[redacted]

Report

MVA-HBV: Intramuscular Administration Toxicity Study to BALB/c Mice of Two Doses 14 Days Apart, With Assessment of Recovery 14 Days After Cessation of Dosing

Covance Study Number:	DM49JM
Sponsor Name:	Vaccitech
Version ID:	Draft
Issue Date:	29 April 2020
Study Director:	[redacted]
Test Facility:	[redacted]

[redacted]

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COMPLIANCE WITH GOOD LABORATORY PRACTICE

MVA-HBV: Intramuscular Administration Toxicity Study to BALB/c Mice of Two Doses 14 Days Apart, With Assessment of Recovery 14 Days After Cessation of Dosing

The study described in this report was conducted in compliance with the following Good Laboratory Practice standards and I consider the data generated to be valid.

- The UK Good Laboratory Practice Regulations (Statutory Instrument 1999 No. 3106, as amended by Statutory Instrument 2004 No. 994).
- OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17.
- EC Commission Directive 2004/10/EC.

These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), Japan (MHLW, MAFF and METI), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

[redacted]

Date

QUALITY ASSURANCE STATEMENT

MVA-HBV: Intramuscular Administration Toxicity Study to BALB/c Mice of Two Doses 14 Days Apart, With Assessment of Recovery 14 Days After Cessation of Dosing

This study has been reviewed by the Quality Assurance Unit of [redacted] and the report accurately reflects the raw data. The following study-specific inspections were conducted, and findings reported to the Study Director (SD) and associated management.

Critical procedures performed routinely in an operational area may be audited as part of a process inspection programme. This can be in addition to phases scheduled on an individual study basis. Selected process inspections conducted and considered applicable to this study are included in the following.

In addition to the inspection programme detailed in the following, a facility inspection programme is also operated. Details of this programme, which covers all areas of the facility annually (at a minimum), are set out in standard operating procedures.

Study based inspections:

Type of Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Study Plan Verification	30 Oct 2019- 31 Oct 2019	31 Oct 2019
Study Plan Amendment No. 1	01 Nov 2019	01 Nov 2019
Bodyweights - Novel Procedure	05 Nov 2019	05 Nov 2019
Study Plan Amendment No. 2	05 Nov 2019	05 Nov 2019
Food consumption Novel Procedure	05 Nov 2019	07 Nov 2019
Study Set-up (dosing 05 Nov 2019)	04 Nov 2019-05 Nov 2019	08 Nov 2019
Pre-terminal	06 Nov 2019-07 Nov 2019	08 Nov 2019
Study Management and Conduct	18 Nov 2019	18 Nov 2019
Study Plan Amendment No. 3	28 Nov 2019	28 Nov 2019
Study Plan Amendment No. 4	02 Dec 2019	02 Dec 2019
Study Plan Amendment No. 5	03 Dec 2019	03 Dec 2019
Study Plan Amendment No. 6	03 Mar 2020	04 Mar 2020
Report Audit	24 Feb 2020-25 Feb 2020, 27 Feb 2020 02 Mar 2020-06 Mar 2020, 09 Mar 2020-13 Mar 2020 & 17 Mar 2020	27 Feb 2020 17 Mar 2020

Process based inspections:

Pharmacy:

Process-Based Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Formulation Procedures - Liquid (weighing, formulating, sampling and check out procedures	18 Oct 2019	30 Oct 2019
Test Item & Material Management: Receipt, Stock Control, Disposal/Return, Reserve/Archive Sample Check	21 Oct 2019, 28 Oct 2019, 30 Oct 2019	30 Oct 2019
Preparation of Liquid Vehicles/ Weighing of Control Diet/Material Management	21 Oct 2019, 08 Nov 2019	11 Nov 2019

Pharmacology:

Process-Based Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Dose Administration	17 Dec 2019	18 Dec 2019
Study Management and Conduct	18 Dec 2019	18 Dec 2019
Observations Manual/Visual	17 Dec 2019	18 Dec 2019
Blood Collection	10 Jan 2020	20 Jan 2020

Bioanalytical-Clinical Sciences:

Process-Based Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Slide Preparation, Staining and Reading	06 Nov 2019	07 Nov 2019
Sample Management	12 Nov 2019	12 Nov 2019
Haematology	12 Nov 2019	15 Nov 2019
Clinical Chemistry	13 Nov 2019	15 Nov 2019
Assay Procedures (cell based)	20 Nov 2019	21 Nov 2019
Results Processing	21 Nov 2019	21 Nov 2019

Pathology

Process-Based Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Materials Management	01 Nov 2019	01 Nov 2019
Slide Reading	13 Jan 2020	13 Jan 2020

Histology

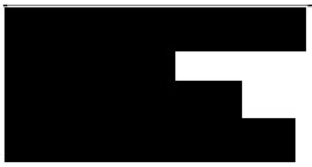
Process-Based Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Sectioning/Slide Preparation, Staining, Slide Collation	28 Nov 2019	28 Nov 2019
Histology Processes Including Tissue Trimming and Decalcification, Tissue Processing, Tissue Embedding	09 Dec 2019, 10 Dec 2019	10 Dec 2019

Necropsy

Process-Based Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Necropsy	03 Sep & 09 Sep 2019	19 Sep 2019

Archives:

Process-Based Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Archiving of Study Materials (including electronic archiving)	06 Feb 2020	07 Feb 2020



Date

1 SUMMARY

The aim of this study was to assess the systemic toxic potential of MVA-HBV when dosed twice, with two weeks between administrations, in BALB/c mice. An additional assessment of acute toxicity was made in animals receiving a single dose of MVA-HBV and recovery from any effects observed after two doses was evaluated during a 14 day recovery period.

The study design was as follows:

Group	Treatment	Number of animals					
		Interim Phase		Main Phase		Recovery phase	
		Male	Female	Male	Female	Male	Female
1	Control	6	6	10	10	5	5
2	MVA-HBV	6	6	10	10	5	5
3	Spare	-	-	5	5	-	-

All study animals received the control, 0.9% saline, or the test item, MVA-HBV, by an intramuscular injection. The main study animals received test item or vehicle on two dosing occasions, Day 1 and Day 15. Interim animals were dosed once, only on Day 1, and terminated on Day 3. Recovery animals were dosed on Days 1 and 15, followed by a 2 week off dose period.

During the study body weight, body temperature, food consumption, hematology (peripheral blood), blood chemistry, organ weight, macropathology and histopathology investigations were undertaken.

Results

Haematology investigations conducted two days after the first dose revealed higher neutrophil, lymphocyte and large unstained cell counts in treated males when lower lymphocyte counts were observed in treated females. Lower erythrocyte and reticulocyte counts haemoglobin concentration, haemotocrit and mean cell haemoglobin values were also observed in females. Two days following the second dosing occasion lower lymphocyte, eosinophil, and monocyte counts in both treated sexes and neutrophil counts in treated females were observed. Lower reticulocyte counts, haemoglobin concentration and haemotocrit were again observed in treated females. These changes showed reversibility.

Blood chemistry investigations conducted two days after the first dose revealed slightly higher alanine aminotransferase and aspartate aminotransferase activity and cholesterol concentration in treated males. However, slightly lower aspartate aminotransferase activity, triglyceride, creatinine, albumin, calcium and phosphorus concentrations and higher chloride concentration was observed in treated females. Two days following the second dosing occasion lower mean alkaline phosphatase activity and creatinine and phosphorus concentration was observed in both sexes of the treated group. These changes showed reversibility however slightly higher urea concentrations were now observed.

Post mortem investigations conducted two days after the first dose on Day 3, revealed higher spleen weights in both sexes of the treated group. In animals killed two days after the second dose on Day 17, enlarged spleens with higher weights, enlarged lumbar and inguinal lymph nodes and enlarged livers with higher weights in both sexes of the treated group and lower thymus weights in females were seen. In animals killed following a two week-off dosing period, slightly higher spleen weights were still noted in the previously treated females.

Conclusion

Intramuscular injection of MVA-HBV dosed at $6.1x10^{10}$ PFU/mL on two occasions to BALB/c mice was well tolerated with some adverse effects following the second dose.

Minor fluctuations in peripheral white and red blood cell count, enlarged spleen, lymph node and liver weights and minor fluctuations in plasma metabolising enzyme, electrolyte and lipid levels were all considered to be associated with a normal immunological response to the presence of a vaccine.

Furthermore, intramuscular administration of MVA-HBV to BALB mice on one occasion, resulted in non-adverse treatment related findings in the femur, left intramuscular injection site, sciatic nerve, inguinal lymph nodes in both sexes; right intramuscular injection site and left axillary lymph nodes in males.

Intramuscular administration of MVA-HBV to BALB mice on two occasions, 14 days apart, resulted in adverse treatment related findings in the femur, intramuscular injection site (left and right), and non-adverse sciatic nerve, spleen, inguinal and lumbar lymph nodes in both sexes.

Following the 14 day recovery period, there was complete reversibility in the femur of females and spleen of both sexes. Partial reversibility was seen in the femur of males, left and right muscular injection sites, inguinal lymph nodes, and sciatic nerves of both sexes. In general, there was a clear decrease in the incidence and severity of the findings, which were all considered nonadverse except for myofiber mineralization one male animal.

2 INTRODUCTION AND PURPOSE

2.1 Purpose

The aim of this study was to assess the systemic toxic potential of MVA-HBV when dosed twice, with two weeks between administrations, in BALB/c mice. An additional assessment of acute toxicity was made in animals receiving a single dose of MVA-HBV and recovery from any effects observed after two doses was evaluated during a 14 day recovery period.

2.2 Animal Model

The mouse was chosen as the test species because it is accepted as a predictor of toxic change in man and the requirement for a rodent species by regulatory agencies. The BALB/c strain was used because of the historical control data available at this laboratory.

2.3 Route of Administration

The Intramuscular route of administration was chosen to simulate the conditions of clinical administration.

2.4 Rationale for Dose Level Selection

The doses used in this study were selected in conjunction with the Sponsor.

The anticipated maximum human dose of MVA-HBV is $1x10^8$ PFU/mL. Based on the concentration of the vaccine preparations used on this study the dose levels of MVA-HBV will be approximately 100% of the maximum anticipated human dose level.

2.5 Study Details

Sponsor	Vaccitech The Schrödinger Building Heatley Road The Oxford Science Park Oxford OX4 4GE
Study Monitor	[redacted]
Alternative Study Monitor Contact	[redacted]
Sponsor's Consultant	[redacted]

Test Facility
[redacted]

(Histology, Formulation, [redacted]

Contributing Scientists

Toxicologist [redacted]

Pathologist [redacted]

Immune Response Evaluation Scientist [redacted]

2.6 Study Schedule

2.6.1 Duration of Treatment

Study period 17 days followed by a 14 days recovery period

Interim animals were treated with one dose.

2.6.2 Time Schedule

Experimental start date (animal arrival) 31 October 2019

Treatment to commence

Interim Phase	05 November 2019
Main Phase	05 November 2019
Recovery study phase	05 November 2019

Terminal sacrifice to commence

Interim Phase	07 November 2019
Main Phase	21 November 2019
Recovery study	03 December 2019

Experimental completion date 22 April 2020

2.7 Animal Welfare

The study was conducted in accordance with the applicable sections of the United Kingdom Animals (Scientific Procedures) Act 1986, Amendment Regulations 2012 (the Act).

2.8 Regulatory Testing Guidelines

The study was designed to meet the requirements of the following guidelines:

European Parliament and Council Directive 2001/83/EC of 6 November 2001 of the Community Code Relating to Medicinal Products for Human Use, OJ L311/67-128, 28 November 2001 as amended Commission Directive 2003/63/EC, OJ L159, 27 June 2003.

The study was conducted in accordance with the requirements of current, internationally recognized Good Laboratory Practice Standards.

3 MATERIALS AND TEST METHODS

3.1 Test Item and Supporting Information

3.1.1 Test Item

Information supplied by the Sponsor regarding the test item is contained in the test item data sheet, which is retained in study records, and the Certificate of Analysis, which will be presented in Annex 2 when available.

The following information is given in summary:

Test item	MVA-HBV
Test item identity (including alternative names)	MVA-HBV, Drug substance, Bulk drug substance or Purified drug substance.
Action of test item	Vaccine
Batch number	Y960
Storage conditions	≤ -70C
Infectious Units	$4.8x10^8$ PFU/mL
Appearance	To be confirmed
Stability/expiry	9 months stability at -70 °C.
Archive sample	A 0.5 mL representative sample was taken from each batch of test item. This sample was placed in a well closed plastic bottle and stored in the archives under the same conditions as the bulk material.

3.2 Test Item Preparation and Analysis

3.2.1 Formulation

Treatment	**Nominal concentration**
Group 1	Vehicle
Group 2	$4.8x10^8$ PFU/mL

Vehicle	0.9% Saline
Method of preparation	Compound was shipped in ready to use containers.
Storage of formulation	Frozen (-65 to -85°C).

Test item accounting	Detailed records of compound usage were maintained. The amount of test item necessary to dose the animals and the amount actually used were determined on each occasion. The difference between these amounts was checked and acknowledged by the Study Director if outside the acceptance limit.
Stability	9 months stability at -70 °C at $4.8x10^8$ PFU/mL has been proven under the separate ABL GLP study no. STABQC103.

3.2.2 Formulation Analysis

Formulation analysis was not required as part of this study.

3.2.3 Vehicle

The following information is given in summary:

Identification	0.9% Saline
Supplier	[redacted]
Batch number	19040823
Expiry date	September 2020

3.3 Animal Information

3.3.1 Animals

Strain/Species	BALB/c mouse.
Supplier	[redacted].
Number of animals	47 males and 47 females.
Duration of acclimatization	5 days before commencement of treatment.
Age of all animals at start of treatment	40 to 53 days old.
Weight range of all animals at the start of treatment	Males: 19.6 to 23.3 g Females: 17.4 to 20.4 g

3.3.2 Allocation and Identification

Allocation	Animals were randomized into study groups using random number tables so that the group mean weights were

	approximately equal. Each sex was allocated separately.
Identification of animals	Each animal was assigned a number and identified uniquely within the study by a microchip inserted shortly after arrival.
Identification of cages	Each cage label was color-coded according to group and was numbered uniquely with study number, as well as the identity of the occupants.

3.3.3 Animal Replacement

No animals were replaced before treatment commenced or during the treatment period on this study.

3.4 Animal Care and Husbandry

3.4.1 Environmental Control

Animal facility	Limited access - to minimize entry of external biological and chemical agents and to minimize the transference of such agents between rooms.
Air supply	Filtered fresh air which was passed to atmosphere and not recirculated.
Temperature and relative humidity	Monitored and set within the range of 20-24ºC and 40-70%. Although humidity was once outside the indicated ranges (39 %), this deviation was minor and was not considered to have influenced the health of the animals or the outcome of the study.
Lighting	Artificial lighting, 12 hours light : 12 hours dark.
Electricity supply	Public supply with automatic stand-by generators.

3.4.2 Animal Accommodation

Cages	Plastic cages with solid floors, changed at appropriate intervals.
Number of animals per cage	Animals were housed up to 5 per cage per sex, dependent on the phase of the study.
Bedding	Wood flake bedding which was changed at appropriate intervals each week.

3.4.3 Environmental Enrichment

Aspen gnawing material	Provided to each cage throughout the study and replaced when necessary.
Plastic shelter	Provided to each cage throughout the study and replaced when necessary.
Nestlet	Provided to each cage throughout the study and replaced at the same time as the cages.

3.4.4 Diet Supply

Diet	Teklad 2014C, pelleted diet.
Availability	Non-restricted.

3.4.5 Water Supply

Supply	Potable water from the public supply via polycarbonate bottles with sipper tubes. Bottles were changed at appropriate intervals.
Availability	Non-restricted.

3.4.6 Supplier Certificates of Analysis

Certificates of analysis for the diet were scrutinized and approved before any batch of diet was released for use. Certificates of analysis are routinely provided by the water supplier.

Certificates of analysis were also received from the suppliers of the wood based bedding, nestlets and aspen gnawing material.

No specific contaminants were known that may have interfered with or prejudiced the outcome of the study and therefore no special assays were performed.

3.5 Dose Administration

3.5.1 Identity of Treatment Groups

The study consisted of 1 control and 1 treated groups identified as follows:

Group	Treatment	Number of animals					
		Interim Phase		Main Phase		Recovery phase	
		Male	Female	Male	Female	Male	Female
1	Control	6	6	10	10	5	5
2	MVA-HBV	6	6	10	10	5	5
3	Spare	-	-	5	5	-	-

Group	Treatment	Interim phase		Main phase		Recovery phase	
		Animal numbers		Animal numbers		Animal numbers	
		Male	Female	Male	Female	Male	Female
1	Control	1-6	101-106	13-22	113-122	33-37	133-137
2	MVA-HBV	7-12	107-112	23-32	123-132	38-42	138-142
3	Spare	-	-	43-47	143-147	-	-

3.5.2 Administration

Route	Intramuscular injection.
Treated at	Constant doses in µL.
Volume dose	100 µL MVA-HBV per animal.
Controls (Group 1)	Vehicle at 100 µL per animal on Day 1 and 15 only.
Frequency	Dosed on Day 1 and 15 only.
Sequence	By group.
Dose sites	Two injection sites were used and the dose volume was split equally between the two sites (50 µL per site): Inside the right and left hindlimb. Dose sites were clipped on the day prior to administration.
Formulation accounting	A record of the usage of formulation was maintained based on weights. This balance was compared with the expected usage as a check of correct administration. No significant discrepancy was found.

3.6 Serial Observations

3.6.1 Clinical Observations

Animals were inspected visually at least twice on each day of dosing for evidence of ill-health or reaction to treatment. Cages were inspected daily for evidence of animal ill-health amongst the occupants. Any deviation from normal was recorded at the time in respect of nature and severity, date and time of onset, duration and progress of the observed condition, as appropriate.

During the acclimatization and recovery period, observations of the animals and their cages were recorded at least once per day.

Signs Associated with Dosing

Detailed observations were recorded on Days 1 and 15 at the following times in relation to dose administration:

- Predose
- 1-2 h after dosing
- As late as possible in the working day.

Injection Site Observations

Injection sites were observed daily in Week 1, and at least twice weekly in Weeks 2-3.

3.6.2 Body Weight

The weight of each animal was recorded once before treatment commenced (Week -1), on the day that treatment commenced (Day 1), and the following days after treatment commenced; Day 2, 8, 15 (prior to dosing), 21 and 28. Terminal bodyweights were also recorded on the day of necropsy.

3.6.3 Food Consumption

The weight of food supplied to each cage, that remaining and an estimate of any spilled was recorded for the week before treatment started and for each week throughout the study.

3.6.4 Body Temperature

Body temperatures were recorded at predose, 4 and 24 h postdose on Days 1 and 15 for all dosed animals.

A thermocouple, attached to an electric thermometer designed by Comark, was inserted into the rectum to a constant depth of 1cm.

3.6.5 Hematology, Peripheral Blood

Blood samples were collected without overnight withdrawal of food as follows:

Occasion	Animals
Day 3 (prior to termination)	All Interim phase animals
Day 17 (prior to termination)	All Main phase animals
Day 29 (prior to termination)	All Recovery study animals

Animals were held under light general anesthesia induced by isoflurane. Blood samples (nominally 0.3 mL) were withdrawn from the orbital sinus, collected into tubes containing EDTA anticoagulant and examined for the following characteristics using a Bayer Advia 120 analyzer:

Hematocrit (Hct)
Hemoglobin concentration (Hb)
Erythrocyte count (RBC)
Absolute reticulocyte count (Retic)
Mean cell hemoglobin (MCH)
Mean cell hemoglobin concentration (MCHC)
Mean cell volume (MCV)
Red cell distribution width (RDW)
Total leucocyte count (WBC)
Differential leucocyte count:
- Neutrophils (N)
- Lymphocytes (L)
- Eosinophils (E)
- Basophils (B)
- Monocytes (M)
- Large unstained cells (LUC)

Platelet count (Plt)

3.6.6 Blood Chemistry

Blood samples were collected without overnight withdrawal of food as follows:

Occasion	Animals
Day 3 (prior to termination)	All Interim phase animals
Day 17 (prior to termination)	All Main phase animals
Day 29 (prior to termination)	All Recovery study animals

Animals were held under light general anesthesia induced by isoflurane. Blood samples (nominally 0.5 mL) were withdrawn from the orbital sinus and collected into tubes containing lithium heparin as anticoagulant. After separation, the plasma was examined using a Cobas 6000 in respect of:

Alkaline phosphatase (ALP)

Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Total bilirubin (Bili)
Urea
Creatinine (Creat)
Glucose (Gluc)
Total cholesterol (Chol)
Triglycerides (Trig)
Sodium (Na)
Potassium (K)
Chloride (Cl)
Calcium (Ca)
Phosphorus (Phos)
Total protein (Total Prot)
Albumin (Alb)

Albumin/globulin ratio (A/G Ratio) was calculated from total protein concentration and analyzed albumin concentration.

