliac lymph node. These findings correlated with the slightly higher weights recorded for these tissues, and with the gross finding of enlargement of the lymph node in one female. At Days 1 and 15 administration sites, there was a higher incidence and severity of mononuclear cell infiltration of fascia/striated muscle, with striated muscle degeneration/regeneration at Day 15.

At Day 52: following the 3-week recovery period there was good evidence of partial reversibility of the microscopic findings associated with the previous administration of [REDACTED]. Findings at all administration sites were similar, and included mononuclear cell infiltration in the striated muscle with degeneration/regeneration at Day 15.

Increased lymphoid cellularity of the germinal center in the iliac lymph node and spleen was still recorded but at lower severity and incidence; increased generalised lymphoid cellularity of the iliac lymph node was no longer recorded. These findings correlated with slightly higher spleen (males and females) and lymph node weights (males).

2. INTRODUCTION

This report presents the pathology findings in rabbits assigned to the study entitled *An Intramuscular Repeated Dose Combined Toxicity and Local Tolerance Study [REDACTED] Vaccine in New Zealand White Rabbits with a 3 Week Recovery Period* (Study No. [REDACTED]). The test item is [REDACTED] replication incompetent non-pathogenic [REDACTED] based vaccine encoding [REDACTED] antigens. The vaccine is being developed for the prophylactic immunisation against [REDACTED] infection. The objective of this study was to determine the potential toxicity and local tolerance of homologous prime boost combinations of [REDACTED] when given by intramuscular injection on 3 occasions (Days 1, 15 and 29) to rabbits, and to evaluate the potential reversibility of any findings during a 3-week recovery period.

The study was sponsored by [REDACTED] Research & Development, a division of [REDACTED]

[REDACTED] was the Study Director.

Appendix 22**3. MATERIALS AND METHODS**

All animals were submitted for necropsy on Day 31 (Terminal Euthanasia) or Day 52 (Recovery Euthanasia).

All tissues were processed at Charles River [REDACTED] Microscopic evaluation was conducted by the undersigned senior veterinary pathologist on all protocol-specified tissues and gross lesions from all animals.

Experimental procedures applicable to pathology investigations are summarised in [Text Table 1](#).

Text Table 1
Experimental Design

Group No.	Treatment	Dosage	Dose Volume	Animal Numbers			
				Main Study		Recovery Study	
				Males	Females	Males	Females
1	Control	0	1 mL	1001-1005	1501-1505	1006-1010	1506-1510
2	[REDACTED]	[REDACTED]	1 mL	2001-2005	2501-2505	2006-2010	2506-2510

VP =Virus particles

Dose Sites

Group No.	Treatment	Dosing days (dosing site)		
		1	15	29
1	Control	Site 1	Site 2	Site 3
2	[REDACTED]	Site 1	Site 2	Site 3

Site 1: Day 1= right thigh (posterior)

Site 2: Day 15 = left thigh

Site 3: Day 29 = right thigh (anterior)

3.1. Peer Review

A peer review was performed by the Sponsor's Pathologist according to the [REDACTED] SOP. Any differences in recording, grading or description of the findings were discussed by the Study Pathologist and the Peer Reviewing Pathologist, such that the data in this report reflects their consensus view. Details pertaining to the peer review are contained in the study report.

3.2. Computerised Systems

Critical computerised systems used in this study phase are listed in [Text Table 2](#).

Text Table 2
Computerised Systems

System Name	Version No.	Description of Data Collected and/or Analysed
Provantis	8	Gross/Organ Weights/Histopathology

4. RESULTS AND DISCUSSIONS**4.1. Mortality**

There were no unscheduled deaths during the course of this study.

Appendix 22**4.2. Gross Pathology****4.2.1. Scheduled Euthanasia Animals (Day 31)**Test item-related Gross Findings

There was bilateral enlargement of the iliac lymph node in one female (F2502) which was associated with the administration of [REDACTED] No enlargement was noted in Control Group 1.

