STATISTICAL ANALYSIS PLAN

BAVARIAN NORDIC A/S

Trial No. POX-MVA-037

NCT02038881

Randomized, open-label Phase II trial to assess the safety and immunogenicity of MVA-BN® smallpox vaccine when increasing the number of injections compared to the standard regimen in immunocompromised subjects with HIV infection

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Table of Contents

List of Abbreviations and Definitions

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical-Therapeutical-Chemical
BMI	Body Mass Index
BN	Bavarian Nordic
CI	Confidence Interval
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
DL	Detection Limit
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
e.g.	exempli gratia [Latin], for example
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full Analysis Set
FU	Follow-up
FU 1	6 month FU period
FU 2	1 year FU period
GMT	Geometric Mean Titer
HCG	Human Choriogonadotropin
HDL	High Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
i.e.	id est [Latin] in expression
LDL	Low Density Lipoprotein
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular/Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MVA-BN®	Modified Vaccinia Ankara – Bavarian Nordic also named IMVAMUNE® or IMVANEX®
N	Number of Observations
N.A.	Not applicable
No.	Number
PPS	Per Protocol Set
PRNT	Plaque Reduction Neutralization Test
PT	Preferred Term
RDW	Red Blood Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software

SCR	Screening Visit
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
$TCID_{50}$	Tissue Culture Infectious Dose 50
WBC	White Blood Cells
WHO-DD	Word Health Organization Drug Dictionary
WOCBP	Women of Child Bearing Potential

Statistical Analysis Plan

This Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing clinical trial data and outlines the statistical programming specifications, tables, figures, and listings for clinical trial POX-MVA-037. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical trial protocol (CTP).

This SAP will be followed completely for the analysis of data derived from the clinical trial POX-MVA-037. If any unforeseen additional analysis is included in the clinical study report (CSR) they will be clearly flagged as an additional unplanned analysis.

The analyses described are based on the final CTP for POX-MVA-037 (Doc. No. 92000015) Edition 5.0 dated 18 November 2014.

General Definitions

Enrolled Subjects

Subjects are considered enrolled once they have received the first trial vaccine injection.

Vaccination

For this trial, vaccination means the subject received all planned injections of MVA-BN® at the respective visit, i.e. a single injection per visit for subjects in Group 1 and Group 3, and two injections per visit for Group 2 constitute a vaccination (see Section 1.1).

Injection

An injection refers in this trial to a single injection with the trial vaccine.

Trial Day

The individual subject's day of trial is calculated from the day of the first injection. The day of first injection is defined as Day 0 and the day after first injection is Day 1, and so on. Equally, the day before first injection is defined as Day -1, and so on. In particular, no reference is made to the time of the injection in the calculation of the trial day, i.e. at midnight a new trial day begins regardless of the time of first injection. Note that it is possible for Visit 1 to be performed, for example, on trial Day -1.

Baseline

If not otherwise specified, 'Baseline' refers to the last measurement before the first injection of trial drug for a given parameter. This is either at Visit 1 or Screening Visit (SCR), or latest re-screening as appropriate. If there is missing vital sign data at Visit 1 then data obtained at the Screening Visit or latest re-screening visit will be used to impute the missing data. These data

will be summarized as Baseline data without specification of which visit was used. However, at all other visits no imputation will be used and the actual visit used will be specified in tables or listings.

Screening Phase

The screening phase is defined from the Screening Visit up to Visit 1 before the first injection. This includes any re-screening visits that are conducted.

Vaccination Period

A vaccination period is defined as the period of time starting after each vaccination (for Group 2: after the first injection) and ending 28 days after the vaccination, or, if it occurs first, until the subject receives another vaccination or discontinues the trial (see Table 1).

Pre-Booster Period

The pre-booster period applies only to Group 3 and is defined as the period of time starting at completion Visit 5 up to Visit 6 before the booster vaccination (see Table 1).

Active Trial Phase

The active trial phase covers the period from the first injection until the beginning of FU phase (see Table 1). Hence:

- For Group 1 and 2 the active trial phase is the time period between Visit 1 and 5 (starting with the first injection on Visit 1 and including Visit 5). Specifically, this includes possible periods where the second vaccination is 29 days or longer after the first vaccination (i.e. between Day 28 after the first vaccination until the second vaccination), and where Visit 5 is 29 days or longer after second vaccination (i.e. between Day 28 after the second vaccination until Visit 5).
- For Group 3 the active trial phase is the time period between Visit 1 and 8 (starting with the injection on Visit 1 and including Visit 8). This includes
    - possible periods where the second vaccination is 29 days or longer after the first vaccination,
    - possible periods where Visit 5 is 29 days or longer after the second vaccination,
    - the pre-booster period from completion of Visit 5 until the vaccination at Visit 6, and
    - possible time periods where Visit 8 is 29 days or longer after the third vaccination.