3.6.7 Immune Response Evaluation (ELISpot Assay)

Occasion	**Animals**
Day 17	All Group 2 main study animals.
Day 29	The first 3 Recovery Group 1 males and females, and the all Recovery Group 2 males and females.

Splenocytes were prepared and an assessment of the cellular immune response to the test material was made using an ELISpot assay, according to authorised method BBC 0260.

Test compound administered: MVA-HBV

Batch number: Y960

Species: Mouse (BALB/c)

Validation study number: HLS0766

Method number: BBC 0260

Analytical matrix: Spleenocytes

Number of samples 36

Sample status on receipt Samples were placed in C-MACs tubes containing 10 mL of complete RPMI on ice. Tubes and RPMI were supplied to necropsy by BBC.

Analytical technique: ELISpot assay

3.6.7.1 Summary of methodology

For this assay, splenocytes, at a cell concentration of 50,000/well, were treated with one concentration (2 µg/mL) of P4 peptide pool, Concanavalin A (Con A; positive control at 0.5µg/mL), anti-CD3 (a second positive control), or medium (background control) for 18-20 h on IFNγ-coated membranes in microtitre plates. During this incubation period secreted IFN-γ was bound by the immobilised antibody in the immediate vicinity of the secreting cells. After washing away cells and residual antigen, a biotinylated monoclonal antibody specific for mouse IFN-γ was added to the wells. Following a wash to remove any unbound biotinylated antibody, Alkaline Phosphatase (ALP) conjugated to streptavidin was added. Unbound enzyme was subsequently removed by washing and a substrate solution (BCIP/NBT) was added. A blue-black coloured precipitate formed at the sites of cytokine localisation and appears as spots, with each individual spot representing an individual IFN-γ secreting cell.

Results from the ELISpot reader software was transferred and processed using Microsoft® Excel spreadsheets. Data is presented as spot forming cells (SFC) per $1x10^6$ cells.

3.7 Terminal Investigations

3.7.1 Method of Kill

Carbon dioxide asphyxiation with subsequent exsanguination.

3.7.2 Necropsy

All interim, main study and recovery animals were subject to a detailed necropsy. After a review of the history of each animal, a full macroscopic examination of the tissues was performed according to the table below. All external features and orifices were examined visually. Any abnormality in the appearance or size of any organ and tissue (external and cut surface) was recorded and the required tissue samples preserved in appropriate fixative.

Schedule	Interim animals were killed two days after the first dose (Day 3). Main study animals were killed two days after the second dose (Day 17). Recovery animals were killed fourteen days after the second dose (Day 29).
Sequence	To allow satisfactory inter-group comparison.

The organs weighed, tissue samples fixed and sections examined microscopically are detailed as follows:

Tissue and regions to be examined	Necropsy		Histology	Pathology
	Weigh	Fix		Light microscopy
Abnormalities		*	*	*
Adrenals		*	*	*
Aorta - thoracic		*	*	*
Bone marrow smear		*		b)
Brain (cerebellum, cerebrum, midbrain)	*	*	*	*
Cecum		*	*	*
Colon		*	*	*
Duodenum		*	*	*
Epididymides	*	*	*	*
Esophagus		*	*	*
Eyes		*	*	*
Femur and marrow (femorotibial joint)		@	@	@
Gall bladder		*	*	*
Harderian glands		*	*	*
Head		*	#	#
Heart (including auricular and ventricular regions)	*	*	*	*
Ileum		*	*	*
Injection Site (right and left hindlimbs)		*	*	*
Jejunum		*	*	*
Kidneys	*	*	*	*
Liver (section from 2 lobes)	*	*	*	*
Lungs (section from two major lobes including bronchi)		*	*	*
Lymph nodes - mesenteric		*	*	*
- left axillary		*	*	*
- mandibular		*	*	*
- right and left inguinal (sampled separately)		*	*	*
Ovaries	*	*	*	*
Pancreas		*	*	*
Pituitary		*	*	*
Prostate	*	*	*	*
Salivary glands - submandibular		*	†	†
- sublingual		*	†	†
Sciatic nerves		@	†	†
Seminal vesicles		*	*	*
Skeletal muscle		@	†	†
Skin with mammary glands (inguinal area)		*	*	*
Spinal cord (transverse and longitudinal sections at the cervical level)		*	*	*
Spleen	*	*	*	*
Sternum and marrow		*	*	*
Stomach		*	*	*
Testes	*	*	*	*
Thymus	*	*	*	*
Thyroid with parathyroids		*	*	*
Trachea		*	*	*
Urinary bladder		*	*	*
Uterus with cervix	*	*	*	*
Vagina		*	*	*

In addition, carcass was retained.

b) Was examined by the Department of Biomarkers, Bioanalysis and Clinical Sciences (if required).

* Organs weighed, samples fixed or sections examined microscopically.

\# Examined if effects suspected during the study.

† Only one examined.

@ Only one taken per animal.

Bone Marrow

Bone marrow smears were prepared for all main animals immediately following death, on completion of the scheduled treatment period.

Fixation	Smears were air dried and subsequently fixed in methanol.
Analysis	No examinations were performed, however, the smears were retained for possible future examination.
Retention	The smears were transferred to archives and will be retained for the same period as the study raw data.

Organ Weights

For bilateral organs, left and right organs were weighed together, unless specified above. Requisite organs were weighed for interim, main study and recovery animals killed at scheduled intervals.

Fixation

Tissues were routinely preserved in 10% Neutral Buffered Formalin with the exception of those detailed below:

Testes	In modified Davidson's fluid.
Eyes	In Davidson's fluid.
Bone marrow smears:	See Section above.

3.7.3 Histology

Processing	Tissue samples were dehydrated, embedded in paraffin wax and sectioned at a nominal four to five micron thickness. For bilateral organs, sections of both organs were prepared. A single section was prepared from each of the remaining tissues required.
Full List	All animals interim and main study animals.
Routine staining	Sections were stained with hematoxylin and eosin; in addition samples of the testes were stained using a standard periodic acid/Schiff (PAS) method.

3.7.4 Light Microscopy

Tissues preserved for examination were examined as follows:

Category	Animals		Tissues
Scheduled kill	Interim	All animals.	All specified in Section 3.7.2.
	Main study	All animals.	All specified in Section 3.7.2.

Tissues preserved for examination were examined for all animals sacrificed on completion of the scheduled treatment period.

Findings were either reported as "present" or assigned a severity grade. In the latter case one of the following five grades was used - minimal, slight, moderate, marked or severe. A reviewing pathologist undertook a peer review of the microscopic findings.

3.8 Data Evaluation

This report contains serial observations pertaining to all weeks of study completed, together with signs data collected during the necropsy period.

Summary statistics (e.g. means and standard deviations) presented in this report were calculated from computer-stored individual raw data (except body weights, body temperature, food consumption and organ weights). Group mean values and standard deviations were frequently calculated using a greater number of decimal places than presented in the appendices. It is, therefore, not always possible to derive exact group values from the data presented in the appendices.

Throughout the report the following abbreviations are used:

M	Male
F	Female
SD	Standard deviation
N	Number of animals/cages examined
I	Interim
R	Recovery

3.8.1 Serial Observations

3.8.2 Clinical Observations

There were no signs associated with dosing or clinical signs seen and so no appendix is included in this report. The only exception was animal 146 which was noticed to have bruising around the injection site.

Body Weight

Group mean body weight and mean body weight changes were calculated from the weight changes of individual animals.

Food Consumption

Group mean food consumptions and standard deviations for each period were derived from unrounded cage values.

Body temperature

Body temperatures were recorded for all animals prior to dosing, at 4 and 24 h postdose on both dosing occasions. A thermocouple, attached to an electric thermometer designed by Comark, was inserted into the rectum to a constant depth of 1 cm.

Occasion	Animals
Day 1 - Predose, 4 and 24 h postdose	All animals.
Day 15 - Predose, 4 and 24 h postdose	All main and recovery study animals.

Hematology, Peripheral Blood

The abbreviations used have the following meanings:

CTD Clotted sample
INS Insufficient sample
NVR No valid result

If platelet clumping was confirmed by light microscopy then the platelet count parameter was reported as NVR and, where considered appropriate, a manual count of the differential white blood cell parameters was performed. The group mean, standard deviation and statistical analysis data presented for the differential white blood cell count parameters (for neutrophils, lymphocytes, eosinophils, basophils and monocytes) in the hematology table were derived from automated and manually derived data.

Blood Chemistry

The abbreviations used have the following meanings:

INS Insufficient sample
NSR No sample received
NVR No valid result
ND Not defined

Albumin to globulin ratio (A/G Ratio) was calculated as:

$$\text{A/G Ratio} = \frac{\text{Albumin concentration}}{\text{Total protein} - \text{albumin concentration}}$$

3.8.3 Terminal Investigations

Organ Weights

Organ weights were presented both as absolute and adjusted for terminal body weight, using the weight recorded on the day of necropsy.

Pathology

The abbreviations used have the following meanings:

Lt	Left
Rt	Right
IS	Injection site

3.9 Statistical Analysis

All statistical analyses were carried out separately for males and females. Data relating to food consumption were analyzed on a cage basis but due to the low cage numbers no statistical analysis was performed. For all other parameters, the analyses were carried out using the individual animal as the basic experimental unit.

The following data types were analyzed at each timepoint separately:

Body weight, using gains over appropriate study periods
Body temperature
Hematology
Blood chemistry
Organ weights, absolute and adjusted for terminal body weight
Pathological findings, for the number of animals with and without each finding

The following comparisons were performed:

Group 1 vs 2

The following sequence of statistical tests was used for body weight, body temperature, organ weight and clinical pathology data:

A parametric analysis was performed if Bartlett's test for variance homogeneity (Bartlett 1937) was not significant at the 1% level. Groups were compared using two-tailed t-tests.

A non-parametric analysis was performed if Bartlett's test was still significant at the 1% level following both logarithmic and square-root transformations. Groups were compared using two-tailed Wilcoxon rank sum tests (Wilcoxon 1945).

~~For histopathology [or non-neoplastic histopathology] findings, if the one-tailed Cochran-Armitage test (Armitage 1955) for an increase was significant at the 5% level, one-tailed~~

~~step-down testing was performed. If the one-tailed Cochran-Armitage test for an increase was not significant at the 5% level, then a Chi-square test (Armitage et al 2002) was applied. If the Chi-square test was significant at the 5% level, the treatment groups were compared using pairwise comparisons of each dose group against the Control using one-tailed Fisher's exact tests (Fisher 1973) for an increase, otherwise, no further comparisons were made. For histopathology comparisons involving Control and high dose group only, Fisher's exact tests for an increase were applied.~~

Significant differences between the groups compared were expressed at the 5% ($p<0.05$) or 1% ($p<0.01$) level. The key to the annotation used on the tables that contain statistical results is given below:

l	Data were log transformed for the statistical analysis
Tt	Group 2 compared with Control using *t*-test
Wc	Group 2 compared with Control using Wilcoxon rank sum test
*	$p<0.05$
**	$p<0.01$

3.10 Major Computerized Systems

The computer systems used include those listed below:

ClinAxys II:	In-life data collection
Pristima:	Pharmacy test item management, in-life, necropsy and pathology data collection
Quasar:	In-house statistical analysis
SAS:	Statistical evaluation
StarTox:	In-house statistical analysis

3.11 Quality Assurance

Details of the Quality Assurance inspections and audits undertaken at Covance are presented on the Quality Assurance Statement.

4 DEVIATIONS FROM STUDY PLAN

Section 4.1 of the Study Plan states that the stability and expiry information of the test item will be available prior to reporting. The Study Director was informed by the Sponsor that the stability testing is still undergoing to prove 9 months stability, and as a result the stability report will not be available at the time of reporting for this study. This deviation is not considered to have affected the integrity of the study as the stability report will still be provided by the Sponsor when the stability testing has been completed.

There were no further deviations from study plan.

5 ARCHIVING

Records and documentation relating to this study (including electronic records) will be maintained in the archives of [redacted] for a period of five years from the issue of the final report. This will include raw data, specimens, and sample of test and reference items that support the reconstruction of the study. Test Facility-generated electronic raw data will be stored on the computer system on which the data application resides or archived off-line. Specimens that no longer afford evaluation will be discarded in accordance with Standard Operating Procedures and without further notice.

At termination of the aforementioned period, the Sponsor will be contacted in order to determine the final disposition of these records and materials. After the specified period, the Sponsor is responsible for all costs associated with the retention, retrieval, onward transfer or destruction/disposal of these materials. If the Sponsor is unresponsive the records will be destroyed in accordance with the [redacted] Standard Operating Procedure.

In case records are transferred, the Sponsor should ensure that the materials and records in support of regulatory studies are retained and maintained under conditions that guarantee their integrity and continued access according to archiving requirements of the principles of GLP. The Sponsor should also ensure that such materials and records are retained for as long as required by relevant authorities.

[redacted] will retain the study plan (electronically), final report and any amendments indefinitely.

6 RESULTS

6.1 Clinical signs

There were no unscheduled deaths during the study.

There were no clinical signs observed that were considered to be related to treatment.

A small amount of bruising was observed at the intramuscular injection site of one animals receiving MVA-HBV vaccine however this is a normal background observation seen in mice dosed by this route of administration at this Test Facility and is therefore considered to be procedural in origin.

6.2 Body Weight

Figure 1 to Figure 3, Table 1 to Table 3, Appendix 1 to Appendix 2

Slightly higher than control bodyweight gains were observed in both sexes of the interim phase animals two days after the first dose (Day 3) and main phase animals two days after the second dose (Day 17). However slightly lower than control gains were observed in both sexes of the recovery phase animals. Given the slight nature and inconsistency of these differences they are considered to represent normal biological variability and unrelated to treatment.

A low bodyweight gain was observed in previously treated females in comparison with the controls during the recovery period. This was mainly due to the weight loss observed in one female (No. 141) and is therefore considered not to be treatment related.

6.3 Body temperature

Table 4 to Table 6, Appendix 3 to Appendix 4

There was considered to be no effect of treatment on the body temperature during the study for animals dosed with the MVA-HBV vaccine.

A slightly higher mean body temperature than control and from pretreatment, was observed in the MVA-HBV vaccine treated interim phase males 4 hours after the first dose; main phase males 24 hours after the second dose on Day 15 and main phase females 4 hours after the first dose and immediately prior to the second dose. These differences although attaining statistical significance were slight, showed inconsistency between sexes and timepoints and are therefore considered to show normal variability and unrelated to treatment.

6.4 Food Consumption

Table 7 to Table 9, Appendix 5 to Appendix 6

There was considered to be no effect of treatment on the overall group mean food consumption during the study for animals dosed with the MVA-HBV vaccine.

6.5 Hematology, Peripheral Blood

Table 10 to Table 15, Appendix 7 to Appendix 8

Hematology investigations conducted two days after the first dose revealed higher than control mean neutrophil, lymphocyte and large unstained cell counts and consequently total leucocyte counts in treated males. The higher neutrophil and large unstained cells counts attained statistical significance. Conversely, however, a lower than control mean lymphocyte and consequently total leucocyte count was observed in treated females at this timepoint.

In addition, a lower than control mean erythrocyte and reticulocyte count and consequently lower hemoglobin concentration, hemotocrit and mean cell hemoglobin value was observed in females at this timepoint that generally achieved statistical significance but was not apparent in males.

Two days following the second dosing occasion lower than control mean lymphocyte, eosinophil, and monocyte count, and consequently total leucocyte count in both treated sexes and neutrophil count in treated females was observed. These differences generally showed statistical significance.

Again at this timepoint a lower statistically significant reticulocyte count and consequently lower haemoglobin concentration and haemotocrit was observed in treated females but not in treated males.

Following a two week-off dosing period both red and white blood cell populations in previously treated animals were considered to be similar to the controls.

Other differences between the control and treated group means, including those attaining a level of statistical significance were slight in degree or there was considerable overlap between groups in the range of the individual data.

6.6 Blood Chemistry

Table 16 to Table 21, Appendix 9 to Appendix 10

Blood chemistry investigations conducted two days after the first dose revealed slightly higher than control mean alanine aminotransferase and aspartate aminotransferase activity and cholesterol concentration in treated males. However, this was not observed in treated females where slightly lower aspartate aminotransferase activity and triglyceride concentration was observed.

In treated females at this timepoint lower than control mean creatinine, albumin, and consequently total protein, calcium and phosphorus concentration and higher chloride concentration was also observed.

Two days following the second dosing occasion lower than control mean alkaline phosphatase activity and creatinine and phosphorus concentration was observed in both sexes of the treated group.

Following a two week off-dosing period alkaline phosphatase activity and creatinine and phosphorus concentration in previously treated animals were considered to be similar to the controls. However a higher than control urea concentration was observed in both sexes of the previously treated group.

Other differences between the control and treated group means, including those attaining a level of statistical significance were slight in degree or there was considerable overlap between groups in the range of the individual data.

6.7 Organ Weights

Table 22 to Table 27, Appendix 11 to Appendix 12

Analysis of organ weights obtained from animals killed on Day 3, two days after the first dose, revealed higher than control spleen weights, absolute and when adjusted for terminal bodyweight, in both sexes of the treated group.

In animals killed two days after the second dose on Day 17 statistically significant higher than control spleen weights, absolute and when adjusted for terminal bodyweight, in both sexes was again observed. Statistically significant higher than control liver weights, absolute and when adjusted for terminal bodyweight, were observed in both sexes of the treated group. A statistically significant lower than control thymus weight, absolute and when adjusted for terminal bodyweight, was also seen in treated females.

In animals killed following a two week-off dosing period slightly higher than control spleen weights, absolute and when adjusted for terminal bodyweight, were still observed in the previously treated females.

All intergroup differences in organ weights were considered to fall within the expected range for this age and strain of animal.

6.8 Macropathology

Table 28 to Table 30, Appendix 13

Macroscopic examination of animals killed on Day 3, two days after the first dose, revealed a slightly higher incidence of dark areas at the intramuscular injection site. This is a normal background observation seen in mice dosed by this route of administration at this Test Facility and is therefore considered to be procedural in origin and unrelated to treatment.

In animals killed two days after the second dose on Day 17 enlargement of the liver, spleen and lumbar and inguinal lymph nodes were observed in treated animals of both sexes which was not observed amongst the controls.

In animals killed following a two week off-dosing period, one male mouse previously from the treated group was observed to have small testes when compared to the control group.

Other macroscopic observations were considered to fall within the expected range for this age and strain of animal.

6.9 Pathology

Annex 1

Interim animals

Intramuscular injection of MVA-HBV, in BALB/c mice resulted in treatment related changes in the femur, left muscular injection site, sciatic nerve, inguinal lymph nodes in both sexes; right muscular injection site and left axillary lymph nodes in males.

In the femur and muscular injection sites, mixed inflammatory cell infiltrate of the fibrous connective tissue was characterized by increased numbers of inflammatory cells, including lymphocytic, monocytic and polymorphonuclear cells, which extended from the intramuscular injection site into the connective tissue around the femoro-tibial joint. Perineural mixed inflammatory cell infiltrate was observed associated with the sciatic nerve but there was no evidence of axonal or myelin damage. Focal to multifocal myofiber degeneration was seen at a low incidence and severity, sometimes accompanied by minimal to slight myofiber necrosis.

In the inguinal lymph nodes, increased general cellularity was considered to represent a mild immunological response to the antigenic stimulation caused by intramuscular administration of MVA-HBV and to the inflammatory changes in the muscle of the injection site. Increased general cellularity of the inguinal lymph nodes correlated with macroscopic enlargement in one male and one female.

Main animals

Changes related to treatment with MVA-HBV, after two doses of treatment 14 days apart, were seen in the femur, muscular injection site (left and right), sciatic nerve, spleen, inguinal and lumbar lymph nodes in both sexes.