Findings considered to be procedurally related included the dark discoloration observed at the administration sites at similar incidence in controls and rabbits given [REDACTED]. There was no microscopic correlate for the dark focus recorded in the skeletal muscle of one female given [REDACTED].

Other gross findings observed were of the nature commonly observed in this strain and age of rabbit, or occurred at a similar incidence in control and treated animals, and, therefore, were considered not to be test item-related.

4.2.2. Scheduled Euthanasia Animals (Day 52)

Test item-related gross pathology findings noted at the terminal euthanasia in the iliac lymph node were not observed at the end of the recovery period (Day 52).

All gross findings observed were of the nature commonly observed in this strain and age of rabbit, or occurred at a similar incidence in control and treated animals, and, therefore, were considered not to be test item-related.

4.3. Organ Weights**4.3.1. Scheduled Euthanasia Animals (Day 31)**Test item-related Organ Weight Differences

Group mean spleen weights were higher in males (up to 1.2x fold) and females (up to 1.4x fold) given [REDACTED] when compared with controls. This achieved statistical significance in females after analysis as a percentage of brain weight. Group mean iliac lymph node weights were statistically significantly higher in males (up to 8.6 x fold) and females (up to 10.7x fold) given [REDACTED] when compared with controls.

Test item-related organ weight differences are summarised in [Text Table 3](#).

Appendix 22

Text Table 3
Summary Group Mean Organ Weight Data – Scheduled Euthanasia (Day 31)

	Males		Females	
	Group	1	2	1
[REDACTED]	Dosage	0	[REDACTED]	0
No. animals per group	5	5	5	5
Spleen (No. weighed)	(5)	(5)	(5)	(5)
Absolute value	1.2210	1.2680	1.6214	2.2210
% of brain weight	12.08496	13.41060	15.73427	22.31558a
% of body weight	0.03945	0.04549	0.05337	0.07265
Iliac lymph node (No. weighed)	(5)	(5)	(5)	(5)
Absolute value	0.0296	0.2300d	0.0378	0.3918d
% of brain weight	0.29525	2.40250d	0.36805	3.94573d
% of body weight	0.00098	0.00838d	0.00124	0.01286d

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

When compared with controls, there were other statistically significant organ weight differences in animals given [REDACTED] which were considered not to be test item related. The differences in absolute weight were considered to be related to the slightly lower terminal body weight in males given [REDACTED] and individual variation within the data that was considered to be normal biological variation. There were other isolated organ weight values that were different from their respective controls. There were, however, no patterns, trends, or correlating data to suggest these values were toxicologically relevant. In all cases, the organ weight differences observed were considered incidental and unrelated to test item-administration.

4.3.2. Scheduled Euthanasia Animals (Day 52)

Test item-related Organ Weight Differences

Slightly higher group mean spleen weights in males and females (up to 1.3x fold) and slightly higher iliac lymph node weights (up to 1.7x fold) were noted in males previously given [REDACTED] when compared with controls. There were no differences that were statistically significant.

Test item-related organ weight differences noted at the terminal euthanasia observed at the end of the recovery period (Day 52) are summarised in [Text Table 4](#).

Appendix 22

Text Table 4
Summary Group Mean Organ Weight Data – Scheduled Euthanasia (Day 52)

	Males		Females		
	Group	1	2	1	2
[REDACTED]	Dosage	0	[REDACTED]	0	[REDACTED]
No. animals per group	5	5	5	5	5
Spleen (No. weighed)	(5)	(5)	(5)	(5)	(5)
Absolute value	1.0392	1.3672	1.3702	1.6460	
% of brain weight	10.79100	14.04464	13.33676	17.01429	
% of body weight	0.03437	0.04380	0.04342	0.04898	
Iliac lymph node (No. weighed)	(5)	(5)	(5)	(5)	(5)
Absolute value	0.0234	0.0396	-	-	-
% of brain weight	0.24504	0.41181	-	-	-
% of body weight	0.00076	0.00131	-	-	-

There were individual organ weight values that were different from their respective controls. There were, however, no patterns or correlating data to suggest these values were test item-related.