Treatment Phase / Overall Vaccination Period

The treatment phase is defined as the sum of all vaccination periods for each subject (see Table 1). This means the treatment phase comprises:

- for Groups 1 and 2 the sum of vaccination periods 1 and 2.

- for Group 3 the sum of vaccination periods 1, 2 and 3.

FU Phase

All data collected after completion of Visit 5 (Groups 1 & 2) or Visit 8 (Group 3) until, and including, the 1 year Follow-up (FU 2) Visit. Note that for some subjects for whom the six months FU 1 Visit was not performed there may be FU 2 data available. Missing FU 1 or FU 2 Visit data will be considered a minor protocol violation (see Table 1).

Table 1 Schematic presentation of trial phases

Group	Active Trial Phase							FU Phase	
	Vacc. Period 1	Day 29 – Visit 3	Vacc. Period 2	Day 29 – Visit 5	Pre-Booster Period	Vacc. Period 3	Day 29 – Visit 8	Visit 5 or 8 – FU 1	FU 1 – FU 2
	X		X			(X)			
	Belongs to Treatment Phase / Overall vaccination period								
1 & 2	Yes	No	Yes	No	N/A	N/A	N/A	No	No
3 only	Yes	No	Yes	No	No	Yes	No	No	No

X: vaccination occurs at the beginning of the respective period; (X) Group 3 only

Eligible Subjects

A subject is eligible if the question "is the subject eligible for the trial?" is answered with "yes" and there are no subsequent major protocol deviations that affect the eligibility of the subject.

Subjects Receiving All Vaccinations

A subject received all doses of trial vaccination according to the randomized group assignment if a date of drug administration is given for the vaccination at Visit 1, Visit 3, and in addition in Group 3 for the vaccination at Visit 6, and no major deviation is recorded on the electronic Case Report Form (eCRF).

Treatment Emergent Adverse Event

An adverse event (AE) with onset either on the day of a vaccination, but after injection, or within the 28 days following injection. AEs recorded outside the 28 day window after the last injection of trial vaccine will be classified as non-treatment emergent AEs.

Pre-treatment Adverse Events

AEs recorded after the signing of the informed consent form but before the first injection of trial vaccine are considered pre-treatment AEs.

Non-treatment Emergent Adverse Events

Events recorded in the active trial phase but not in the treatment phase. New non-serious or non-special interest AEs according to protocol will not be recorded in the FU phase. However, should any such events be recorded they will also be considered as non-treatment emergent. The classification of AEs into treatment emergent or non-treatment emergent will be decided based on the onset date/time of the AE.

Note that all Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) within the active and FU phases are considered treatment emergent. SAEs and AESIs within the screening phase are considered non-treatment emergent.

Adverse Drug Reaction

An Adverse Drug Reaction (ADR) is an AE with either a 'possible', 'probable', 'definite' or missing relationship to the vaccine.

Treatment Emergent ADR

A treatment emergent Adverse Drug Reaction, i.e. an adverse event with either a 'possible', 'probable', 'definite' or missing relationship to the vaccine with onset either on the day of a vaccination, but after injection, or within the 28 days following injection.

Treatment Emergent Serious Adverse Event

All SAEs recorded within the active trial phase (see Table 1) and FU phase (see Table 1) are considered as treatment emergent regardless of the day of onset.

Treatment Emergent Adverse Events of Special Interest

Any AESI which is also classified as serious will be included in the analysis of SAEs and will not be included in the analysis of AESIs. All AESIs recorded within the active trial phase (see Table 1) and FU phase (see Table 1) are considered as treatment emergent regardless of the day of onset.

Detection Limit

The Detection Limit (DL) for the vaccinia-specific Enzyme-linked Immunosorbent Assay (ELISA) can be found in SOP BN0002809: "Automated ELISA for Detection of Vaccinia Specific Antibodies in Human Sera", and for the vaccinia-specific Plaque Reduction Neutralization Test (PRNT) can be found in SOP BN0003536: "Human Plaque Reduction Neutralization Test Using Vaccinia Western Reserve".