In the femur and muscular injection site, the incidence and/or severity of inflammatory cell infiltrate of the fibrous connective tissue, myofiber degeneration and myofiber necrosis in both sexes after two doses of treatment, was higher when compared to the group given one dose of treatment. Myofiber degeneration was seen in the majority of males and females and this finding was more extensive than in animals killed, with a higher incidence of myofiber necrosis in both sexes.

In the sciatic nerve, the incidence and/or severity of perineural inflammatory cell infiltrate were increased in animals killed after two doses of treatment when compared to animals given one dose of treatment, but there was no evidence of axonal or myelin damage. This inflammatory cell infiltration spread from the injection site due to its anatomical proximity.

In the spleen, increased extramedullary hemopoiesis was seen in response to the inflammatory changes in the injection site induced by the vaccine, which mostly correlated with enlarged spleens, and statistically significant increased absolute and body weight adjusted spleen weights in both sexes.

In the inguinal and lumbar lymph nodes, increased general cellularity was considered to represent a mild immunological response to the intramuscular administration of MVA-HBV and to the inflammatory changes in the skeletal muscle of the injection site. This finding correlated with macroscopic enlargement of the lymph nodes.

There were no histopathological findings that correlated with liver enlargement and increased liver weight in females.

Following the first dose, the local inflammatory changes and myofiber degeneration in the femur and mostly left injection site were seen at a minimal to slight severity and therefore these findings were considered nonadverse. Following the second dose, increased local inflammatory reaction induced by the vaccine have resulted in increased severity of myofiber degeneration and necrosis in the femur and injection site, and therefore these findings were considered adverse.

Changes in the femur (in connective tissue and muscle) and the sciatic nerve (perineural infiltrate) represent extension of the inflammatory changes at the injection site, rather than primary test item induced changes. The findings in the spleen, sciatic nerve and lymph nodes were considered secondary to a mild immune response and/or local inflammatory changes, and therefore adaptive and nonadverse.

Recovery animals

Following the 14 day recovery period, there was complete reversibility in the femur of females and spleen of both sexes. Partial reversibility was seen in the femur of males, left and right muscular injection sites, inguinal lymph nodes, and sciatic nerves of both sexes.

In the femur, injection sites and sciatic nerves the findings were mostly minimal and focal and therefore nonadverse, except for Animal No. 38 which showed slight mineralization in the left and right injection sites. There were no histopathological findings that correlated with slightly increased spleen weights in females. The lumbar lymph nodes were not evaluated because of lack of macroscopic findings.

7 DISCUSSION AND CONCLUSION

This study was performed to assess the toxic effects of MVA-HBV vaccine (nominal dose $4.8x10^8$ PFU/mL) when administered by intramuscular injection twice, with two weeks between administrations, to BALB/C mice. All study animals received the control, 0.9% saline, or the test item, MVA-HBV ($4.8x10^8$ PFU/mL) by an intramuscular injection. The main study animals were dosed on two dosing occasions, Day 1 and Day 15. Interim animals were dosed once only on Day 1, and terminated on Day 3. Recovery animals were dosed on Days 1 and 15, followed by a 2 week off-dose period. MVA-HBV vaccine was well tolerated, no premature deaths occurred and there were no clinical signs, bodyweight, food consumption or body temperature changes that were considered to be related to treatment.

Interim animals

Two days after the first administration of MVA-HBV treated male mice did show a slightly high neutrophil and lymphocyte count when females showed a slightly low lymphocyte count in the peripheral blood. A small inflammatory response is expected in response to the presence of a vaccine which subsequently results in a small decrease in cell numbers shortly afterwards as these cells are sequestered. This difference in sexes may reflect the relative timing of the blood sample with small differences in the rate of response between sexes. Two days following the second dose a generalized lowering in several leucocyte populations this time was similarly observed. The small reduction seen in red blood cell count is a normal homeostatic response to an increase in white blood cell production, in response to the observed reduced levels.

Treatment related changes in the femur, left muscular injection site, sciatic nerve, inguinal lymph nodes in both sexes; right muscular injection site and left axillary lymph nodes in males were also observed during the microscopic analysis. In the femur and muscular injection sites, mixed inflammatory cell infiltrate of the fibrous connective tissue was characterized by increased numbers of inflammatory cells, including lymphocytic, monocytic and polymorphonuclear cells, which extended from the intramuscular injection site into the connective tissue around the femoro-tibial joint. Perineural mixed inflammatory cell infiltrate was observed associated with the sciatic nerve but there was no evidence of axonal or myelin damage. Focal to multifocal myofiber degeneration was seen at a low incidence and severity, sometimes accompanied by minimal to slight myofiber necrosis.

Two days after the first dose administration, in the inguinal lymph nodes, increased general cellularity was considered to represent a mild immunological response to the antigenic stimulation caused by intramuscular administration of MVA-HBV and to the inflammatory changes in the muscle of the injection site. Increased general cellularity of the inguinal lymph nodes correlated with macroscopic enlargement in one male and one female. Following the first dose, the local inflammatory changes and myofiber degeneration in the femur and mostly left injection site were seen at a minimal to slight severity and therefore these findings were considered non-adverse.

Main animals

The enlarged spleens with higher weights and enlarged lymph nodes local to the site of injection which were observed two days after the final dose (and in the case of the spleen was still apparent at the end of the recovery period) are again consistent with the normal immunological response to the presence of a vaccine. In the spleen, increased extramedullary hemopoiesis was seen in response to the inflammatory changes in the injection site induced by the vaccine, which mostly correlated with enlarged spleens, and statistically significant increased absolute and body weight adjusted spleen weights in both sexes. In the inguinal and lumbar lymph nodes, increased general cellularity was considered to represent a mild immunological response to the intramuscular administration of MVA-HBV and to the inflammatory changes in the skeletal muscle of the injection site. This finding correlated with macroscopic enlargement of the lymph nodes. The lower thymus weights may be related to the same immunological response but are also consistent with a non-specific stress response. Enlarged livers with higher weights were observed in the treated group two days after the final dose. There were no histopathological findings that correlated with liver enlargement and increased liver weight in females. Although minor increases in metabolizing enzymes and cholesterol concentration in the plasma of males were observed two days after the first dose such modest increases are likely associated with adaptive changes rather than dysfunction.

Changes related to treatment with MVA-HBV, after two doses of treatment 14 days apart, were seen in the femur, muscular injection site (left and right), sciatic nerve, spleen, inguinal and lumbar lymph nodes in both sexes. In the femur and muscular injection site, the incidence and/or severity of inflammatory cell infiltrate of the fibrous connective tissue, myofiber degeneration and myofiber necrosis in both sexes after two doses of treatment, was higher when compared to the group given one dose of treatment. Myofiber degeneration was seen in the majority of males and females and this finding was more extensive than in animals killed on Day 3, with a higher incidence of myofiber necrosis in both sexes. In the sciatic nerve, the incidence and/or severity of perineural inflammatory cell infiltrate were increased in animals killed after two doses of treatment when compared to animals killed after one dose, but there was no evidence of axonal or myelin damage. This inflammatory cell infiltration spread from the injection site due to its anatomical proximity.

Following the second dose, increased local inflammatory reaction induced by the vaccine resulted in increased severity of myofiber degeneration and necrosis in the femur and injection site, and therefore these findings were considered adverse. The findings in the spleen, sciatic nerve and lymph nodes were considered secondary to a mild immune response and/or local inflammatory changes, and are therefore adaptive and nonadverse.

Lower plasma creatinine concentrations were associated with lower albumin, calcium, phosphorus, triglyceride concentration and aspartate aminotransferase activity with a higher chloride concentration in females two days after the first dose and alkaline phosphatase and phosphorus levels in both sexes two days after the second dose. These changes are consistent with an adaptive response by the kidneys to an increase in clearance from the blood. These observations were not present at the end of the off dose period but instead slightly high urea

levels were observed which may also support this. Similarly, given the small nature of these changes these may simply be associated with differences in food consumption.

8 CONCLUSION

Intramuscular injection of MVA-HBV dosed at $4.8x10^8$ PFU/mL on two occasions to BALB/c mice was well tolerated with some adverse effects following the second dose.

Minor fluctuations in peripheral white and red blood cell count, enlarged spleen, lymph node and liver weights and minor fluctuations in plasma metabolising enzyme, electrolyte and lipid levels were all considered to be associated with a normal immunological response to the presence of a vaccine.

Furthermore, intramuscular administration of MVA-HBV to BALB mice on one occasion, resulted in non-adverse treatment related findings in the femur, left intramuscular injection site, sciatic nerve, inguinal lymph nodes in both sexes; right intramuscular injection site and left axillary lymph nodes in males.

Intramuscular administration of MVA-HBV to BALB mice on two occasions, 14 days apart, resulted in adverse treatment related findings in the femur, intramuscular injection site (left and right), and non-adverse sciatic nerve, spleen, inguinal and lumbar lymph nodes in both sexes.

Following the 14 day recovery period, there was complete reversibility in the femur of females and spleen of both sexes. Partial reversibility was seen in the femur of males, left and right muscular injection sites, inguinal lymph nodes, and sciatic nerves of both sexes. In general, there was a clear decrease in the incidence and severity of the findings, which were all considered nonadverse except for myofiber mineralization in male No. 38.

9 REFERENCES

Angervall L and Carlström E (1963). Theoretical criteria for the use of relative organ weights and similar ratios in biology. *J Theoret Biol* **4**, 254-9.

Armitage P (1955) Tests for linear trends in proportions and frequencies. *Biometrics*, **11**, 375-386.

Armitage P, Berry G and Matthews JNS (2002) *Statistical Methods in Medical Research*, 4th edn., p.227. Blackwell Science, UK.

Bartlett MS (1937). Properties of sufficiency and statistical tests. Proceedings of the Royal Society. *Series A* **160**, 268-282.

Dunnett CW (1955). A multiple comparison procedure for comparing several treatments with a control. *Journal of the American Statistical Association* **50**, 1096-1121.

Dunnett CW (1964). New tables for multiple comparisons with a control. *Biometrics* **20**, 482-491.

Fisher RA (1973). *Statistical Methods for Research Workers*, 14th edn., p.96. Hafner Publishing Company, New York, USA.

Shirley EAC (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* **33**, 386-389.

Steel RGD (1959). A multiple comparison rank sum test: treatments versus control. *Biometrics* **15**, 560-572.

Wilcoxon F. (1945) Individual comparisons by ranking methods. *Biometrics Bulletin*, **1**, 80-83.

Williams DA (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams DA (1972). The comparison of several dose levels with a zero dose control. *Biometrics*, **28**, 519-531.

FIGURES

Figure 1 Effects of MVA-HBV on bodyweight in mice - Interim phase

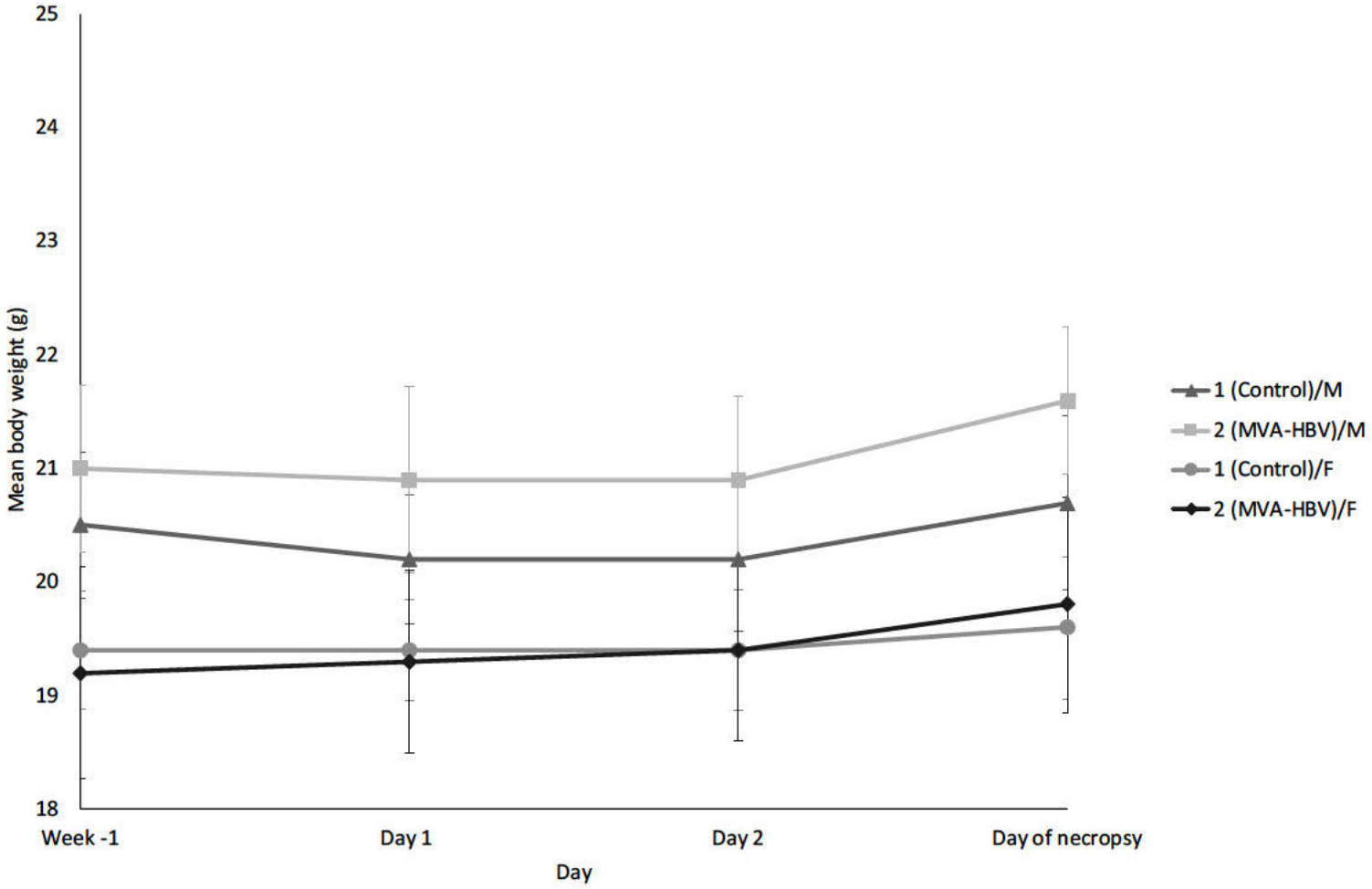


Figure 2 Effects of MVA-HBV on bodyweight in mice - Main phase

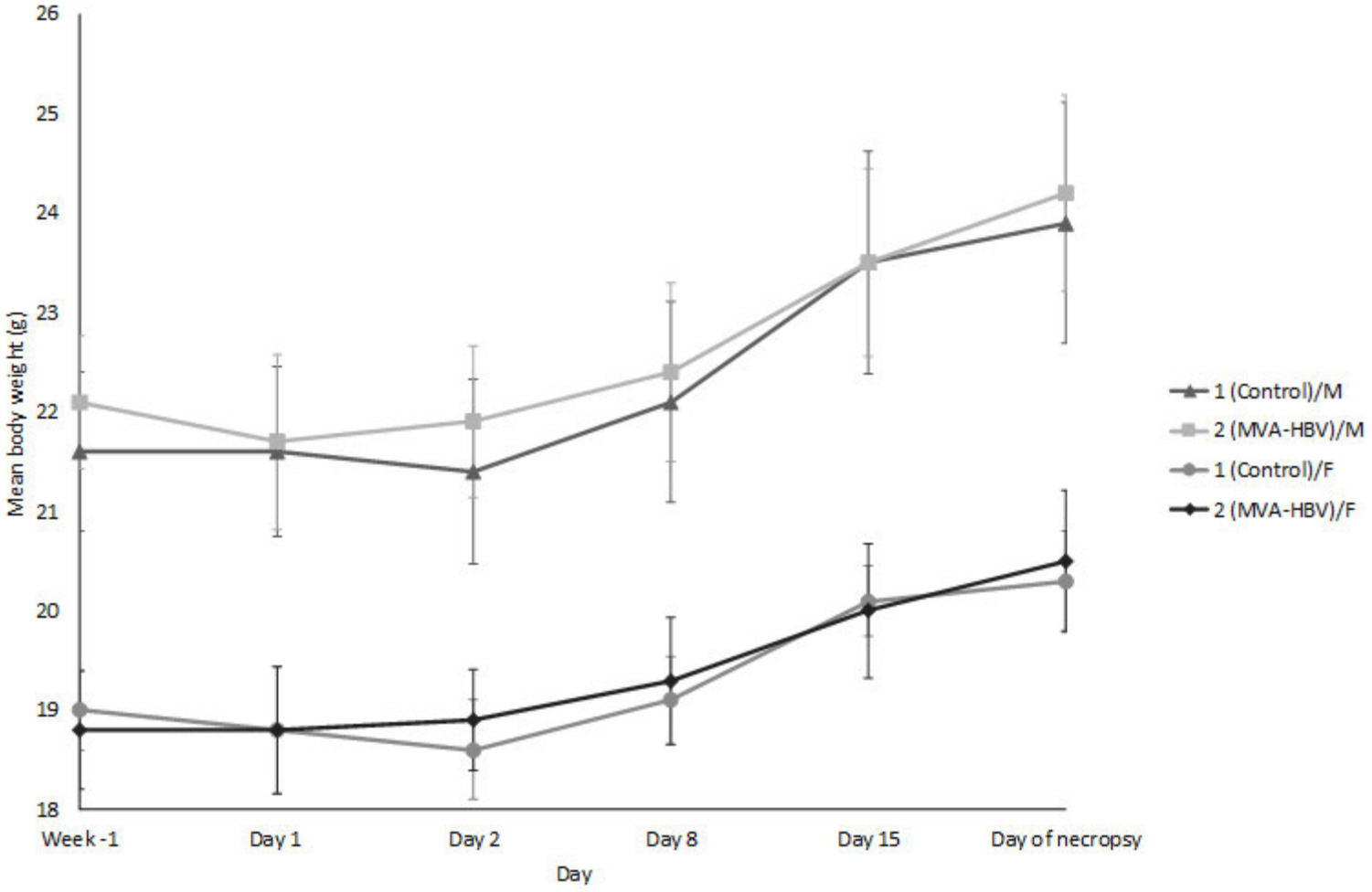
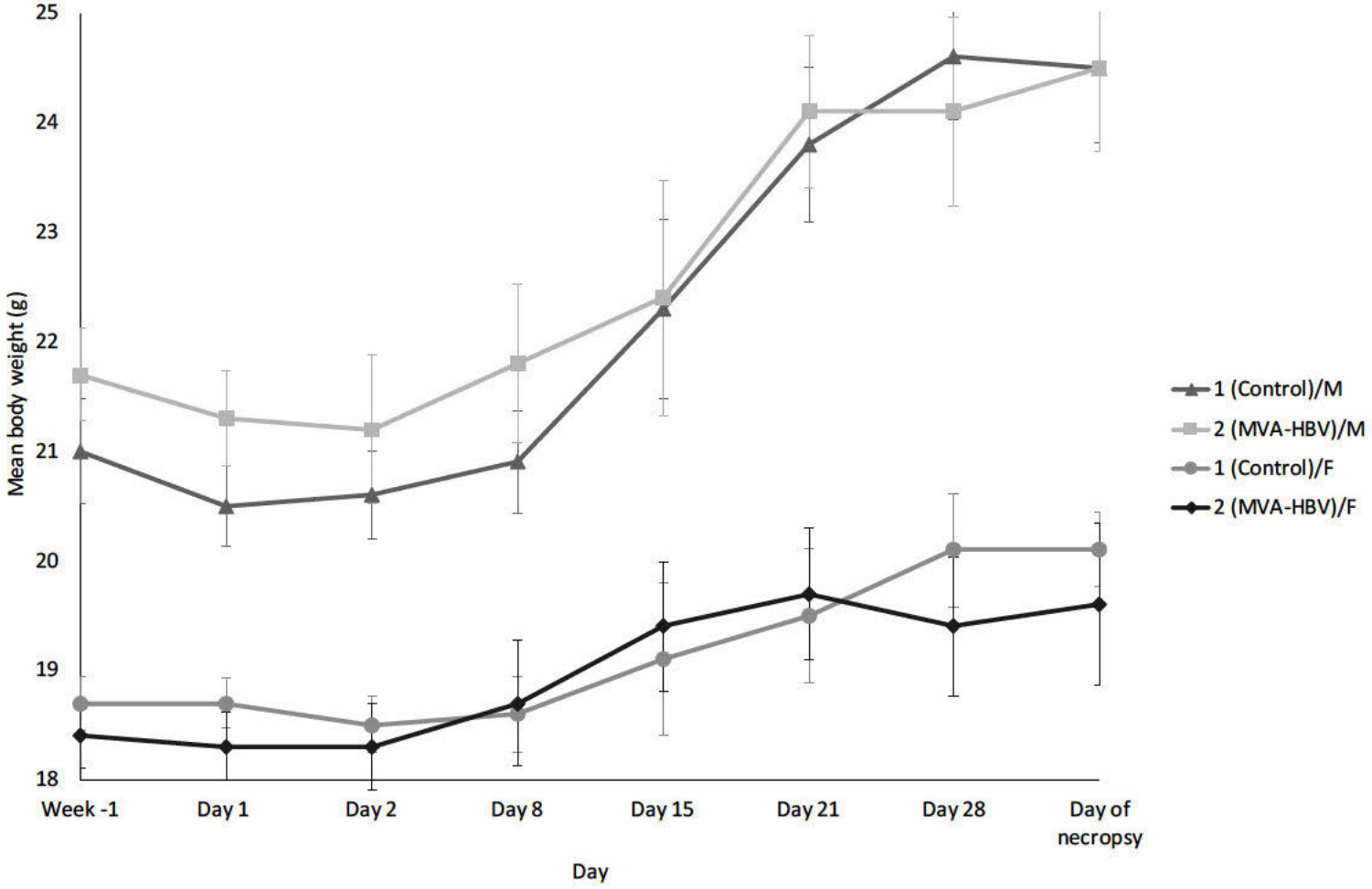