4.4. Histopathology

4.4.1. Scheduled Euthanasia Animals (Day 31)

Test item-related Microscopic Findings

In the iliac lymph node, there was increased lymphoid cellularity of the germinal center (mild) in all rabbits given [REDACTED] with accompanying increased generalised lymphoid cellularity, (mild or moderate) in 7/10 individuals. This correlated with the bilateral enlargement observed grossly in the node of F2502, and also correlated with the higher lymph node weight in rabbits given [REDACTED]

In the spleen, there was increased lymphoid cellularity of the germinal center (minimal or mild) in all rabbits given [REDACTED] correlating with the higher spleen weight recorded in females.

At Day 29 (site 3) administration site, there were clear inflammatory reactions in 4/10 rabbits given [REDACTED]. The reactions in those individuals were characterised by striated muscle necrosis with mixed cell inflammation; and haemorrhage in striated muscle or the fascia. In rabbits given [REDACTED] there was also a higher incidence of inflammatory cell infiltration in the fascia/subcutaneous tissue, when compared with controls.

At Days 1 (site 1) and 15 (site 2) administration sites, there was higher incidence and slightly higher grade of mononuclear cell infiltration of the fascia/striated muscle, when compared with controls. Minimal striated muscle degeneration/regeneration was noted at Day 15 administration site. These findings were considered to provide evidence that the reactions present at earlier administrations of [REDACTED] were resolving.

Test item-related microscopic findings are summarised in [Text Table 5](#).

Appendix 22

Text Table 5
Summary Test Item-related Microscopic Findings – Scheduled Euthanasia Animals (Day 31)

	Males		Females	
	1	2	1	2
Group	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Dosage	0	[REDACTED]	0	[REDACTED]
No. animals per group	5	5	5	5
Administration site 1 – Day 1 (No. Examined)	(5)	(5)	(5)	(5)
Infiltration, mononuclear cell, striated muscle/fascia	0	3	1	3
Minimal	0	3	1	2
Mild	0	0	0	1
Administration site 2 – Day 15 (No. Examined)	(5)	(5)	(5)	(5)
Infiltration, mononuclear, striated muscle, mild	0	0	0	1
Degeneration/regeneration, striated muscle, minimal	0	0	0	1
Administration site 3 – Day 29 (No. Examined)	(5)	(5)	(5)	(5)
Necrosis, striated muscle	0	3	0	1
Mild	0	1	0	0
Moderate	0	2	0	1
Inflammation, mixed cell, striated muscle	0	3	0	1
Mild	0	1	0	0
Moderate	0	2	0	1
Inflammation, mixed cell, fascia, mild	0	0	0	1
Haemorrhage, striated muscle, moderate	0	0	0	1
Haemorrhage, fascia, mild	0	2	0	0
Infiltration, mixed cell, fascia/subcutaneous tissue	0	3	0	3
Minimal	0	3	0	1
Mild	0	0	0	2
Spleen (No. Examined)	(5)	(5)	(5)	(5)
Increased cellularity, lymphoid, germinal center	0	5	0	5
Minimal	0	1	0	1
Mild	0	4	0	4
Iliac lymph node (No. Examined)	(5)	(5)	(5)	(5)
Increased cellularity, lymphoid, generalised	0	4	0	3
Mild	0	2	0	1
Moderate	0	2	0	2
Increased cellularity, lymphoid, germinal center, mild	0	5	0	5

Appendix 22

There were additional findings at the administration sites which were related to the injection procedure rather than to [REDACTED]. Included were those in the epidermis, and also the subcutaneous haemorrhage/inflammation (occasionally with pigmented macrophages), where all sites were affected with a comparable incidence and severity in controls and treated rabbits.

Other microscopic findings observed were of the nature commonly observed in this strain and age of rabbit, or occurred at a similar incidence in control and treated animals, and, therefore, were considered not to be test item-related.