Geometric Mean Titer

The Geometric Mean Titer (GMT) is calculated by taking the antilogarithm of the mean of the $\log_{10}$ transformed titers. Antibody titers below the DL will be given an arbitrary value of "1" (one) for the purpose of this calculation.

Seronegative and Seropositive Result

A seronegative result is a titer below the DL, while a seropositive result is a titer equal to or above the DL.

Seroconversion

Seroconversion is defined as either the appearance of antibody titers ≥ DL for initially seronegative subjects or a doubling or more of the antibody titer compared to baseline titer at Visit 1 for initially seropositive subjects. Seroconversion is not defined for subjects with missing Visit 1 titers.

1 Trial Overview

1.1 Trial Description

This trial is a randomized, open-label Phase II trial to assess the safety and immunogenicity of MVA-BN smallpox vaccine when increasing the number of injections compared to the standard regimen in immunocompromised subjects with HIV infection.

In total, ninety (90) vaccinia-naïve Human Immunodeficiency Virus (HIV) infected subjects will be enrolled in this trial. All subjects will be randomly assigned (1:1:1) to one of three groups (Groups 1-3) to receive:

Group 1:

One injection at Day 0 and Day 28 with 0.5 mL Modified Vaccinia Ankara Strain – Bavarian Nordic (MVA-BN) smallpox vaccine containing at least 1 x 10^8 Tissue Culture Infectious Dose 50% ($TCID_{50}$) per mL (standard regimen)

Group 2:

Two injections at Day 0 and two injections at Day 28 with 0.5 mL MVA-BN smallpox vaccine each containing at least 1 x 10^8 $TCID_{50}$ per mL (double dose regimen)

Group 3:

One injection at Day 0 and Day 28 with 0.5 mL MVA-BN smallpox vaccine containing at least 1 x 10^8 $TCID_{50}$ per mL (standard regimen) and one booster injection at Day 84 (Week 12) with 0.5 mL MVA-BN smallpox vaccine containing at least 1 x 10^8 $TCID_{50}$ per mL (booster regimen)

1.2 Objectives

1.2.1 Primary Objective

To assess the safety of MVA-BN smallpox vaccine when increasing the dose or number of injections compared to the standard 2-dose regimen.

1.2.2 Secondary Objectives

To compare the immunogenicity and safety of three different vaccination strategies of MVA-BN smallpox vaccine.

1.3 Trial Population

Ninety (90) vaccinia-naïve HIV-infected women and men of any ethnicity aged 18 to 45 years who meet all of the inclusion and none of the exclusion criteria are able to enroll into this trial.

1.4 Endpoints

1.4.1 Primary Endpoint

Occurrence, relationship and intensity of any serious and / or unexpected Adverse Events at any time during the trial.

1.4.2 Secondary Endpoints

Immunogenicity

- Geometric mean titers (GMTs) after vaccination with MVA-BN smallpox vaccine measured by Enzyme-linked Immunosorbent Assay (ELISA) and Plaque Reduction Neutralization Test (PRNT) at trial Visit 4 for Group 2 compared to Group 1 and Group 3 (combined).
- GMTs after vaccination with MVA-BN smallpox vaccine measured by ELISA and PRNT at trial Visit 7 of Group 3 compared to Visit 4 of Group 1 and Group 2 (separately).
- GMTs after vaccination with MVA-BN smallpox vaccine measured by ELISA and PRNT at six months Follow-up 1 (FU 1) and one year FU 2 Visit of Group 3 compared to respective FU Visits of Group 1 and Group 2 (separately).
- Seroconversion after vaccination with MVA-BN smallpox vaccine measured by ELISA and PRNT at trial Visit 4 of Group 2 compared to Group 1 and 3 (combined).
- Seroconversion after vaccination with MVA-BN smallpox vaccine measured by ELISA and PRNT at trial Visit 7 of Group 3 compared to Visit 4 of Group 1 and Group 2 (separately).
- Seroconversion after vaccination with MVA-BN smallpox vaccine measured by ELISA and PRNT at six months FU 1 and one year FU 2 Visit of Group 3 compared to respective FU Visits of Group 1 and Group 2 (separately).
- GMTs and seroconversion after vaccination with MVA-BN smallpox vaccine measured by ELISA and PRNT at all other immunogenicity sampling points (Visit 1, 3, 4, six months FU 1, one year FU 2) of Group 2 and 3 (separately) compared to Group 1.
- GMTs and seroconversion after vaccination with MVA-BN smallpox vaccine measured by ELISA and PRNT at trial Visit 6 and 7 of Group 3.