Figure 3 Effects of MVA-HBV on bodyweight in mice - Recovery phase



TABLES

Table 1 The effect of intramuscular administration of MVA-HBV on mean body weight in mice - Interim phase

Group /Sex	Intramuscular treatment (PFU/mL)		Group mean body weight (g ± SD): Week -1	1[1]	2	Day of necropsy
1M	Control (0)	Mean	20.5	20.2	20.2	20.7
		SD	±0.64	±0.57	±0.64	±0.77
		n	6	6	6	6
2M	MVA-HBV ($4.8x10^8$)	Mean	21.0	20.9	20.9	21.6
		SD	±0.74	±0.82	±0.74	±0.65
		n	6	6	6	6
1F	Control (0)	Mean	19.4	19.4	19.4	19.6
		SD	±0.52	±0.44	±0.53	±0.63
		n	6	6	6	6
2F	MVA-HBV ($4.8x10^8$)	Mean	19.2	19.3	19.4	19.8
		SD	±0.93	±0.80	±0.80	±0.95
		n	6	6	6	6

[1] Day 1 data was collected prior to dosing

Table 2 The effect of intramuscular administration of MVA-HBV on bodyweight in mice - Main phase

Group /Sex	Intramuscular treatment (PFU/mL)		Group mean body weight (g ± SD): Week -1	1[1]	2	8	15[1]	Day of necropsy
1M	Control (0)	Mean	21.6	21.6	21.4	22.1	23.5	23.9
		SD	±0.80	±0.86	±0.93	±1.01	±1.12	±1.21
		n	10	10	10	10	10	10
2M	MVA-HBV ($4.8x10^8$)	Mean	22.1	21.7	21.9	22.4	23.5	24.2
		SD	±0.67	±0.88	±0.76	±0.90	±0.94	±0.98
		n	10	10	10	10	10	10
1F	Control (0)	Mean	19.0	18.8	18.6	19.1	20.1	20.3
		SD	±0.40	±0.64	±0.50	±0.44	±0.36	±0.50
		n	10	10	10	10	10	10
2F	MVA-HBV ($4.8x10^8$)	Mean	18.8	18.8	18.9	19.3	20.0	20.5
		SD	±0.59	±0.64	±0.51	±0.64	±0.68	±0.71
		n	10	10	10	10	10	10

[1] Day 1and 15 data was collected prior to dosing

Table 3 The effect of intramuscular administration of MVA-HBV on bodyweight in mice - Recovery phase

Group /Sex	Intramuscular treatment (PFU/mL)		Group mean body weight (g ± SD): Week -1	1[1]	2	8	15[1]	21	28	Day of necropsy
1M	Control (0)	Mean	21.0	20.5	20.2	20.9	22.3	23.8	24.6	24.5
		SD	±0.48	±0.37	±0.40	±0.47	±0.82	±0.71	±0.58	±0.68
		n	5	5	5	5	5	5	5	5
2M	MVA-HBV ($4.8x10^8$)	Mean	21.7	21.3*	21.2*	21.8	22.4	24.1	24.1	24.5
		SD	±0.43	±0.44	±0.68	±0.72	±1.07	±0.70	±0.86	±0.77
		n	5	5	5	5	5	5	5	5
1F	Control (0)	Mean	18.7	18.7	18.5	18.6	19.1	19.5	20.1	20.1
		SD	±0.24	±0.23	±0.26	±0.35	±0.70	±0.61	±0.52	±0.34
		n	5	5	5	5	5	5	5	5
2F	MVA-HBV ($4.8x10^8$)	Mean	18.4	18.3*	18.3	18.7	19.4	19.7	19.4	19.6
		SD	±0.30	±0.31	±0.40	±0.57	±0.59	±0.60	±0.64	±0.74
		n	5	5	5	5	5	5	5	5

[1] Day 1 and 15 data was collected prior to dosing

Statistical significance compared to vehicle-treated control animals: * $p<0.05$

Table 4 The effect of intramuscular administration of MVA-HBV on body temperature in mice - Interim phase

Group /Sex	Intramuscular treatment (PFU/mL)		Group mean body temperature (°C ± SD): Predose Day 1	4 h Post dose Day 1	24 h Post dose Day 1
1M	Control (0)	Mean SD n	35.5 ±0.21 6	35.3 ±0.45 6	35.3 ±0.39 6
2M	MVA-HBV ($4.8x10^8$)	Mean SD n	35.3 ±0.12 6	36.0* ±0.52 6	35.5 ±0.29 6
1F	Control (0)	Mean SD n	35.8 ±0.72 6	35.5 ±0.50 6	35.8 ±0.27 6
2F	MVA-HBV ($4.8x10^8$)	Mean SD n	36.0 ±0.46 6	36.1 ±0.27 6	35.6 ±0.52 6

Statistical significance compared to vehicle-treated control animals: * $p<0.05$

Table 5 The effect of intramuscular administration of MVA-HBV on body temperature in mice - Main phase

Group /Sex	Intramuscular treatment (PFU/mL)		Group mean body temperature (°C ± SD): Predose Day 1	4 h Post dose Day 1	24 h Post dose Day 1	Predose Day 15	4 h Post dose Day 15	24 h Post dose Day 15
1M	Control (0)	Mean	35.6	35.5	35.3	35.9	34.8	34.4
		SD	±0.29	±0.41	±0.30	±0.26	±0.49	±0.41
		n	10	10	10	10	10	10
2M	MVA-HBV ($4.8x10^8$)	Mean	35.1**	35.2	35.2	35.9	34.9	35.7**
		SD	±0.39	±0.47	±0.21	±0.51	±0.35	±0.52
		n	10	10	10	10	10	10
1F	Control (0)	Mean	36.1	35.8	35.6	36.6	35.1	35.9
		SD	±0.33	±0.51	±0.35	±0.21	±0.11	±0.46
		n	10	10	10	10	10	10
2F	MVA-HBV ($4.8x10^8$)	Mean	36.1	36.3*	35.3	36.2*	35.2	36.0
		SD	±0.30	±0.39	±0.26	±0.34	±0.18	±0.40
		n	10	10	10	10	10	10

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Table 6 The effect of intramuscular administration of MVA-HBV on body temperature in mice - Recovery phase

Group /Sex	Intramuscular treatment (PFU/mL)		Group mean body temperature (°C ± SD): Predose Day 1	4 h Post dose Day 1	24 h Post dose Day 1	Predose Day 15	4 h Post dose Day 15	24 h Post dose Day 15
1M	Control (0)	Mean	35.5	35.5	35.3	36.0	34.9	35.5
		SD	±0.40	±0.51	±0.08	±0.55	±0.31	±0.40
		n	5	5	5	5	5	5
2M	MVA-HBV ($4.8x10^8$)	Mean	35.2	35.6	35.4	35.6	35.1	36.1
		SD	±0.15	±0.41	±0.46	±0.39	±0.11	±0.54
		n	5	5	5	5	5	5
1F	Control (0)	Mean	35.9	35.6	35.3	36.5	35.3	35.3
		SD	±0.42	±0.34	±0.22	±0.34	±0.21	±0.50
		n	5	5	5	5	5	5
2F	MVA-HBV ($4.8x10^8$)	Mean	35.9	35.9	35.6	36.3	35.3	35.1
		SD	±0.17	±0.36	±0.41	±0.41	±0.13	±0.43
		n	5	5	5	5	5	5

Table 7 The effect of intramuscular administration of MVA-HBV on food consumption in mice - Interim phase

Group /Sex	Intramuscular treatment (PFU/mL)		Group mean estimated food consumption (g/cage/week ± SD) on week: 1	2
1M	Control (0)	Mean SD n (n/cage)	53.0 ±1.0 6 (3)	21.5 ±0.5 6 (3)
2M	MVA-HBV ($4.8x10^8$)	Mean SD n (n/cage)	54.5 ±1.5 6 (3)	21.5 ±0.5 6 (3)
1F	Control (0)	Mean SD n (n/cage)	46.0 ±3.0 6 (3)	21.0 ±2.0 6 (3)
2F	MVA-HBV ($4.8x10^8$)	Mean SD n (n/cage)	47.0 ±1.0 6 (3)	18.5 ±0.5 6 (3)

Table 8 The effect of intramuscular administration of MVA-HBV on food consumption in mice - Main phase

Group /Sex	Intramuscular treatment (PFU/mL)		Group mean estimated food consumption (g/cage/week ± SD) on week:		
			1	2	3
1M	Control (0)	Mean SD n (n/cage)	90.5 ±2.5 10 (5)	118.5 ±2.5 10 (5)	121.5 ±0.5 10 (5)
2M	MVA-HBV ($4.8x10^8$)	Mean SD n (n/cage)	91.0 ±3.0 10 (5)	123.0 ±1.0 10 (5)	121.0 ±2.0 10 (5)
1F	Control (0)	Mean SD n (n/cage)	69.0 ±1.0 10 (5)	98.0 ±1.0 10 (5)	96.0 ±4.0 10 (5)
2F	MVA-HBV ($4.8x10^8$)	Mean SD n (n/cage)	78.5 ±3.5 10 (5)	102.5 ±0.5 10 (5)	102.0 ±5.0 10 (5)

Table 9 The effect of intramuscular administration of MVA-HBV on food consumption in mice - Recovery phase

Group /Sex	Intramuscular treatment (PFU/mL)		Group mean estimated food consumption (g/cage/week) on week:				
			1	2	3	4	5
1M	Control (0)	Mean	85.0	117.0	124.0	164.0	121.0
		n (n/cage)	5(5)	5(5)	5(5)	5(5)	5(5)
2M	MVA-HBV ($4.8x10^8$)	Mean	94.0	126.0	127.0	127.0	124.0
		n (n/cage)	5(5)	5(5)	5(5)	5(5)	5(5)
1F	Control (0)	Mean	87.0	97.0	95.0	96.0	103.0
		n (n/cage)	5(5)	5(5)	5(5)	5(5)	5(5)
2F	MVA-HBV ($4.8x10^8$)	Mean	85.0	101.0	96.0	91.0	96.0
		n (n/cage)	5(5)	5(5)	5(5)	5(5)	5(5)

Note- There is no Standard deviation presented for the recovery phase food consumption as there is only one cage/group for this phase.

Table 10 The effect of intramuscular administration of MVA-HBV on haematology parameters in male mice - Interim phase

Group /Sex	Intramuscular treatment (PFU/mL)		Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
1M	Control (0)	Mean	0.537	15.9	10.29	0.158	15.5	29.6	52.3	16.2
		SD	0.0237	0.52	0.471	0.0227	0.25	0.98	1.53	0.50
		n	6	6	6	6	6	6	6	6
2M	MVA-HBV ($4.8x10^8$)	Mean	0.532	15.4	10.27	0.148	15.0	29.0	51.8	16.8
		SD	0.0112	0.81	0.272	0.0182	0.52	1.22	0.89	0.57
		n	6	6	6	5	6	6	6	6

Group /Sex	Intramuscular treatment (PFU/mL)		WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
1M	Control (0)	Mean	3.07	0.62	2.30	0.08	0.01	0.05	0.02	980
		SD	0.883	0.126	0.735	0.015	0.008	0.028	0.008	156.7
		n	6	6	6	6	6	6	6	6
2M	MVA-HBV ($4.8x10^8$)	Mean	3.66	0.85**	2.61	0.08	0.01	0.05	0.07**	827
		SD	0.442	0.119	0.437	0.012	0.000	0.015	0.016	287.3
		n	6	6	6	6	6	6	6	6

Statistical significance compared to vehicle-treated control animals: ** $p<0.01$

Table 11 The effect of intramuscular administration of MVA-HBV on haematology parameters in female mice - Interim phase

Group /Sex	Intramuscular treatment (PFU/mL)		Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
1F	Control (0)	Mean	0.527	16.6	10.43	0.179	15.9	31.4	50.6	14.5
		SD	0.0087	0.50	0.318	0.0072	0.10	1.00	1.72	0.52
		n	4	4	4	4	4	4	4	4
2F	MVA-HBV ($4.8x10^8$)	Mean	0.480**	15.5*	9.96	0.135*	15.5**	32.3	48.1	14.6
		SD	0.0125	0.06	0.115	0.0318	0.06	1.04	1.82	1.15
		n	3	3	3	3	3	3	3	3

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Group /Sex	Intramuscular treatment (PFU/mL)		WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
1F	Control (0)	Mean	3.14	0.54	2.42	0.11	0.02	0.03	0.03	834
		SD	0.819	0.111	0.722	0.047	0.006	0.016	0.013	195.8
		n	4	4	4	4	4	4	4	4
2F	MVA-HBV ($4.8x10^8$)	Mean	2.25	0.59	1.42	0.11	0.02	0.03	0.03	967
		SD	0.394	0.156	0.361	0.000	0.007	0.007	0.014	64.1
		n	3	2	2	2	2	2	2	3

Table 12 The effect of intramuscular administration of MVA-HBV on haematology parameters in male mice - Main phase

Group /Sex	Intramuscular treatment (PFU/mL)		Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
1M	Control (0)	Mean	0.526	15.8	10.54	0.222	15.0	30.1	49.9	13.0
		SD	0.0191	0.49	0.375	0.0227	0.22	0.46	0.78	0.24
		n	10	10	10	10	10	10	10	10
2M	MVA-HBV ($4.8x10^8$)	Mean	0.525	15.4	10.46	0.227	14.7	29.3*	50.2	13.4**
		SD	0.0193	0.40	0.365	0.0197	0.51	1.00	1.09	0.30
		n	8	8	8	8	8	8	8	8

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Group /Sex	Intramuscular treatment (PFU/mL)		WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
1M	Control (0)	Mean	4.33	0.74	3.36	0.13	0.02	0.06	0.03	866
		SD	0.783	0.115	0.681	0.037	0.008	0.019	0.013	62.9
		n	10	10	10	10	10	10	10	10
2M	MVA-HBV ($4.8x10^8$)	Mean	2.91**	0.71	1.96**	0.06**	0.01	0.04*	0.03	887
		SD	0.962	0.198	0.781	0.019	0.010	0.014	0.013	61.5
		n	8	7	7	7	7	7	7	8

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Table 13 The effect of intramuscular administration of MVA-HBV on haematology parameters in female mice - Main phase

Group /Sex	Intramuscular treatment (PFU/mL)		Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
1F	Control (0)	Mean	0.507	15.2	9.98	0.242	15.2	29.9	50.8	12.4
		SD	0.0100	0.32	0.179	0.0250	0.16	0.61	0.89	0.27
		n	10	10	10	10	10	10	10	10
2F	MVA-HBV ($4.8x10^8$)	Mean	0.484	14.2	9.57	0.221	14.8	29.2	50.5	12.6
		SD	0.0462	2.08	0.871	0.0320	1.12	2.08	1.00	0.22
		n	10	10	10	10	10	10	10	10

Group /Sex	Intramuscular treatment (PFU/mL)		WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
1F	Control (0)	Mean	5.04	0.79	3.97	0.14	0.02	0.08	0.04	824
		SD	2.217	0.220	1.983	0.057	0.016	0.031	0.035	118.0
		n	10	10	10	10	10	10	10	10
2F	MVA-HBV ($4.8x10^8$)	Mean	2.34**	0.44**	1.82**	0.05**	0.01	0.02**	0.07	819
		SD	0.707	0.143	0.572	0.014	0.010	0.007	0.036	76.7
		n	10	9	9	9	9	9	9	10

Statistical significance compared to vehicle-treated control animals: ** $p<0.01$

Table 14 The effect of intramuscular administration of MVA-HBV on haematology parameters in male mice - Recovery phase

Group /Sex	Intramuscular treatment (PFU/mL)		Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
1M	Control (0)	Mean	0.529	15.5	10.43	0.222	14.9	29.4	50.7	12.9
		n	1	1	1	1	1	1	1	1
2M	MVA-HBV ($4.8x10^8$)	Mean	0.546	15.5	10.60	0.219	14.7	28.5	51.4	12.9
		SD	0.0144	0.21	0.188	0.0199	0.45	1.17	0.75	0.10
		n	3	3	3	3	3	3	3	3

Group /Sex	Intramuscular treatment (PFU/mL)		WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
1M	Control (0)	Mean	4.49	0.69	3.49	0.18	0.02	0.08	0.04	882
		n	1	1	1	1	1	1	1	1
2M	MVA-HBV ($4.8x10^8$)	Mean	4.05	0.68	3.09	0.18	0.01	0.06	0.03	903
		SD	1.196	0.155	0.972	0.060	0.010	0.023	0.010	26.1
		n	3	3	3	3	3	3	3	3

Note- There is no Standard deviation presented for the control group as only one blood sample was analyzed due to clotting of other samples.