4.4.2. Scheduled Euthanasia Animals (Day 52)

Test item-related Microscopic Findings

Following the 3-week recovery period, findings in the iliac lymph node and spleen (increased lymphoid cellularity of the germinal center), persisted; but incidence and severity (minimal or mild) were lower. Increased generalised lymphoid cellularity was no longer recorded in the iliac lymph node in rabbits previously given [REDACTED]. These findings correlated in males and females with the higher spleen and in males with the higher iliac lymph node weights.

The inflammatory reactions recorded at Days 1, 15 and 29 administration sites were diminished, comprising only mononuclear inflammatory cell infiltration (minimal and mild) in striated muscle with occasional degeneration/regeneration (minimal). There was no evidence of striated muscle necrosis with mixed cell inflammation, nor of any haemorrhage.

Test item-related microscopic findings noted at the terminal euthanasia which were recorded at the end of the recovery period are summarised in [Text Table 6](#).

Appendix 22

Text Table 6
Summary Test Item-related Microscopic Findings – Scheduled Euthanasia Animals (Day 52)

	Group	Males		Females	
		1	2	1	2
[REDACTED]	Dosage	0	[REDACTED]	0	[REDACTED]
	No. animals per group	5	5	5	5
Administration site 1 – Day 1 (No. Examined)		(5)	(5)	(5)	(5)
Infiltration, mononuclear, striated muscle, minimal		0	2	0	0
Administration site 2 – Day 15 (No. Examined)		(5)	(5)	(5)	(5)
Infiltration, mononuclear, striated muscle, mild		0	0	0	1
Degeneration/regeneration, striated muscle, minimal		0	0	0	1
Administration site 3 – Day 29 (No. Examined)		(5)	(5)	(5)	(5)
Infiltration, mononuclear, striated muscle, minimal		0	1	0	0
Spleen (No. Examined)		(5)	(5)	(5)	(5)
Increased cellularity, lymphoid, germinal center		0	4	0	4
Minimal		0	3	0	3
Mild		0	1	0	1
Iliac lymph node (No. Examined)		(5)	(5)	(5)	(5)
Increased cellularity, lymphoid, germinal center		0	4	0	2
Minimal		0	2	0	0
Mild		0	2	0	2

Other microscopic findings observed were of the nature commonly observed in this strain and age of rabbit, or occurred at a similar incidence in control and treated animals, and, therefore, were considered not to be test item-related.

5. CONCLUSIONS

Intramuscular administration of [REDACTED] to rabbits on 3 occasions (Days 1, 15 and 29), was associated with slightly higher spleen and iliac lymph node weights; and microscopic findings consistent with local inflammatory effects at the administration sites; and an immunologic response in the draining iliac lymph node and spleen. The findings were not unexpected and were considered tolerable and not adverse. Following the 3-week recovery period both local and immunological responses were diminished, indicating partial recovery.

Appendix 22

6. REPORT APPROVAL

[REDACTED]
Study Pathologist

Version: Final

Date: 19 March 2018

Appendix 23

PATHOLOGY PEER REVIEW MEMORANDUM

STUDY EXPERIMENT NUMBER: [REDACTED]

To:

Date: 21 March 2018

From:

Start date of peer review: 06 December 2017

Methods:

All tissues were examined microscopically from the following animals:

Vaccine Group (Group 2): male 2001-2003; female 2501-2503

Control/vehicles: male 1001 and female 1501

Tissues from controls and/or vehicles and other dosed groups were reviewed randomly.

Slides for the following organs were examined from all animals including the recovery group: administration/injection sites, iliac lymph nodes and spleen, and adrenal glands from all female main study animals.

Conclusion:

The quality of the slides and tissue accountability was acceptable. Based on my review of the study data, pathology report and microscopic examination of slides, I am in agreement with the overall interpretation and conclusions of the study. I checked that the agreement on the terminology and diagnoses was implemented in the pathology data.

[REDACTED]
Reviewing Pathologist

Date: 21 March 2018