Safety and Reactogenicity

- Occurrence, relationship to the trial vaccine and intensity of any Adverse Event of Special Interest (AESI).
- Occurrence of any Grade 3 or 4 Adverse Events (AEs) probably, possibly or definitely related to the trial vaccine within 28 days after each vaccination.
- Occurrence, relationship to the trial vaccine and intensity of unsolicited non-serious AEs within 28 days after each vaccination.

- Occurrence, intensity and duration of solicited local AEs (redness, swelling, induration, pruritus and pain) during the 8-day period (day of vaccination and the following seven days) after each vaccination.
- Occurrence, relationship to the trial vaccine, intensity and duration of solicited general AEs (pyrexia, headache, myalgia, nausea, fatigue and chills) during the 8-day period (day of vaccination and the following seven days) after each vaccination.
- Change in CD4 T cell counts in Human Immunodeficiency Virus (HIV)-infected subjects two weeks after each vaccination.

1.5 Interim Analysis

No interim analysis is planned for this trial.

1.6 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) is an independent expert panel appointed by the sponsor. This board is in charge of surveying the subjects' safety throughout the course of the trial. All relevant roles, responsibilities and procedures for the DSMB are described in the DSMB charter. Initial review will be done on summaries of the safety, disposition and demographic data prepared by the [redacted] biostatistician and will be provided directly and securely to the DSMB members.

A summary of the activities and recommendations of the DSMB will be provided in the CSR.

2 Trial Design

Visit (V)	SCR	V1	V2	V3	V4	V5	V6*	V7*	V8*	FU 1	FU 2
Day / Visit +… Day	-28--1	0	V1+ 12-16	V1+ 28-35	V3+ 12-16	V3+ 28-35	V1+ 84-96	V6+ 12-16	V6+ 28-35	V3 (V6*)+ 182-210	V3 (V6*)+ 364-392
Target week	- 4	0	2	4	6	8	12	14	16	30 (38*)	56 (64*)
Procedures											
Informed consent & HIPAA	X										X[8]
Check incl. / excl. criteria	X	X									
Medical History/HIV specific medical history	X										
Check criteria for withdrawal of next vaccination				X			X				
Assessment for previous smallpox vaccination including check for a scar	X										
Complete physical exam	X										
Evaluation of vital signs	X	X	X	X	X	X	X	X	X	X	X
Calculate individual cardiac risk factor	X										
Evaluation of family cardiac risk factors	X										
Targeted physical exam incl. auscultation of the heart and lung		X	X	X	X	X	X	X	X	X	X
ECG[4]	X		X		(X)[1]			(X)[1]			
Recording of prior and concomitant medication	X	X	X	X	X	X	X	X	X		
Counseling on avoidance of pregnancy for WOCBP[6]	X	X		X			X				
AE/SAE/AESI recording	X	X	X	X	X	X	X	X	X	X[2]	X[2]
Lab											
Pregnancy test for WOCBP[3]	X	X		X		X	X		X		

Visit (V)	SCR	V1	V2	V3	V4	V5	V6*	V7*	V8*	FU 1	FU 2
Day / Visit +… Day	**-28--1**	**0**	**V1+ 12-16**	**V1+ 28-35**	**V3+ 12-16**	**V3+ 28-35**	**V1+ 84-96**	**V6+ 12-16**	**V6+ 28-35**	**V3 (V6*)+ 182-210**	**V3 (V6*)+ 364-392**
Target week	**- 4**	**0**	**2**	**4**	**6**	**8**	**12**	**14**	**16**	**30 (38*)**	**56 (64*)**
Obtaining blood for safety lab[4]	X		X		X			X		(X)[1]	(X)[1]
Total, HDL and LDL cholesterol	X										
Troponin I testing[4]	X		X		X			X			
Serum collection for immunogenicity testing		X		X	X		X	X		X	X
CD4 count	X		X		X			X	X	X	X
Viral Load[7]	X		X								
Vaccination											
Vaccine administration & Subject observation		X		X			X				
Recording of immediate AEs		X		X			X				
Handout of memory aid		X		X			X				
Collection of memory aid			X		X			X			
Examination of injection site			X		X			X			

*Visits performed for subjects in Group 3 only

(x), [1] Only to be performed if clinically indicated, i.e. in the presence of cardiac signs or symptoms.