Table 15 The effect of intramuscular administration of MVA-HBV on haematology parameters in female mice - Recovery phase

Group /Sex	Intramuscular treatment (PFU/mL)		Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
1F	Control (0)	Mean	0.508	14.9	9.81	0.198	15.2	29.3	51.8	12.7
		SD	0.0198	0.30	0.232	0.0341	0.49	0.62	2.07	0.12
		n	4	4	4	4	4	4	4	4
2F	MVA-HBV ($4.8x10^8$)	Mean	0.518	15.0	10.17	0.202	14.7	29.0	50.9	12.9
		SD	0.0163	0.69	0.238	0.0324	0.51	1.53	1.36	0.22
		n	5	5	5	5	5	5	5	5

Group /Sex	Intramuscular treatment (PFU/mL)		WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
1F	Control (0)	Mean	4.01	0.59	3.19	0.14	0.01	0.05	0.04	736
		SD	1.264	0.076	1.141	0.054	0.010	0.014	0.013	23.4
		n	4	4	4	4	4	4	4	3
2F	MVA-HBV ($4.8x10^8$)	Mean	3.33	0.45	2.70	0.12	0.01	0.03	0.02	815
		SD	1.389	0.142	1.210	0.040	0.013	0.013	0.013	72.0
		n	5	5	5	5	5	5	5	3

Table 16 The effect of intramuscular administration of MVA-HBV on blood biochemistry parameters in male mice - Interim phase

Group /Sex	Intramuscular treatment (PFU/mL)		ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
1M	Control (0)	Mean	173	55	76	1	5.91	7	10.66	2.99	2.30
		SD	27.7	4.7	13.6	0.5	0.274	3.7	2.153	0.140	0.263
		n	6	6	6	6	6	6	6	6	6
2M	MVA-HBV ($4.8x10^8$)	Mean	165	73	91	1	5.64	8	11.90	3.27**	2.28
		SD	9.4	32.6	31.3	0.4	0.752	2.3	2.262	0.070	0.206
		n	6	6	6	6	6	6	6	6	6

Statistical significance compared to vehicle-treated control animals: ** $p<0.01$

Group /Sex	Intramuscular treatment (PFU/mL)		Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
1M	Control (0)	Mean	153	4.14	108.9	2.60	3.20	49	30	1.53
		SD	1.4	0.281	1.91	0.076	0.592	1.0	1.0	0.072
		n	6	6	6	6	6	6	6	6
2M	MVA-HBV ($4.8x10^8$)	Mean	150	4.29	108.8	2.54	2.76	48	29	1.46
		SD	3.0	0.644	3.59	0.074	0.235	1.0	1.0	0.073
		n	6	6	6	6	6	6	6	6

Table 17 The effect of intramuscular administration of MVA-HBV on blood biochemistry parameters in female mice - Interim phase

Group /Sex	Intramuscular treatment (PFU/mL)		ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
1F	Control (0)	Mean	141	66	106	1	6.19	11	9.63	2.07	1.54
		SD	9.4	23.8	31.4	0.0	0.721	1.6	2.605	0.099	0.078
		n	6	6	6	6	6	6	6	6	6
2F	MVA-HBV ($4.8x10^8$)	Mean	127	42	68*	1	6.72	8*	8.86	2.07	1.05**
		SD	12.7	12.1	10.9	0.5	0.859	2.1	1.247	0.147	0.110
		n	6	6	6	6	6	6	6	6	6

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Group /Sex	Intramuscular treatment (PFU/mL)		Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
1F	Control (0)	Mean	153	4.48	113.4	2.44	3.22	47	31	1.87
		SD	1.9	0.570	2.12	0.075	0.694	1.6	0.8	0.168
		n	6	6	6	6	6	6	6	6
2F	MVA-HBV ($4.8x10^8$)	Mean	153	4.16	116.7**	2.33**	2.49*	45*	29*	1.88
		SD	0.8	0.291	0.76	0.034	0.219	1.3	0.8	0.097
		n	6	6	6	6	6	6	6	6

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Table 18 The effect of intramuscular administration of MVA-HBV on blood biochemistry parameters in male mice - Main phase

Group /Sex	Intramuscular treatment (PFU/mL)		ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
1M	Control (0)	Mean	139	97	125	1	6.39	12	11.84	3.61	2.91
		SD	10.7	39.5	47.9	0.0	0.298	2.2	2.375	0.355	0.828
		n	10	10	10	10	10	10	10	10	10
2M	MVA-HBV ($4.8x10^8$)	Mean	118**	89	111	1	7.26	8**	10.93	3.90	2.95
		SD	8.2	68.4	64.6	0.3	1.156	1.7	1.678	0.333	0.609
		n	10	10	10	10	10	10	10	10	10

Statistical significance compared to vehicle-treated control animals: ** $p<0.01$

Group /Sex	Intramuscular treatment (PFU/mL)		Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
1M	Control (0)	Mean	153	4.50	113.2	2.39	3.01	49	30	1.59
		SD	1.3	0.499	1.92	0.057	0.312	2.2	1.5	0.040
		n	10	10	10	10	10	10	10	10
2M	MVA-HBV ($4.8x10^8$)	Mean	153	4.41	113.3	2.44	2.33**	50	29	1.43**
		SD	1.5	0.680	2.10	0.069	0.541	1.8	0.5	0.093
		n	10	10	10	10	10	10	10	10

Statistical significance compared to vehicle-treated control animals: ** $p<0.01$

Table 19 The effect of intramuscular administration of MVA-HBV on blood biochemistry parameters in female mice - Main phase

Group /Sex	Intramuscular treatment (PFU/mL)		ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
1F	Control (0)	Mean	140	65	103	1	6.97	13	10.78	2.28	1.98
		SD	9.6	31.3	35.7	0.4	0.992	1.9	1.868	0.157	0.595
		n	10	10	10	10	10	10	10	10	10
2F	MVA-HBV ($4.8x10^8$)	Mean	109**	66	117	1	7.68	9**	9.99	2.33	2.14
		SD	12.1	30.1	36.6	0.0	1.031	1.4	1.807	0.196	0.726
		n	10	10	10	10	10	10	10	10	10

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Group /Sex	Intramuscular treatment (PFU/mL)		Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
1F	Control (0)	Mean	153	4.09	114.7	2.37	2.89	46	30	1.87
		SD	1.0	0.384	1.80	0.059	0.468	1.4	0.9	0.087
		n	10	10	10	10	10	10	10	10
2F	MVA-HBV ($4.8x10^8$)	Mean	152*	4.04	115.9	2.38	2.37*	47	30	1.70**
		SD	1.5	0.642	1.75	0.070	0.316	1.6	0.7	0.086
		n	10	10	10	10	10	10	10	10

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Table 20 The effect of intramuscular administration of MVA-HBV on blood biochemistry parameters in male mice - Recovery phase

Group /Sex	Intramuscular treatment (PFU/mL)		ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
1M	Control (0)	Mean	121	76	84	1	5.12	11	13.82	3.23	2.06
		SD	4.0	94.9	69.5	0.0	0.345	4.1	2.833	0.253	0.303
		n	5	5	5	5	5	5	5	5	5
2M	MVA-HBV ($4.8x10^8$)	Mean	122	54	87	1	6.15*	11	15.12	3.51	2.07
		SD	8.6	23.1	41.8	0.0	0.924	5.5	2.105	0.244	0.599
		n	5	5	5	5	5	5	5	5	5

Statistical significance compared to vehicle-treated control animals: * $p<0.05$

Group /Sex	Intramuscular treatment (PFU/mL)		Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
1M	Control (0)	Mean	151	4.04	112.0	2.43	2.69	47	30	1.78
		SD	1.3	0.565	0.53	0.068	0.392	1.1	0.8	0.105
		n	5	5	5	5	5	5	5	5
2M	MVA-HBV ($4.8x10^8$)	Mean	152	3.97	113.0	2.39	2.65	49*	29	1.50**
		SD	1.7	0.995	2.35	0.068	0.270	1.4	0.5	0.082
		n	5	5	5	5	5	5	5	5

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Table 21 The effect of intramuscular administration of MVA-HBV on blood biochemistry parameters in female mice - Recovery phase

Group /Sex	Intramuscular treatment (PFU/mL)		ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
1F	Control (0)	Mean	119	41	80	1	4.91	10	13.22	2.19	1.77
		SD	10.8	18.3	20.7	0.4	0.776	1.3	1.548	0.150	0.519
		n	5	5	5	5	5	5	5	5	5
2F	MVA-HBV ($4.8x10^8$)	Mean	134	39	84	1	7.93**	12	12.05	1.99	2.12
		SD	12.9	16.1	32.4	0.0	1.607	4.6	2.730	0.211	0.542
		n	5	5	5	5	5	5	5	5	5

Statistical significance compared to vehicle-treated control animals: ** $p<0.01$

Group /Sex	Intramuscular treatment (PFU/mL)		Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
1F	Control (0)	Mean	150	3.19	113.7	2.44	2.98	45	31	2.16
		SD	2.7	0.698	2.02	0.030	0.572	1.1	0.9	0.080
		n	5	5	5	5	5	5	5	5
2F	MVA-HBV ($4.8x10^8$)	Mean	152	3.62	116.3*	2.30**	2.49	46	30	1.87**
		SD	1.2	0.486	1.31	0.061	0.373	1.1	0.4	0.125
		n	5	5	5	5	5	5	5	5

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Table 22 The effect of intramuscular administration of MVA-HBV on group mean absolute and adjusted organ weights in male mice - Interim phase

Group /Sex	Intramuscular treatment (PFU/mL)		Terminal Body weight	Group mean organ weights (g ± SD): Brain	Epididymides	Heart	Kidneys	Liver	Spleen	Testes	Thymus	Prostate
Statistics test			Tt									
1M	Control (0)	Mean	20.7	0.3885	0.0398	0.1225	0.2866	1.1266	0.0659	0.1368	0.0488	0.0280
		SD	0.8	0.0254	0.0061	0.0121	0.0168	0.0898	0.0087	0.0115	0.0079	0.0086
		n	6	6	6	6	6	6	6	6	6	6
2M	MVA-HBV ($4.8x10^8$)	Mean	21.6	0.3903	0.0458	0.1257	0.3006	1.1713	0.0799	0.1476	0.0458	0.0327
		SD	0.6	0.0298	0.0044	0.0068	0.0184	0.0618	0.0068	0.0114	0.0064	0.0135
		n	6	6	6	6	6	6	6	6	6	6
Statistics test				Tt	Tt	Tt	Tt	Tt	Tt	Tt	Tt	Tt
1M	Control (0)	Adjusted mean		0.3943	0.0407	0.1240	0.2933	1.1584	0.0688	0.1413	0.0497	0.0307
2M	MVA-HBV ($4.8x10^8$)	Adjusted mean		0.3846	0.0449	0.1242	0.2939	1.1394	0.0770	0.1430	0.0449	0.0300

Table 23 The effect of intramuscular administration of MVA-HBV on group mean absolute and adjusted organ weights in female mice - Interim phase

Group /Sex	Intramuscular treatment (PFU/ml)		Terminal Body weight	Group mean organ weights (g ± SD): Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus	Uterus and cervix
Statistics tests			Tt			Wc					
1F	Control (0)	Mean	19.6	0.4037	0.1167	0.2338	0.8399	0.0046	0.0689	0.0570	0.0711
		SD	0.6	0.0315	0.0110	0.0047	0.0670	0.0008	0.0081	0.0164	0.0230
		n	6	6	6	6	6	6	6	6	6
2F	MVA-HBV ($4.8x10^8$)	Mean	19.8	0.4054	0.1137	0.2227	0.7917	0.0042	0.0855	0.0545	0.1016
		SD	0.9	0.0193	0.0060	0.0188	0.0515	0.0015	0.0099	0.0103	0.0710
		n	6	6	6	6	6	6	6	6	6
Statistics test				Tt	Tt		Tt	Tt	Tt	Tt	Tt
1F	Control (0)	Adjusted mean		0.4030	0.1169		0.8430	0.0046	0.0689	0.0573	0.0714
2F	MVA-HBV ($4.8x10^8$)	Adjusted mean		0.4061	0.1134		0.7886	0.0041	0.0854*	0.0542	0.1013

Statistical significance compared to vehicle-treated control animals: * $p<0.05$

Table 24 The effect of intramuscular administration of MVA-HBV on group mean absolute and adjusted organ weights in male mice - Main phase

Group /Sex	Intramuscular treatment (PFU/ml)		Terminal Body weight	Group mean organ weights (g ± SD): Brain	Epididymides	Heart	Kidneys	Liver	Spleen	Testes	Thymus	Prostate
Statistics test			Tt									
1M	Control (0)	Mean	23.9	0.4063	0.0589	0.1331	0.3230	1.2841	0.0755	0.1612	0.0382	0.0532
		SD	1.2	0.0152	0.0077	0.0072	0.0198	0.1324	0.0052	0.0110	0.0090	0.0187
		n	10	10	10	10	10	10	10	10	10	10
2M	MVA-HBV ($4.8x10^8$)	Mean	24.2	0.3968	0.0567	0.1368	0.3240	1.3816	0.1032	0.1546	0.0328	0.0425
		SD	1.0	0.0186	0.0129	0.0104	0.0232	0.0902	0.0115	0.0136	0.0077	0.0156
		n	10	10	10	10	10	10	10	10	10	10
Statistics test				Tt	Tt	Tt	Tt	Tt	Tt	Tt	Tt	Tt
1M	Control (0)	Adjusted mean		0.4070	0.0589	0.1331	0.3251	1.2989	0.0757	0.1618	0.0380	0.0527
2M	MVA-HBV ($4.8x10^8$)	Adjusted mean		0.3962	0.0567	0.1368	0.3219	1.3669*	0.1029**	0.1540	0.0329	0.0430

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Table 25 The effect of intramuscular administration of MVA-HBV on group mean absolute and adjusted organ weights in female mice - Main phase

Group /Sex	Intramuscular treatment (PFU/ml)		Terminal Body weight	Group mean organ weights (g ± SD): Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus	Uterus and cervix
Statistics tests			Tt								
1F	Control (0)	Mean	20.3	0.4151	0.1125	0.2246	0.9110	0.0074	0.0797	0.0485	0.1214
		SD	0.5	0.0114	0.0069	0.0141	0.0629	0.0016	0.0083	0.0082	0.0630
		n	10	10	10	10	10	10	10	10	10
2F	MVA-HBV ($4.8x10^8$)	Mean	20.5	0.4158	0.1099	0.2292	1.0751	0.0064	0.1458	0.0387	0.0875
		SD	0.7	0.0103	0.0111	0.0195	0.0702	0.0017	0.0222	0.0081	0.0478
		n	10	10	10	10	10	10	10	10	10
Statistics test				Tt	Tt	Tt	Tt	Tt	lTt	Tt	Tt
1F	Control (0)	Adjusted mean		0.4155	0.1130	0.2264	0.9203	0.0074	0.0799	0.0482	0.1264
2F	MVA-HBV ($4.8x10^8$)	Adjusted mean		0.4153	0.1094	0.2273	1.0658**	0.0063	0.1431**	0.0390*	0.0825

Statistical significance compared to vehicle-treated control animals: * $p<0.05$, ** $p<0.01$

Table 26 The effect of intramuscular administration of MVA-HBV on group mean absolute and adjusted organ weights in male mice - Recovery phase

Group /Sex	Intramuscular treatment (PFU/ml)		Terminal Body weight	Group mean organ weights (g ± SD): Brain	Epididymides	Heart	Kidneys	Liver	Spleen	Testes	Thymus	Prostate
Statistics tests			Tt									
1M	Control (0)	Mean	24.5	0.4125	0.0533	0.1359	0.3227	1.2597	0.0887	0.1695	0.0428	0.0456
		SD	0.7	0.0135	0.0048	0.0107	0.0058	0.0612	0.0053	0.0134	0.0059	0.0273
		n	5	5	5	5	5	5	5	5	5	5
2M	MVA-HBV ($4.8x10^8$)	Mean	24.5	0.3996	0.0513	0.1387	0.3421	1.2770	0.0894	0.1626	0.0433	0.0419
		SD	0.8	0.0143	0.0067	0.0153	0.0287	0.0844	0.0096	0.0325	0.0024	0.0141
		n	5	5	5	5	5	5	5	5	5	5
Statistics test				Tt	Tt	Tt	lTt	Tt	Tt	Tt	Tt	Tt
1M	Control (0)	Adjusted mean		0.4125	0.0533	0.1360	0.3228	1.2605	0.0887	0.1697	0.0428	0.0457
2M	MVA-HBV ($4.8x10^8$)	Adjusted mean		0.3997	0.0512	0.1386	0.3410	1.2762	0.0894	0.1624	0.0433	0.0418

Table 27 The effect of intramuscular administration of MVA-HBV on group mean absolute and adjusted organ weights in female mice - Recovery phase

Group /Sex	Intramuscular treatment (PFU/ml)		Group mean organ weights (g ± SD): Terminal Body weight	Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus	Uterus and cervix
Statistics test			Tt								
1F	Control (0)	Mean	20.1	0.4182	0.1130	0.2282	0.9904	0.0076	0.0827	0.0415	0.1446
		SD	0.3	0.0110	0.0066	0.0243	0.0836	0.0016	0.0209	0.0046	0.0655
		n	5	5	5	5	5	5	5	5	5
2F	MVA-HBV ($4.8x10^8$)	Mean	19.6	0.4018	0.1083	0.2117	0.7901	0.0073	0.0934	0.0408	0.1027
		SD	0.7	0.0087	0.0077	0.0205	0.0527	0.0012	0.0082	0.0037	0.0627
		n	5	5	5	5	5	5	5	5	5
Statistics test				Tt	Tt	Tt	Tt	Tt	Tt	Tt	Tt
1F	Control (0)	Adjusted mean		0.4163	0.1114	0.2221	0.9712	0.0074	0.0854	0.0405	0.1329
2F	MVA-HBV ($4.8x10^8$)	Adjusted mean		0.4037	0.1098	0.2178	0.8093**	0.0075	0.0907	0.0419	0.1144

Statistical significance compared to vehicle-treated control animals: ** $p<0.01$

Table 28 The effect of intramuscular MVA-HBV on the group distribution of macropathology findings - Interim phase

Tissue/ Organ	Finding	Group/Sex Dose (PFU/mL) No. of animals	1 (Control)/M 0 6	2(MVA-HBV)/M $4.8x10^8$ 6	1 (Control)/F 0 6	2(MVA-HBV)/F $4.8x10^8$ 6
Number of animals within normal limits			5	4	4	3
Heart	Pale area(s)		1	0	0	0
Lymph node Inguinal Lt	Enlarged		0	1	1	0
Lymph node Inguinal Rt	Enlarged		0	0	0	1
Muscular IS, Thigh M. Region, Lt	Dark area(s)		0	0	0	3
Skin and Subcutis	Dark area(s)		0	1	1	2

Table 29 The effect of intramuscular MVA-HBV on the group distribution of macropathology findings - Main phase

Tissue/ Organ	Finding	Group/Sex Dose (PFU/mL) No. of animals	1 (Control)/M 0 10	2(MVA-HBV)/M $4.8x10^8$ 10	1 (Control)/F 0 10	2(MVA-HBV)/F $4.8x10^8$ 10
Number of animals within normal limits			9	2	10	0
Heart	Pale area(s)		1	0	0	0
Liver	Enlarged		0	0	0	3
Lymph node, Inguinal Lt	Enlarged		0	4	0	3
Lymph node, Inguinal Rt	Enlarged		0	2	0	4
Lymph Node, Lumbar	Enlarged		0	7	0	10
Muscular IS, Thigh M. Region, Lt	Dark area(s)		0	0	0	1
Muscular IS, Thigh M. Region, Rt	Dark area(s)		0	0	0	1
Spleen	Enlarged		0	1	0	9

Table 30 The effect of intramuscular MVA-HBV on the group distribution of macropathology findings - Recovery phase

Tissue/ Organ	Finding	Group/Sex Dose (PFU/mL) No. of animals	1 (Control)/M 0 5	2(MVA-HBV)/M $4.8x10^8$ 5	1 (Control)/F 0 5	2(MVA-HBV)/F $4.8x10^8$ 5
Number of animals within normal limits			4	4	5	4
Heart	Pale area(s)		1	1	0	1
Testes	Small		0	1	-	-

- Macroscopic observation not relevant in group

APPENDICES

Appendix 1 Effects of intramuscular administration of MVA-HBV on bodyweights in male mice - Individual animal values

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Bodyweight (g) on Day: Week -1	1[1]	2	8	15[1]	21	28	Day of necropsy
1M	Control	0	1	20.0	19.9	20.3	-	-	-	-	20.4
			2	20.3	19.9	20.0	-	-	-	-	20.4
			3	20.0	19.6	19.5	-	-	-	-	19.6
			4	20.3	20.2	19.9	-	-	-	-	20.6
			5	21.7	21.2	21.4	-	-	-	-	21.8
			6	20.7	20.5	20.3	-	-	-	-	21.3
			13	22.0	22.1	22.1	22.9	24.6	-	-	25.0
			14	21.2	20.9	20.5	21.8	22.5	-	-	23.1
			15	23.2	23.3	23.1	23.9	25.4	-	-	25.9
			16	21.8	21.7	21.6	22.6	24.2	-	-	24.3
			17	22.0	22.5	21.6	22.4	23.8	-	-	24.3
			18	21.0	21.1	21.3	22.1	24.1	-	-	24.8
			19	20.4	20.4	20.3	21.0	22.1	-	-	22.1
			20	20.8	21.0	20.1	20.7	22.5	-	-	22.6
			21	21.5	21.4	21.2	21.1	22.3	-	-	22.8
			22	22.0	22.0	22.1	22.9	23.9	-	-	23.9
			33	20.8	20.4	20.1	21.0	22.6	24.0	25.0	25.0
			34	21.8	20.7	20.5	20.8	21.5	22.9	24.0	23.7
			35	21.2	21.0	20.6	21.0	22.7	24.1	24.6	24.8
			36	20.6	20.5	20.0	21.6	23.3	24.7	25.3	25.1
			37	20.8	20.0	19.6	20.3	21.4	23.3	24.0	23.8

[1] Day 1 and 15 data was collected prior to dosing

\- No data was collected on this day as the animals had already been terminated

Appendix 1 Continued

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Bodyweight (g) on Day: Week -1	1[1]	2	8	15[1]	21	28	Day of necropsy
2M	MVA-HBV	$4.8x10^8$	7	20.3	20.2	20.4	-	-	-	-	21.1
			8	21.0	21.1	21.2	-	-	-	-	21.9
			9	21.7	21.8	21.6	-	-	-	-	22.0
			10	21.8	21.6	21.4	-	-	-	-	22.2
			11	20.0	19.7	19.6	-	-	-	-	20.5
			12	21.3	21.2	20.9	-	-	-	-	21.8
			23	22.0	21.8	21.5	21.9	22.8	-	-	23.9
			24	22.7	22.9	22.7	22.7	24.2	-	-	24.9
			25	21.8	21.5	21.8	22.9	23.2	-	-	24.5
			26	22.3	22.6	22.7	23.8	24.8	-	-	25.2
			27	23.3	23.1	23.2	23.7	24.7	-	-	25.6
			28	21.6	20.9	20.8	21.5	22.7	-	-	22.8
			29	21.8	21.2	21.4	22.3	23.3	-	-	24.3
			30	22.3	21.7	21.6	22.2	23.9	-	-	24.4
			31	20.8	20.4	21.2	20.9	21.8	-	-	22.5
			32	21.9	21.3	21.8	22.3	23.3	-	-	24.0
			38	22.0	21.6	22.2	22.0	22.7	24.2	24.5	24.9
			39	21.6	21.4	21.1	22.2	23.6	24.7	24.7	25.2
			40	21.7	21.5	21.3	22.1	22.8	24.3	24.0	24.0
			41	21.0	20.5	20.3	20.5	20.7	22.9	22.7	23.4
			42	22.1	21.4	21.0	22.1	22.4	24.4	24.8	25.0

[1] Day 1 and 15 data was collected prior to dosing

\- No data was collected on this day as the animals had already been terminated

Appendix 2 Effects of intramuscular administration of MVA-HBV on bodyweights in female mice - Individual animal values

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Bodyweight (g) on Day: Week -1	1[1]	2	8	15[1]	21	28	Day of necropsy
1F	Control	0	101	19.0	19.4	18.9	-	-	-	-	19.3
			102	19.5	19.1	19.4	-	-	-	-	19.5
			103	18.9	19.0	18.9	-	-	-	-	18.8
			104	19.9	20.1	20.1	-	-	-	-	20.5
			105	20.0	19.7	19.9	-	-	-	-	20.1
			106	18.8	19.0	19.0	-	-	-	-	19.2
			113	19.3	19.1	18.9	19.2	19.9	-	-	20.6
			114	19.4	19.5	19.2	19.2	20.2	-	-	20.6
			115	18.7	18.5	18.6	18.8	20.0	-	-	20.2
			116	19.1	19.1	18.8	19.8	20.6	-	-	20.7
			117	19.6	19.6	18.9	19.5	20.4	-	-	20.9
			118	18.8	18.3	18.1	18.7	19.7	-	-	19.5
			119	18.8	18.8	18.6	19.1	20.3	-	-	20.1
			120	18.9	18.9	18.7	19.5	20.4	-	-	20.1
			121	18.9	18.7	18.6	19.2	20.2	-	-	20.4
			122	18.2	17.4	17.4	18.3	19.4	-	-	19.4
			133	19.0	19.0	18.6	18.2	18.4	19.1	19.4	19.7
			134	18.8	18.9	18.4	18.4	18.8	19.5	20.1	20.4
			135	18.4	18.5	18.1	18.6	19.9	19.7	20.5	19.9
			136	18.6	18.5	18.8	18.8	18.5	18.8	19.8	20.0
			137	18.5	18.8	18.6	19.1	19.7	20.4	20.7	20.5

[1] Day 1 and 15 data was collected prior to dosing

\- No data was collected on this day as the animals had already been terminated

Appendix 2 Continued

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Bodyweight (g) on Day: Week -1	1[1]	2	8	15[1]	21	28	Day of necropsy
2F	MVA-HBV	$4.8x10^8$	107	18.5	19.0	18.8	-	-	-	-	18.7
			108	19.4	19.9	19.6	-	-	-	-	19.6
			109	19.1	19.5	19.5	-	-	-	-	20.1
			110	20.8	20.4	20.6	-	-	-	-	21.1
			111	19.2	19.1	19.8	-	-	-	-	20.3
			112	18.1	18.1	18.3	-	-	-	-	18.7
			123	19.3	19.0	19.2	19.3	20.1	-	-	21.2
			124	18.4	18.3	18.4	18.5	19.4	-	-	19.8
			125	18.9	18.9	18.9	19.3	19.9	-	-	20.4
			126	19.9	20.1	19.6	20.4	21.3	-	-	21.2
			127	18.7	18.9	18.7	18.9	19.4	-	-	20.0
			128	18.2	18.2	18.5	18.9	19.7	-	-	19.8
			129	18.4	18.2	18.8	19.1	19.9	-	-	20.5
			130	17.9	17.9	18.0	18.4	19.0	-	-	19.6
			131	19.2	19.1	19.4	19.7	20.6	-	-	21.2
			132	18.8	19.0	19.4	20.0	20.5	-	-	21.5
			138	18.7	18.8	18.7	19.1	19.5	19.6	19.1	19.7
			139	18.4	18.3	18.7	19.2	19.7	19.9	19.6	19.8
			140	18.7	18.4	18.4	19.1	20.1	20.7	20.5	20.6
			141	18.0	18.1	17.9	18.1	19.0	19.2	19.0	18.6
			142	18.3	18.0	17.9	18.1	18.6	19.3	19.0	19.2

[1] Day 1 and 15 data was collected prior to dosing

\- No data was collected on this day as the animals had already been terminated

Appendix 3 Effects of intramuscular administration of MVA-HBV on body temperature in male mice - Individual animal values

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Temperature (℃) on Day:					
				Predose Day 1	4 h Post dose Day 1	24 h Post dose Day 1	Predose Day 15	4 h Post dose Day 15	24 h Post dose Day 15
1M	Control	0	1	35.3	34.6	34.8	-	-	-
			2	35.5	35.0	35.0	-	-	-
			3	35.4	35.1	35.9	-	-	-
			4	35.6	35.8	35.3	-	-	-
			5	35.9	35.6	35.5	-	-	-
			6	35.4	35.5	35.2	-	-	-
			13	35.2	35.6	35.1	35.9	33.9	34.3
			14	35.3	36.2	35.2	36.1	34.4	34.1
			15	35.7	35.6	35.3	36.0	35.1	33.8
			16	35.8	35.3	35.1	35.8	35.1	34.6
			17	35.2	35.1	35.5	36.1	35.2	34.9
			18	35.5	35.2	35.0	35.6	35.1	35.1
			19	35.9	36.1	35.1	35.8	34.0	34.0
			20	35.6	35.1	36.0	36.4	35.1	34.5
			21	36.0	35.1	35.2	35.6	34.7	34.5
			22	35.4	35.3	35.1	35.6	34.9	34.1
			33	35.1	35.0	35.2	36.3	35.0	35.5
			34	35.5	35.7	35.3	36.3	34.4	35.0
			35	35.2	35.2	35.4	35.6	34.9	35.2
			36	36.0	36.3	35.2	35.3	35.2	35.7
			37	35.9	35.3	35.3	36.6	35.1	36.0

- No data was collected on this day as the animals had already been terminated

Appendix 3 Continued

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Temperature (℃) on Day:					
				Predose Day 1	4 h Post dose Day 1	24 h post dose Day 1	Predose Day 15	4 h Post dose Day 15	24 h post dose Day 15
2M	MVA-HBV	$4.8x10^8$	7	35.2	36.4	35.5	-	-	-
			8	35.4	36.2	35.0	-	-	-
			9	35.3	36.7	35.9	-	-	-
			10	35.5	35.6	35.5	-	-	-
			11	35.2	35.6	35.4	-	-	-
			12	35.3	35.4	35.6	-	-	-
			23	35.4	35.4	35.0	35.4	34.5	35.8
			24	35.5	35.6	35.2	36.0	35.0	35.7
			25	34.8	35.1	35.5	35.9	34.8	35.0
			26	34.8	35.1	35.2	36.9	34.5	35.4
			27	35.3	35.0	35.4	36.4	34.3	35.2
			28	35.0	34.9	35.6	35.8	35.1	35.7
			29	34.2	34.4	35.2	35.6	35.4	36.1
			30	35.4	35.2	35.1	36.2	35.2	36.0
			31	35.0	34.7	35.1	35.3	35.0	35.4
			32	35.1	36.1	35.0	35.4	35.0	36.8
			38	35.3	35.2	35.0	35.9	35.1	36.8
			39	35.4	36.2	35.3	36.0	34.9	36.1
			40	35.2	35.9	36.1	35.5	35.0	36.2
			41	35.0	35.4	35.6	35.6	35.1	36.0
			42	35.2	35.4	35.0	35.0	35.2	35.3

- No data was collected on this day as the animals had already been terminated

Appendix 4 Effects of intramuscular administration of MVA-HBV on body temperature in female mice - Individual animal values

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Temperature (℃) on Day:					
				Predose Day 1	4 h Post dose Day 1	24 h Post dose Day 1	Predose Day 15	4 h Post dose Day 15	24 h Post dose Day 15
1F	Control	0	101	36.4	36.0	35.6	-	-	-
			102	36.8	36.2	36.1	-	-	-
			103	35.3	35.7	36.1	-	-	-
			104	35.9	35.2	35.6	-	-	-
			105	35.0	35.1	35.9	-	-	-
			106	35.2	35.0	35.5	-	-	-
			113	36.1	35.3	35.8	36.4	34.9	35.9
			114	36.1	35.7	35.3	36.6	35.1	36.2
			115	35.9	35.8	35.8	36.7	35.1	36.2
			116	36.2	36.2	35.4	36.6	35.1	36.4
			117	36.5	36.5	36.2	36.7	35.2	36.6
			118	35.9	35.4	35.0	36.3	35.0	35.5
			119	35.9	35.9	35.3	36.7	35.1	35.3
			120	36.4	35.8	35.6	36.7	35.3	35.5
			121	35.4	34.9	35.9	36.1	35.1	35.5
			122	36.4	36.5	35.5	36.7	35.2	36.3
			133	35.6	35.5	35.0	36.8	35.5	35.0
			134	36.3	35.2	35.6	35.9	35.3	34.7
			135	35.4	35.4	35.4	36.6	35.2	35.5
			136	36.1	35.6	35.3	36.4	35.1	36.0
			137	36.3	36.1	35.4	36.6	35.6	35.4

- No data was collected on this day as the animals had already been terminated

Appendix 4 Continued

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Temperature (℃) on Day:					
				Predose Day 1	4 h Post dose Day 1	24 h Post dose Day 1	Predose Day 15	4 h Post dose Day 15	24 h Post dose Day 15
2F	MVA-HBV	$4.8x10^8$	107	36.1	36.1	36.1	-	-	-
			108	36.1	35.7	35.5	-	-	-
			109	35.1	36.4	35.1	-	-	-
			110	36.2	35.8	35.0	-	-	-
			111	36.4	36.3	35.7	-	-	-
			112	36.2	36.1	36.3	-	-	-
			123	36.1	36.7	35.2	36.6	35.3	36.0
			124	36.1	36.0	35.2	35.9	35.5	36.3
			125	35.9	36.1	35.4	35.8	35.0	36.7
			126	35.8	36.4	35.5	35.9	35.3	35.5
			127	36.6	36.8	35.5	36.7	35.3	36.6
			128	36.3	35.6	35.1	36.4	35.3	35.6
			129	35.5	36.1	35.0	36.2	35.0	35.8
			130	36.2	35.9	35.0	35.8	35.5	36.0
			131	36.1	36.6	35.4	36.5	35.1	35.8
			132	36.2	36.5	35.8	36.2	35.1	36.1
			138	35.9	36.0	35.1	36.9	35.2	34.8
			139	35.8	35.6	35.6	36.0	35.4	34.9
			140	36.0	36.5	36.0	36.1	35.3	35.7
			141	35.8	35.7	35.3	36.6	35.4	35.4
			142	36.2	35.8	36.0	36.0	35.1	34.7

- No data was collected on this day as the animals had already been terminated

Appendix 5 Effects of intramuscular administration of MVA-HBV on food consumption in male mice - Individual animal values

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Food consumption (g/cage/day) on Day: Week 1	Week 2	Week 3	Week 4	Week 5
1M	Vehicle	0	1-3	52.0	21.0	-	-	-
			4-6	54.0	22.0	-	-	-
			13-17	93.0	121.0	122.0	-	-
			18-22	88.0	116.0	121.0	-	-
			33-37	85.0	117.0	124.0	164.0	121.0
2M	MVA-HBV	$4.8x10^8$	7-9	53.0	21.0	-	-	-
			10-12	56.0	22.0	-	-	-
			23-27	94.0	124.0	123.0	-	-
			28-32	88.0	122.0	119.0	-	-
			38-42	94.0	126.0	127.0	127.0	124.0

- No data was collected on this day as the animals had already been terminated

Appendix 6 Effects of intramuscular administration of MVA-HBV on food consumption in female mice - Individual animal values

Group/ Sex	Intramuscular treatment	Dose (PFU/mL)	Animal No.	Food consumption (g/cage/day) on Day: Week 1	Week 2	Week 3	Week 4	Week 5
1F	Vehicle	0	101-103	43.0	19.0	-	-	-
			104-106	49.0	23.0	-	-	-
			113-117	70.0	97.0	100.0	-	-
			118-122	68.0	99.0	92.0	-	-
			133-137	87.0	97.0	95.0	96.0	103.0
2F	MVA-HBV	$4.8x10^8$	107-109	48.0	18.0	-	-	-
			110-112	46.0	19.0	-	-	-
			123-127	75.0	102.0	107.0	-	-
			128-132	82.0	103.0	97.0	-	-
			138-142	85.0	101.0	96.0	91.0	96.0

- No data was collected on this day as the animals had already been terminated

Appendix 7 Effects of intramuscular administration of MVA-HBV on blood haematology parameters in male mice - Individual animal values

Group/ Sex	Dose (PFU/mL)	Animal No.	Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
1M	Control	1	0.531	15.7	10.11	0.172	15.5	29.6	52.5	16.0
	(0)	2	0.556	15.6	10.22	0.148	15.3	28.1	54.4	16.9
		3	0.548	16.5	10.77	0.155	15.3	30.2	50.9	16.6
		4	0.547	16.5	10.83	0.150	15.2	30.1	50.6	16.0
		5	0.550	15.9	10.24	0.195	15.5	28.9	53.7	16.3
		6	0.492	15.2	9.55	0.129	15.9	30.8	51.6	15.5
		13	0.553	16.6	11.28	0.244	14.7	30.0	49.0	12.9
		14	0.533	15.8	10.50	0.196	15.1	29.7	50.7	13.5
		15	0.543	15.9	10.64	0.230	14.9	29.2	51.0	13.2
		16	0.523	15.9	10.72	0.244	14.8	30.3	48.7	13.0
		17	0.502	15.1	10.17	0.226	14.9	30.1	49.4	12.9
		18	0.503	15.4	10.19	0.199	15.1	30.7	49.3	13.0
		19	0.531	15.9	10.51	0.181	15.1	29.9	50.5	12.6
		20	0.498	15.2	9.95	0.228	15.3	30.6	50.0	13.0
		21	0.536	16.0	10.74	0.222	14.9	29.9	49.9	12.9
		22	0.540	16.5	10.71	0.248	15.4	30.5	50.5	13.2
		33	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		34	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		35	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		36	0.529	15.5	10.43	0.222	14.9	29.4	50.7	12.9
		37	INS	INS	INS	INS	INS	INS	INS	INS

Appendix 7 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
2M	MVA-HBV ($4.8x10^{8}$)	7	0.529	15.7	10.04	ND	15.6	29.7	52.6	17.7
		8	0.522	14.0	9.92	0.163	14.1	26.8	52.6	16.5
		9	0.539	16.2	10.59	0.150	15.3	30.1	50.9	16.0
		10	0.527	15.7	10.41	0.159	15.1	29.8	50.6	16.8
		11	0.523	14.9	10.15	0.117	14.7	28.5	51.5	17.0
		12	0.551	15.9	10.51	0.152	15.1	28.8	52.4	17.0
		23	0.546	15.0	11.00	0.217	13.6	27.4	49.6	13.6
		24	0.554	15.8	10.75	0.251	14.7	28.5	51.5	13.0
		25	0.529	15.8	10.89	0.199	14.5	29.8	48.6	13.4
		26	0.502	14.8	10.06	0.245	14.7	29.5	50.0	13.2
		27	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD
		28	0.515	15.4	10.32	0.232	14.9	29.8	49.9	13.3
		29	0.513	15.0	10.12	0.225	14.8	29.2	50.7	14.0
		30	0.504	15.6	10.22	0.201	15.2	30.8	49.3	13.5
		31	0.535	15.7	10.33	0.242	15.2	29.4	51.8	13.4
		32	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD
		38	INS	INS	INS	INS	INS	INS	INS	INS
		39	0.535	15.7	10.40	0.233	15.1	29.4	51.4	12.9
		40	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD
		41	0.540	15.6	10.64	0.227	14.7	29.0	50.7	13.0
		42	0.562	15.3	10.77	0.196	14.2	27.2	52.2	12.8

Appendix 7 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
1M	Control	1	2.83	0.56	2.14	0.08	0.01	0.04	0.02	962
	(0)	2	2.59	0.69	1.81	0.05	0.01	0.02	0.01	1256
		3	2.16	0.48	1.53	0.09	0.00	0.04	0.01	797
		4	4.08	0.76	3.11	0.09	0.02	0.07	0.02	918
		5	4.27	0.74	3.31	0.08	0.02	0.09	0.03	906
		6	2.50	0.49	1.89	0.08	0.01	0.02	0.01	1039
		13	5.82	0.71	4.78	0.19	0.03	0.07	0.05	866
		14	5.06	0.86	3.92	0.14	0.03	0.09	0.04	951
		15	4.75	0.89	3.66	0.09	0.02	0.08	0.03	898
		16	4.19	0.73	3.17	0.17	0.02	0.08	0.02	903
		17	2.97	0.53	2.29	0.10	0.01	0.03	0.01	849
		18	4.18	0.81	3.17	0.10	0.01	0.06	0.03	848
		19	4.61	0.75	3.64	0.11	0.02	0.06	0.04	902
		20	3.78	0.71	2.83	0.16	0.01	0.06	0.01	910
		21	4.13	0.83	3.10	0.10	0.02	0.05	0.03	733
		22	3.80	0.59	3.03	0.09	0.01	0.04	0.03	799
		33	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		34	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		35	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		36	4.49	0.69	3.49	0.18	0.02	0.08	0.04	882
		37	INS	INS	INS	INS	INS	INS	INS	INS

Appendix 7 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
2M	MVA-HBV ($4.8x10^8$)	7	3.57	1.00	2.32	0.09	0.01	0.06	0.09	1015
		8	3.92	0.97	2.74	0.07	0.01	0.07	0.05	886
		9	3.24	0.88	2.18	0.08	0.01	0.03	0.06	897
		10	4.43	0.82	3.41	0.08	0.01	0.04	0.07	931
		11	3.36	0.71	2.46	0.09	0.01	0.04	0.05	249
		12	3.46	0.74	2.53	0.06	0.01	0.04	0.08	982
		23	3.57	NVR	NVR	NVR	NVR	NVR	NVR	831
		24	1.75	0.56	1.08	0.06	0.01	0.02	0.02	816
		25	2.06	0.61	1.33	0.04	0.01	0.03	0.03	876
		26	2.31	0.60	1.56	0.06	0.00	0.05	0.04	857
		27	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD
		28	4.39	1.12	3.05	0.09	0.02	0.06	0.05	931
		29	3.91	0.78	2.93	0.08	0.02	0.05	0.05	968
		30	2.27	0.58	1.58	0.04	0.01	0.04	0.02	848
		31	3.03	0.70	2.19	0.05	0.03	0.03	0.03	972
		32	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD
		38	INS	INS	INS	INS	INS	INS	INS	INS
		39	5.28	0.83	4.12	0.19	0.02	0.07	0.04	878
		40	CTD	CTD	CTD	CTD	CTD	CTD	CTD	CTD
		41	3.99	0.68	2.96	0.24	0.01	0.07	0.03	901
		42	2.89	0.52	2.19	0.12	0.00	0.03	0.02	930

Appendix 8 Effects of intramuscular administration of MVA-HBV on blood haematology parameters in female mice - Individual animal values

Group/ Sex	Dose (PFU/mL)	Animal No.	Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
1F	Control (0)	101	0.538	16.4	10.28	0.181	16.0	30.6	52.3	14.1
		102	0.517	16.6	10.40	0.180	15.9	32.0	49.7	15.2
		103	0.525	16.0	10.15	0.169	15.8	30.5	51.7	14.1
		104	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		105	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		106	0.529	17.2	10.88	0.186	15.8	32.5	48.6	14.5
		113	0.511	15.9	10.32	0.193	15.4	31.1	49.6	12.1
		114	0.516	15.4	10.09	0.238	15.3	29.9	51.1	12.1
		115	0.509	15.0	9.82	0.241	15.2	29.4	51.8	12.3
		116	0.516	15.3	10.20	0.275	15.0	29.7	50.6	13.0
		117	0.510	15.0	9.90	0.237	15.2	29.4	51.5	12.4
		118	0.483	15.0	9.76	0.220	15.3	31.0	49.4	12.3
		119	0.515	15.3	9.91	0.275	15.4	29.6	52.0	12.6
		120	0.503	15.1	10.07	0.255	15.0	30.0	50.0	12.6
		121	0.500	14.8	9.88	0.230	15.0	29.7	50.6	12.4
		122	0.504	14.9	9.89	0.257	15.1	29.6	51.0	12.5
		133	0.481	14.5	9.70	0.214	15.0	30.1	49.6	12.6
		134	0.505	14.8	9.90	0.213	14.9	29.3	51.0	12.8
		135	INS	INS	INS	INS	INS	INS	INS	INS
		136	0.525	15.0	10.09	0.218	14.9	28.6	52.0	12.8
		137	0.520	15.2	9.56	0.147	15.9	29.1	54.5	12.6

Appendix 8 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	Hct (L/L)	Hb (g/dL)	RBC ($x10^{12}$/L)	Retic ($x10^{12}$/L)	MCH (pg)	MCHC (g/dL)	MCV (fL)	RDW (%)
2F	MVA-HBV ($4.8x10^{8}$)	107	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		108	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		109	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		110	0.474	15.5	10.03	0.164	15.5	32.8	47.2	13.7
		111	0.494	15.4	9.83	0.140	15.6	31.1	50.2	14.2
		112	0.471	15.5	10.03	0.101	15.5	33.0	46.9	15.9
		123	0.476	14.6	9.56	0.219	15.3	30.7	49.8	12.9
		124	0.479	14.1	9.45	0.198	14.9	29.4	50.7	12.3
		125	0.359	8.4	7.23	0.168	11.6	23.5	49.6	12.6
		126	0.514	15.5	10.24	0.208	15.1	30.2	50.1	12.5
		127	0.481	14.3	9.42	0.209	15.2	29.8	51.1	12.6
		128	0.503	15.3	10.20	0.222	15.0	30.4	49.3	12.7
		129	0.512	15.2	10.00	0.236	15.2	29.8	51.1	12.6
		130	0.515	14.8	9.90	0.233	15.0	28.7	52.0	12.6
		131	0.492	14.8	9.96	0.293	14.8	30.0	49.4	13.1
		132	0.505	15.0	9.73	0.226	15.4	29.7	51.9	12.5
		138	0.508	15.4	10.36	0.187	14.9	30.4	49.0	13.0
		139	0.497	15.0	9.95	0.181	15.1	30.2	50.0	12.8
		140	0.515	14.0	9.87	0.178	14.2	27.2	52.2	12.6
		141	0.534	15.8	10.33	0.208	15.3	29.7	51.7	13.2
		142	0.534	14.7	10.33	0.256	14.2	27.5	51.7	12.9

Appendix 8 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
1F	Control	101	3.52	0.70	2.63	0.09	0.01	0.05	0.04	768
	(0)	102	4.04	0.48	3.29	0.18	0.02	0.03	0.03	616
		103	2.83	0.54	2.15	0.08	0.02	0.03	0.02	868
		104	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		105	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		106	2.16	0.45	1.59	0.09	0.01	0.01	0.01	1083
		113	4.38	1.12	2.90	0.23	0.02	0.10	0.01	865
		114	3.37	0.66	2.55	0.08	0.01	0.04	0.02	881
		115	3.52	0.78	2.56	0.10	0.01	0.04	0.03	964
		116	2.58	0.59	1.78	0.14	0.03	0.05	0.01	567
		117	2.63	0.55	1.93	0.05	0.01	0.07	0.02	846
		118	6.21	0.72	5.09	0.22	0.03	0.11	0.04	737
		119	9.67	1.24	7.96	0.16	0.06	0.13	0.13	790
		120	5.11	0.74	4.12	0.11	0.01	0.10	0.03	901
		121	6.61	0.78	5.55	0.12	0.03	0.08	0.05	943
		122	6.29	0.75	5.23	0.15	0.03	0.09	0.05	750
		133	2.41	0.52	1.69	0.13	0.01	0.05	0.02	751
		134	5.03	0.62	4.11	0.20	0.00	0.06	0.04	NVR
		135	INS	INS	INS	INS	INS	INS	INS	INS
		136	5.01	0.68	4.04	0.15	0.02	0.06	0.05	748
		137	3.57	0.53	2.90	0.07	0.00	0.03	0.03	709

Appendix 8 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	WBC ($x10^9$/L)	N ($x10^9$/L)	L ($x10^9$/L)	E ($x10^9$/L)	B ($x10^9$/L)	M ($x10^9$/L)	LUC ($x10^9$/L)	Plt ($x10^9$/L)
2F	MVA-HBV ($4.8x10^8$)	107	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		108	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		109	NVR	NVR	NVR	NVR	NVR	NVR	NVR	NVR
		110	2.37	NVR	NVR	NVR	NVR	NVR	NVR	988
		111	1.81	0.48	1.16	0.11	0.02	0.02	0.02	1018
		112	2.57	0.70	1.67	0.11	0.01	0.03	0.04	895
		123	1.61	0.27	1.21	0.03	0.02	0.01	0.07	854
		124	2.96	0.66	2.13	0.07	0.03	0.02	0.05	945
		125	1.90	0.41	1.35	0.07	0.01	0.03	0.03	709
		126	1.66	NVR	NVR	NVR	NVR	NVR	NVR	703
		127	1.64	0.37	1.17	0.04	0.00	0.02	0.04	798
		128	3.48	0.57	2.68	0.05	0.01	0.03	0.14	856
		129	1.70	0.30	1.30	0.04	0.01	0.02	0.04	887
		130	2.82	0.31	2.35	0.04	0.01	0.01	0.10	824
		131	2.97	0.54	2.27	0.05	0.03	0.02	0.05	847
		132	2.65	0.57	1.91	0.04	0.01	0.02	0.09	764
		138	3.79	0.52	3.07	0.13	0.01	0.04	0.02	897
		139	5.48	0.64	4.54	0.18	0.03	0.05	0.04	NVR
		140	1.86	0.39	1.36	0.09	0.00	0.02	0.01	762
		141	2.57	0.46	1.98	0.10	0.00	0.02	0.01	786
		142	2.95	0.26	2.57	0.08	0.00	0.03	0.01	NVR

Appendix 9 Effects of intramuscular administration of MVA-HBV on the blood biochemical parameters in male mice - Individual animal values

Group /Sex	Dose (PFU/mL)	Animal No.	ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
1M	Control (0)	1	182	55	86	1	5.99	11	10.07	3.08	2.21
		2	118	48	72	0	6.04	6	12.60	3.14	2.04
		3	193	62	98	1	5.94	0	10.39	2.82	2.17
		4	180	58	62	1	5.48	8	8.27	2.88	2.68
		5	190	55	73	0	5.72	8	13.80	2.88	2.57
		6	173	53	65	1	6.27	8	8.81	3.11	2.11
		13	150	75	103	1	6.72	11	9.04	3.85	3.76
		14	136	80	88	1	6.23	11	12.75	4.03	3.34
		15	129	55	54	1	6.39	9	10.73	4.05	3.34
		16	126	113	182	1	6.36	16	17.35	3.04	1.21
		17	135	163	196	1	6.46	12	10.63	3.48	2.14
		18	152	63	72	1	6.35	11	9.49	3.89	3.37
		19	138	121	132	1	5.71	15	12.05	3.30	2.17
		20	140	43	113	1	6.82	11	10.66	3.51	3.18
		21	128	125	132	1	6.48	13	12.95	3.72	3.78
		22	157	135	174	1	6.41	14	12.76	3.20	2.82
		33	126	37	59	1	5.36	9	11.41	3.35	2.37
		34	121	26	46	1	5.35	8	15.98	3.44	1.99
		35	122	245	208	1	4.69	18	10.11	3.34	2.09
		36	115	42	51	1	4.81	9	16.03	2.80	1.59
		37	119	28	56	1	5.41	11	15.55	3.22	2.27

Appendix 9 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
2M	MVA-HBV ($4.8x10^8$)	7	164	53	80	1	5.75	6	11.68	3.27	2.40
		8	170	74	66	1	5.12	8	13.83	3.33	2.39
		9	148	38	69	1	5.78	11	9.24	3.28	2.45
		10	164	106	131	1	4.48	8	9.13	3.20	1.90
		11	170	117	131	1	6.64	11	13.45	3.36	2.35
		12	175	47	69	0	6.06	6	14.06	3.18	2.19
		23	103	57	63	1	7.16	7	9.18	4.11	2.28
		24	112	33	48	1	7.87	7	12.51	4.01	3.40
		25	126	46	49	1	6.31	9	9.68	3.99	2.44
		26	118	38	54	1	8.51	10	11.93	3.41	2.41
		27	114	79	149	0	6.47	7	13.18	3.87	2.91
		28	111	188	164	1	8.43	8	10.68	4.06	4.28
		29	128	33	57	1	5.77	5	12.52	3.22	3.15
		30	118	83	154	1	5.58	9	8.10	4.14	2.78
		31	125	105	142	1	7.93	8	11.60	3.90	3.29
		32	126	231	230	1	8.56	11	9.87	4.28	2.52
		38	115	72	122	1	7.32	12	12.31	3.31	1.56
		39	116	36	59	1	6.08	9	17.66	3.24	1.44
		40	127	85	141	1	6.17	20	14.68	3.51	2.65
		41	118	43	62	1	4.75	6	14.25	3.70	1.99
		42	135	34	49	1	6.43	8	16.68	3.81	2.73

Appendix 9 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
1M	Control (0)	1	152	4.58	108.4	2.60	3.38	48	29	1.53
		2	153	4.00	106.7	2.68	4.32	49	29	1.45
		3	153	4.10	108.3	2.67	3.00	51	31	1.55
		4	154	4.36	112.0	2.57	2.78	50	31	1.63
		5	150	3.99	107.8	2.47	2.79	49	29	1.45
		6	153	3.81	110.3	2.60	2.92	49	30	1.58
		13	152	5.09	112.3	2.46	2.68	52	32	1.60
		14	153	4.30	113.6	2.46	2.79	48	29	1.53
		15	153	3.59	111.6	2.46	2.95	50	31	1.63
		16	151	4.99	115.3	2.29	3.20	44	27	1.59
		17	155	4.60	116.7	2.36	3.40	48	29	1.53
		18	152	5.21	111.5	2.39	2.78	50	31	1.63
		19	153	4.54	113.6	2.38	3.37	47	29	1.61
		20	154	4.12	114.7	2.33	2.51	47	29	1.61
		21	155	4.38	112.2	2.38	3.13	49	30	1.58
		22	153	4.17	110.6	2.40	3.29	50	31	1.63
		33	153	4.04	112.8	2.39	2.88	48	30	1.67
		34	150	3.53	111.8	2.42	3.13	45	29	1.81
		35	152	4.90	112.3	2.55	2.39	47	31	1.94
		36	150	4.21	111.5	2.40	2.18	47	30	1.76
		37	151	3.54	111.7	2.39	2.88	46	29	1.71

Appendix 9 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
2M	MVA-HBV ($4.8x10^8$)	7	151	3.80	108.2	2.44	2.71	47	28	1.47
		8	145	3.61	101.8	2.49	2.67	48	28	1.40
		9	154	4.50	110.7	2.66	2.50	50	30	1.50
		10	151	5.24	111.5	2.55	2.81	48	28	1.40
		11	149	4.75	110.4	2.53	2.66	48	28	1.40
		12	150	3.83	110.1	2.55	3.19	49	30	1.58
		23	151	4.12	109.9	2.38	1.94	50	29	1.38
		24	152	3.62	111.5	2.47	2.79	49	29	1.45
		25	153	3.87	113.5	2.43	1.82	49	30	1.58
		26	153	4.18	115.7	2.33	1.36	48	29	1.53
		27	153	5.37	113.2	2.56	3.03	50	29	1.38
		28	152	4.76	113.7	2.39	2.01	51	30	1.43
		29	151	3.60	111.3	2.40	2.30	49	29	1.45
		30	154	5.16	113.6	2.46	2.43	53	30	1.30
		31	153	4.15	113.8	2.49	2.83	48	29	1.53
		32	156	5.29	117.1	2.51	2.79	53	30	1.30
		38	153	4.45	113.4	2.33	2.44	47	29	1.61
		39	149	4.13	109.8	2.40	2.48	50	30	1.50
		40	153	5.29	115.4	2.47	2.99	50	29	1.38
		41	152	3.13	115.0	2.32	2.45	48	29	1.53
		42	151	2.85	111.6	2.45	2.90	50	30	1.50

Appendix 10 Effects of intramuscular administration of MVA-HBV on the blood biochemical parameters in female mice - Individual animal values

Group/ Sex	Dose (PFU/mL)	Animal No.	ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
1F	Control (0)	101	156	89	129	1	6.10	13	8.15	2.16	1.51
		102	149	99	155	1	5.35	13	9.23	1.99	1.61
		103	139	50	65	1	5.72	10	14.15	2.00	1.44
		104	131	36	95	1	7.37	9	8.64	2.21	1.46
		105	139	58	93	1	6.66	11	10.91	1.97	1.56
		106	134	65	100	1	5.96	11	6.71	2.06	1.63
		113	144	48	109	1	7.83	12	6.35	2.40	1.72
		114	142	109	145	2	6.50	15	10.46	2.38	2.16
		115	140	68	96	1	7.57	12	11.67	2.37	2.24
		116	130	61	110	1	8.42	13	9.91	2.19	1.44
		117	130	51	58	1	5.87	11	9.88	2.22	2.15
		118	137	51	106	1	7.98	15	10.53	2.13	0.96
		119	152	55	84	1	6.00	12	12.59	2.43	3.08
		120	126	21	54	2	5.72	10	12.24	2.03	1.54
		121	138	59	98	1	7.51	12	12.56	2.13	2.04
		122	156	129	172	1	6.33	16	11.60	2.50	2.48
		133	134	73	106	1	4.12	12	11.51	2.20	1.35
		134	116	35	91	1	4.89	9	14.48	2.28	2.51
		135	122	34	83	1	4.94	9	14.75	2.38	1.21
		136	104	28	63	0	4.44	11	13.70	2.05	1.97
		137	120	33	55	1	6.16	11	11.64	2.03	1.80

Appendix 10 Continued

Group /Sex	Dose (PFU/mL)	Animal No.	ALP (U/L)	ALT (U/L)	AST (U/L)	Bili (µmol/L)	Urea (mmol/L)	Creat (µmol/L)	Gluc (mmol/L)	Chol (mmol/L)	Trig (mmol/L)
2F	MVA-HBV ($4.8x10^8$)	107	151	25	60	0	6.33	6	8.30	2.05	1.02
		108	113	60	73	1	6.17	9	8.11	2.21	1.00
		109	127	48	76	1	5.87	12	8.56	2.23	1.14
		110	126	47	83	1	6.51	7	8.44	2.12	0.92
		111	122	37	54	1	8.20	7	11.39	1.96	0.99
		112	125	36	64	0	7.25	8	8.38	1.85	1.22
		123	116	38	97	1	8.53	11	8.55	2.10	2.08
		124	92	56	85	1	8.36	9	11.86	2.21	1.79
		125	117	48	93	1	7.99	7	8.10	2.40	3.07
		126	105	100	148	1	6.44	8	7.71	2.80	3.30
		127	93	73	98	1	7.72	8	10.90	2.27	2.05
		128	103	75	160	1	5.95	9	8.00	2.44	1.80
		129	133	61	126	1	8.58	9	11.98	2.17	1.16
		130	107	47	126	1	8.60	7	10.48	2.36	2.88
		131	115	130	175	1	6.35	11	9.90	2.28	1.28
		132	108	32	59	1	8.25	9	12.45	2.25	1.94
		138	139	24	56	1	9.89	10	8.15	2.10	2.98
		139	123	36	73	1	6.01	9	12.16	1.79	1.62
		140	118	28	60	1	8.12	9	15.87	2.29	2.15
		141	148	65	135	1	8.99	20	11.99	1.99	2.16
		142	142	40	95	1	6.65	12	12.10	1.80	1.69

Appendix 10 Continued

Group /Sex	Dose (PFU/mL)	Animal No.	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
1F	Control	101	153	4.85	110.9	2.58	4.53	49	31	1.72
	(0)	102	152	5.27	113.9	2.37	3.30	47	30	1.76
		103	150	3.88	111.1	2.41	3.05	45	30	2.00
		104	155	4.17	115.2	2.39	2.51	47	32	2.13
		105	152	3.91	113.0	2.45	2.86	46	30	1.88
		106	155	4.77	116.1	2.44	3.07	49	31	1.72
		113	154	4.45	113.6	2.30	2.35	48	31	1.82
		114	153	4.12	112.7	2.36	2.49	47	30	1.76
		115	154	3.78	115.0	2.38	2.81	46	30	1.88
		116	152	3.89	111.9	2.38	3.52	48	31	1.82
		117	154	3.28	113.0	2.37	3.66	47	30	1.76
		118	153	4.63	117.3	2.27	2.84	44	29	1.93
		119	151	4.13	115.5	2.44	3.02	46	30	1.88
		120	153	4.29	116.8	2.31	2.30	45	30	2.00
		121	153	3.98	115.7	2.40	2.65	45	29	1.81
		122	152	4.33	115.3	2.45	3.21	48	32	2.00
		133	153	4.37	116.0	2.46	2.46	44	30	2.14
		134	150	3.25	114.7	2.39	2.57	44	30	2.14
		135	146	2.94	110.6	2.45	2.92	46	32	2.29
		136	150	2.72	114.2	2.46	3.02	44	30	2.14
		137	152	2.67	113.2	2.46	3.91	46	31	2.07

Appendix 10 Continued

Group/ Sex	Dose (PFU/mL)	Animal No.	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	Ca (mmol/L)	Phos (mmol/L)	Total Prot (g/L)	Alb (g/L)	A/G (Ratio)
2F	MVA-HBV ($4.8x10^8$)	107	152	4.24	115.3	2.31	2.18	45	29	1.81
		108	153	4.27	117.4	2.35	2.65	46	29	1.71
		109	153	4.08	117.3	2.35	2.28	47	31	1.94
		110	154	4.28	116.9	2.29	2.50	44	29	1.93
		111	153	3.63	116.5	2.37	2.74	44	29	1.93
		112	154	4.48	116.7	2.29	2.60	44	29	1.93
		123	154	4.77	116.6	2.31	2.32	46	30	1.88
		124	152	3.53	115.8	2.27	2.28	46	29	1.71
		125	150	3.76	113.3	2.35	1.97	50	31	1.63
		126	149	3.61	115.3	2.39	2.26	49	30	1.58
		127	153	3.24	119.6	2.42	2.52	46	29	1.71
		128	151	5.15	115.7	2.35	2.31	48	30	1.67
		129	152	4.11	115.6	2.36	2.39	45	29	1.81
		130	151	4.66	115.6	2.43	2.15	48	30	1.67
		131	153	4.16	117.7	2.51	3.17	48	30	1.67
		132	152	3.43	114.2	2.44	2.37	46	29	1.71
		138	154	4.09	116.0	2.33	2.24	47	31	1.94
		139	151	3.30	116.0	2.22	1.97	46	30	1.88
		140	151	3.15	114.5	2.33	2.75	48	30	1.67
		141	152	4.20	118.1	2.26	2.63	45	30	2.00
		142	152	3.37	116.8	2.37	2.86	46	30	1.88

Appendix 11 The effects of intramuscular administration of MVA-HBV on organ weights in male mice - Individual animal values

Group	Intramuscular Treatment	Dose (PFU/mL)	Animal No.	Organ weights (g)								
				Brain	Epididymides	Heart	Kidneys	Liver	Spleen	Testes	Thymus	Prostate
1M	Control	0	1	0.417	0.048	0.112	0.290	1.113	0.070	0.134	0.037	0.024
			2	0.361	0.046	0.137	0.309	1.180	0.075	0.121	0.042	0.031
			3	0.392	0.032	0.112	0.261	0.994	0.051	0.135	0.056	0.019
			4	0.395	0.038	0.121	0.280	1.051	0.071	0.145	0.048	0.026
			5	0.411	0.038	0.138	0.299	1.207	0.068	0.154	0.053	0.044
			6	0.355	0.037	0.114	0.281	1.213	0.061	0.132	0.057	0.025
			13	0.421	0.059	0.139	0.330	1.404	0.076	0.169	0.036	0.052
			14	0.407	0.070	0.137	0.338	1.310	0.071	0.168	0.033	0.057
			15	0.405	0.068	0.124	0.327	1.453	0.069	0.161	0.037	0.025
			16	0.410	0.054	0.138	0.336	1.342	0.080	0.163	0.034	0.053
			17	0.418	0.055	0.146	0.320	1.383	0.080	0.167	0.040	0.086
			18	0.381	0.061	0.127	0.334	1.347	0.083	0.144	0.044	0.072
			19	0.384	0.049	0.126	0.295	1.079	0.068	0.138	0.045	0.057
			20	0.415	0.049	0.135	0.294	1.093	0.075	0.165	0.041	0.031
			21	0.396	0.057	0.128	0.304	1.150	0.072	0.169	0.053	0.062
			22	0.427	0.068	0.131	0.353	1.281	0.080	0.169	0.019	0.036
			33	0.411	0.058	0.143	0.330	1.330	0.084	0.170	0.051	0.079
			34	0.406	0.048	0.118	0.318	1.199	0.097	0.149	0.044	0.033
			35	0.410	0.050	0.140	0.322	1.291	0.087	0.178	0.034	0.020
			36	0.400	0.052	0.145	0.316	1.288	0.085	0.166	0.042	0.070
			37	0.435	0.059	0.134	0.327	1.191	0.090	0.184	0.043	0.025

Appendix 11 Continued

Group	Intramuscular Treatment	Dose (PFU/mL)	Animal No.	Organ weights (g)								
				Brain	Epididymides	Heart	Kidneys	Liver	Spleen	Testes	Thymus	Prostate
2M	MVA-HBV	$4.8x10^8$	7	0.399	0.045	0.125	0.300	1.146	0.075	0.132	0.034	0.028
			8	0.378	0.050	0.132	0.327	1.294	0.081	0.144	0.046	0.059
			9	0.396	0.042	0.133	0.296	1.156	0.085	0.152	0.051	0.024
			10	0.402	0.048	0.115	0.312	1.170	0.089	0.162	0.047	0.033
			11	0.339	0.040	0.128	0.272	1.132	0.070	0.139	0.051	0.032
			12	0.428	0.050	0.120	0.297	1.131	0.080	0.157	0.047	0.021
			23	0.388	0.055	0.137	0.316	1.388	0.091	0.156	0.030	0.023
			24	0.394	0.054	0.128	0.340	1.413	0.113	0.151	0.028	0.063
			25	0.401	0.050	0.125	0.316	1.434	0.110	0.158	0.045	0.028
			26	0.422	0.063	0.155	0.342	1.417	0.109	0.180	0.034	0.040
			27	0.388	0.053	0.132	0.334	1.494	0.094	0.161	0.032	0.039
			28	0.397	0.089	0.126	0.291	1.367	0.095	0.146	0.034	0.041
			29	0.433	0.051	0.144	0.367	1.334	0.104	0.166	0.045	0.030
			30	0.373	0.041	0.134	0.325	1.357	0.090	0.129	0.030	0.036
			31	0.375	0.052	0.153	0.291	1.163	0.099	0.145	0.030	0.072
			32	0.398	0.060	0.133	0.319	1.449	0.126	0.154	0.020	0.053
			38	0.404	0.061	0.160	0.334	1.327	0.096	0.179	0.043	0.022
			39	0.407	0.045	0.133	0.346	1.259	0.090	0.185	0.047	0.060
			40	0.374	0.049	0.147	0.348	1.218	0.095	0.152	0.041	0.037
			41	0.409	0.046	0.119	0.302	1.186	0.073	0.110	0.043	0.046
			42	0.404	0.056	0.135	0.382	1.395	0.093	0.187	0.041	0.045

Appendix 12 The effects of intramuscular administration of MVA-HBV on organ weights in female mice - Individual animal values

Group	Intramuscular Treatment	Dose (PFU/mL)	Animal No.	Organ weights (g)							
				Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus	Uterus and cervix
1F	Control	0	101	0.395	0.104	0.227	0.879	0.005	0.075	0.071	0.098
			102	0.397	0.123	0.232	0.914	0.005	0.065	0.036	0.084
			103	0.405	0.111	0.237	0.812	0.006	0.076	0.059	0.074
			104	0.358	0.135	0.235	0.849	0.003	0.060	0.067	0.030
			105	0.456	0.111	0.240	0.864	0.004	0.078	0.072	0.073
			106	0.413	0.116	0.231	0.722	0.005	0.060	0.037	0.067
			113	0.397	0.120	0.225	0.975	0.009	0.071	0.044	0.065
			114	0.419	0.110	0.235	0.930	0.007	0.080	0.044	0.198
			115	0.423	0.109	0.218	0.972	0.006	0.083	0.058	0.071
			116	0.433	0.115	0.231	0.955	0.004	0.087	0.062	0.098
			117	0.405	0.110	0.240	0.965	0.007	0.075	0.034	0.171
			118	0.407	0.116	0.199	0.811	0.006	0.077	0.053	0.064
			119	0.426	0.123	0.246	0.951	0.009	0.099	0.044	0.246
			120	0.423	0.105	0.212	0.855	0.008	0.079	0.052	0.122
			121	0.411	0.101	0.214	0.841	0.009	0.073	0.053	0.102
			122	0.406	0.116	0.225	0.856	0.008	0.074	0.043	0.077
			133	0.422	0.112	0.192	0.861	0.008	0.093	0.040	0.112
			134	0.410	0.104	0.228	0.989	0.006	0.048	0.044	0.093
			135	0.425	0.121	0.222	0.975	0.010	0.086	0.034	0.259
			136	0.404	0.117	0.242	1.059	0.007	0.103	0.045	0.131
			137	0.431	0.111	0.257	1.069	0.008	0.084	0.045	0.129

Appendix 12 Continued

Group/ Sex	Intramuscular Treatment	Dose (PFU/mL)	Animal No.	Organ weights (g)							
				Brain	Heart	Kidneys	Liver	Ovaries	Spleen	Thymus	Uterus and cervix
2F	MVA-HBV	$4.8x10^8$	107	0.390	0.121	0.204	0.749	0.004	0.090	0.050	0.156
			108	0.407	0.118	0.223	0.785	0.006	0.079	0.043	0.057
			109	0.394	0.106	0.214	0.747	0.003	0.071	0.047	0.041
			110	0.404	0.113	0.244	0.822	0.006	0.100	0.053	0.218
			111	0.395	0.118	0.247	0.880	0.005	0.086	0.067	0.048
			112	0.443	0.108	0.204	0.767	0.002	0.088	0.067	0.090
			123	0.430	0.129	0.256	1.111	0.006	0.173	0.033	0.070
			124	0.415	0.112	0.216	1.061	0.004	0.130	0.037	0.067
			125	0.423	0.097	0.220	1.015	0.005	0.138	0.055	0.066
			126	0.433	0.117	0.258	1.208	0.006	0.182	0.039	0.094
			127	0.407	0.100	0.233	1.047	0.009	0.136	0.037	0.091
			128	0.403	0.096	0.204	0.997	0.007	0.128	0.026	0.055
			129	0.416	0.115	0.233	1.029	0.006	0.115	0.044	0.090
			130	0.419	0.114	0.229	1.076	0.005	0.163	0.046	0.068
			131	0.409	0.099	0.201	1.030	0.006	0.132	0.036	0.056
			132	0.404	0.119	0.241	1.178	0.010	0.162	0.034	0.218
			138	0.399	0.109	0.186	0.761	0.007	0.081	0.037	0.079
			139	0.410	0.105	0.215	0.774	0.008	0.091	0.042	0.077
			140	0.411	0.121	0.241	0.884	0.009	0.094	0.045	0.215
			141	0.398	0.100	0.200	0.772	0.006	0.100	0.036	0.068
			142	0.391	0.107	0.216	0.760	0.007	0.101	0.044	0.075

Appendix 13 The effects of intramuscular MVA-HBV on the individual animal macropathology findings

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
1M	0001	3 (1)	Treatment	All tissues	No macropathology findings
	0002	3 (1)	Treatment	All tissues	No macropathology findings
	0003	3 (1)	Treatment	All tissues	No macropathology findings
	0004	3 (1)	Treatment	Heart	Pale area(s), ventricle(s), right, 2-5mm, 2-5 (few) (epicardial aspect, irregular.)
				Remainder of animal	No macropathology findings
	0005	3 (1)	Treatment	All tissues	No macropathology findings
	0006	3 (1)	Treatment	All tissues	No macropathology findings
	0013	17 (3)	Treatment	All tissues	No macropathology findings
	0014	17 (3)	Treatment	All tissues	No macropathology findings

Group 1 Control - 0 PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
1M	0015	17 (3)	Treatment	All tissues	No macropathology findings
	0016	17 (3)	Treatment	All tissues	No macropathology findings
	0017	17 (3)	Treatment	All tissues	No macropathology findings
	0018	17 (3)	Treatment	Heart	Pale area(s), ventricle(s), 2-5mm, 2-5 (few) (epicardium.)
				Remainder of animal	No macropathology findings
	0019	17 (3)	Treatment	All tissues	No macropathology findings
	0020	17 (3)	Treatment	All tissues	No macropathology findings
	0021	17 (3)	Treatment	All tissues	No macropathology findings
	0022	17 (3)	Treatment	All tissues	No macropathology findings

Group 1 Control - 0 PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
1M	0033	29 (5)	Treatment	All tissues	No macropathology findings
	0034	29 (5)	Treatment	All tissues	No macropathology findings
	0035	29 (5)	Treatment	All tissues	No macropathology findings
	0036	29 (5)	Treatment	Heart	Pale area(s), 2-5mm, 5+ (many)
				Remainder of animal	No macropathology findings
	0037	29 (5)	Treatment	All tissues	No macropathology findings
2M	0007	3 (1)	Treatment	All tissues	No macropathology findings
	0008	3 (1)	Treatment	All tissues	No macropathology findings
	0009	3 (1)	Treatment	All tissues	No macropathology findings

Group 1 Control - 0 PFU/mL
Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2M	0010	3 (1)	Treatment	Skin and Subcutis	Dark Area(s), hindlimb, left, subcutis, red, 6-9mm, 1 (one) (in region overlying injection site.)
				Remainder of animal	No macropathology findings
	0011	3 (1)	Treatment	Lymph Node, Inguinal Lt	Enlarged, 2-5mm
				Remainder of animal	No macropathology findings
	0012	3 (1)	Treatment	All tissues	No macropathology findings
	0023	17 (3)	Treatment	Lymph Node, Lumbar	Enlarged, 2-5mm
				Remainder of animal	No macropathology findings
	0024	17 (3)	Treatment	Lymph Node, Inguinal Lt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, 2-5mm
Group 2	MVA-HBV - $4.8x10^8$ PFU/mL				

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2M	0024	17 (3)	Treatment	Remainder of animal	No macropathology findings
	0025	17 (3)	Treatment	Lymph Node, Inguinal Lt	Enlarged, 2-5mm
				Lymph Node, Inguinal Rt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, 2-5mm
				Remainder of animal	No macropathology findings
	0026	17 (3)	Treatment	Lymph Node, Inguinal Lt	Enlarged, 2-5mm
				Lymph Node, Inguinal Rt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, 2-5mm
				Remainder of animal	No macropathology findings

Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2M	0027	17 (3)	Treatment	Lymph Node, Inguinal Lt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, right, 2-5mm
				Remainder of animal	No macropathology findings
	0028	17 (3)	Treatment	All tissues	No macropathology findings
	0029	17 (3)	Treatment	Lymph Node, Lumbar	Enlarged, 2-5mm
				Remainder of animal	No macropathology findings
	0030	17 (3)	Treatment	All tissues	No macropathology findings
	0031	17 (3)	Treatment	Lymph Node, Lumbar	Enlarged, 2-5mm
				Remainder of animal	No macropathology findings

Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2M	0032	17 (3)	Treatment	Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings
	0038	29 (5)	Treatment	All tissues	No macropathology findings
	0039	29 (5)	Treatment	All tissues	No macropathology findings
	0040	29 (5)	Treatment	All tissues	No macropathology findings
	0041	29 (5)	Treatment	Heart	Pale area(s), 2-5mm, 1 (one)
				Testes	Small, left
				Remainder of animal	No macropathology findings
	0042	29 (5)	Treatment	All tissues	No macropathology findings

Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
1F	0101	3 (1)	Treatment	All tissues	No macropathology findings
	0102	3 (1)	Treatment	All tissues	No macropathology findings
	0103	3 (1)	Treatment	Skin and Subcutis	Dark Area(s), hindlimb, left, red, 10-19mm, 1 (one) (surrounding injection site.)
				Remainder of animal	No macropathology findings
	0104	3 (1)	Treatment	All tissues	No macropathology findings
	0105	3 (1)	Treatment	Lymph Node, Inguinal Lt	Enlarged, 2-5mm
				Remainder of animal	No macropathology findings
	0106	3 (1)	Treatment	All tissues	No macropathology findings
	0113	17 (3)	Treatment	All tissues	No macropathology findings

Group 1 Control - 0 PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
1F	0114	17 (3)	Treatment	All tissues	No macropathology findings
	0115	17 (3)	Treatment	All tissues	No macropathology findings
	0116	17 (3)	Treatment	All tissues	No macropathology findings
	0117	17 (3)	Treatment	All tissues	No macropathology findings
	0118	17 (3)	Treatment	All tissues	No macropathology findings
	0119	17 (3)	Treatment	All tissues	No macropathology findings
	0120	17 (3)	Treatment	All tissues	No macropathology findings
	0121	17 (3)	Treatment	All tissues	No macropathology findings
	0122	17 (3)	Treatment	All tissues	No macropathology findings

Group 1 Control - 0 PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
1F	0133	29 (5)	Treatment	All tissues	No macropathology findings
	0134	29 (5)	Treatment	All tissues	No macropathology findings
	0135	29 (5)	Treatment	All tissues	No macropathology findings
	0136	29 (5)	Treatment	All tissues	No macropathology findings
	0137	29 (5)	Treatment	All tissues	No macropathology findings
2F	0107	3 (1)	Treatment	All tissues	No macropathology findings
	0108	3 (1)	Treatment	Muscular IS, Thigh M. Region, Lt	Dark area(s), red, 2-5mm, 1 (one)
				Skin and Subcutis	Dark Area(s), red, 2-5mm, 1 (one) (surrounding injection site.)
				Remainder of animal	No macropathology findings

Group 1 Control - 0 PFU/mL
Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2F	0109	3 (1)	Treatment	Muscular IS, Thigh M. Region, Lt	Dark area(s), 2-5mm, 1 (one) (extending to femoro-tibial joint.)
				Remainder of animal	No macropathology findings
	0110	3 (1)	Treatment	Lymph Node, Inguinal Rt	Enlarged, 2-5mm
				Muscular IS, Thigh M. Region, Lt	Dark area(s), 2-5mm, 2-5 (few)
				Skin and Subcutis	Dark Area(s), red, 2-5mm, 1 (one) (surrounding injection site.)
				Remainder of animal	No macropathology findings
	0111	3 (1)	Treatment	All tissues	No macropathology findings
	0112	3 (1)	Treatment	All tissues	No macropathology findings
	0123	17 (3)	Treatment	Liver	Enlarged, noted

Group 2 MVA-HBV - 4.8×10^8 PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2F	0123	17 (3)	Treatment	Lymph Node, Inguinal Rt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, 2-5mm
				Muscular IS, Thigh M. Region, Rt	Dark area(s), red, diffuse, 1 (one)
				Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings
	0124	17 (3)	Treatment	Lymph Node, Lumbar	Enlarged, left, 2-5mm
				Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings
	0125	17 (3)	Treatment	Lymph Node, Inguinal Lt	Enlarged, 2-5mm

Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2F	0125	17 (3)	Treatment	Lymph Node, Inguinal Rt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, left, 2-5mm
				Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings
	0126	17 (3)	Treatment	Liver	Enlarged, noted
				Lymph Node, Inguinal Lt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, 2-5mm
				Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings

Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2F	0127	17 (3)	Treatment	Lymph Node, Inguinal Lt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, left, 2-5mm
				Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings
	0128	17 (3)	Treatment	Lymph Node, Lumbar	Enlarged, right, 2-5mm
				Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings
	0129	17 (3)	Treatment	Lymph Node, Lumbar	Enlarged, 2-5mm
				Muscular IS, Thigh M. Region, Lt	Dark area(s), red, 2-5mm, 1 (one) (slight, on muscle surface.)

Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2F	0129	17 (3)	Treatment	Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings
	0130	17 (3)	Treatment	Lymph Node, Lumbar	Enlarged, 2-5mm
				Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings
	0131	17 (3)	Treatment	Lymph Node, Inguinal Rt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, right, 2-5mm
				Remainder of animal	No macropathology findings
	0132	17 (3)	Treatment	Liver	Enlarged, noted
Group 2	MVA-HBV - $4.8x10^8$ PFU/mL				

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2F	0132	17 (3)	Treatment	Lymph Node, Inguinal Rt	Enlarged, 2-5mm
				Lymph Node, Lumbar	Enlarged, 2-5mm
				Spleen	Enlarged, noted
				Remainder of animal	No macropathology findings
	0138	29 (5)	Treatment	All tissues	No macropathology findings
	0139	29 (5)	Treatment	All tissues	No macropathology findings
	0140	29 (5)	Treatment	All tissues	No macropathology findings
	0141	29 (5)	Treatment	All tissues	No macropathology findings
	0142	29 (5)	Treatment	Heart	Pale area(s), ventricle(s), bilateral, 2-5mm, 5+ (many) (epicardium.)

Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

Appendix 13 Continued

Group /Sex	Animal Number	Day (Week) of Death	Phase	Tissue	Findings
2F	0142	29 (5)	Treatment	Remainder of animal	No macropathology findings

Group 2 MVA-HBV - $4.8x10^8$ PFU/mL

ANNEXES

Annex 1 Pathology report

To be included once received.

Annex 2 Immune Response Evaluation Contributing Report

To be added once finalised.

Annex 3 Certificate of Analysis

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Verified by (date and signature)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Annex 4 GLP certificate

Department of Health

THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE IN ACCORDANCE WITH DIRECTIVE 2004/9/EC

TEST FACILITY

[redacted]

TEST TYPE(S)

Analytical/Clinical Chemistry
Environmental Fate
Environmental Toxicity
Ecosystems
Physical/Chemical Testing
Mutagenicity
Toxicology

DATE OF INSPECTION: 02/04/2019

DATE OF ISSUE: 01/08/2019

An Inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above named test facility as part of the UK Good Laboratory Practice Compliance Monitoring Programme.

This statement confirms that, on the date of issue, the UK Good Laboratory Practice Monitoring Authority were satisfied that the above named test facility was operating in compliance with the OECD Principles of Good Laboratory Practice.

This statement constitutes a Good Laboratory Practice Instrument (as defined in the UK Good Laboratory Practice Regulations 1999).

Issued by
Mr Stephen Vinter
Head, UK GLP Monitoring Authority

Medicines & Healthcare products Regulatory Agency

MHRA