[2] New Serious Adverse Events (SAEs)/ AESIs and changes to SAEs/AESIs/AEs ongoing at V5 (Group 1/2) or V8 (Group 3) only.

[3] At SCR, a serum test must be performed. At other visits, a urine pregnancy test will be performed.

[4] If clinically indicated, additional safety measures can be taken at any other trial visits or at unscheduled visits.

[5] N.A.

[6] Review of acceptable contraceptive methods and recent menstrual history with Women of Child Bearing Potential (WOCBP).

[7] Viral load will be determined during treatment period if clinically indicated.

[8] FU 2 procedures added after initial trial entry informed consent; i.e. subjects need to sign updated informed consent form at or before FU 2.

3 Statistical Methods

3.1 Planned Sample Size

In addition to the below sample size calculations for the immunogenicity endpoints, a sample size of 30 per treatment group also allows for the detection of AEs with an incidence of at least 1 in 10 with a probability of detection of at least 95%.

A sample size of 30 in each group will have 80% power to detect a difference in means of 0.74 x standard deviation (SD) using a two-group t-test with a 5% two-sided significance level. This means that a difference Δ can be detected with $\Delta / SD > 0.74$. Taking into account the SD of 0.85 for the $\log_{10}$ PRNT titers the detection of a $\log_{10}$ PRNT difference of 0.629 can be detected (or a difference in titers on the original titer scale by a factor of 4). For the ELISA where the $\log_{10}$ SD is at most 0.42 a difference of 0.311 can be detected, i.e. a difference in titers by a factor of 2 on the original scale can be detected.

3.2 Analysis Populations

3.2.1 Full Analysis Set (FAS)

This is the subset of subjects who received at least one injection and for whom any data are available.

The main analysis of safety will be performed on this analysis set.

3.2.2 Per Protocol Set (PPS)

This is the subset of subjects in the FAS who have received all vaccinations, completed all visits of the active trial phase (Visit 1 to Visit 5 and additionally Visit 6 to Visit 8 for Group 3; see Table 1) and adhered to all protocol conditions. Subjects with only minor (not relevant) protocol deviations are included into this dataset.

The decision whether a protocol deviation is major or not will be made on a case-by-case basis in a data review meeting (DRM) prior to database lock.

Examples of major protocol violations are:

1. Premature discontinuation of the trial before Visit 5 for Groups 1 and 2 or Visit 8 for Group 3 (the question “prematurely terminated the trial?” is answered with “yes” even where no other reason exists to exclude the subject from further participation in accordance with the protocol)
2. Subject did not meet all of the inclusion criteria
3. Subject met one or more of the exclusion criteria
4. Withdrawal from the second and/or third vaccination

5. Major vaccine preparation and administration deviation from specification as given in the protocol including cases where the subject fulfils at least one of the criteria specified in the protocol for withdrawal from vaccination
6. Major deviations of the visit window as determined during the DRM(s)
7. Unallowed prior or concomitant medication
8. Missing humoral immune response data (ELISA and PRNT) at Visit 1 or 4 (or Visit 7 for Group 3)

A classification of all subjects in the FAS for major protocol deviations will be performed at the time of the DRM.

The main analysis of the immunogenicity endpoints will be performed on the PPS. The same statistical procedures will also be applied to the FAS.

3.3 Definitions, Data Conventions and Handling of Missing Data

3.3.1 Missing Data

No imputation of missing titers will be performed.

For the analysis of safety data incomplete AE and medication start and end dates will be imputed in order to assign these events to the correct vaccination period.

Missing Vital Signs data for Visit 1 will be imputed using screening (or latest re-screening) values. However, this will be displayed as 'Baseline' values in the tables and listing for Vital Signs data without reference to whether the data originated from Visit 1 or SCR.

For prior and concomitant medication and AEs imputation of partial start and end dates will be done for analysis purpose according to the following rules:

Missing	**Rule for start date**	**Rule for end date**	**Flag for imputation**
Day	First of month*	Last of month*	D
Month†	1. January*	31. December*	M
Year†	no imputation	Last visit date	Y

* Unless the imputed start date is before first visit date, in which case first visit date is used; or the imputed end date is after last visit date in which case last visit date available is used.

† It is assumed that a missing month implies a missing day as well, and that a missing year implies a missing month and day.

All data will be listed and summarized as captured in the eCRF. All listings will display the original dates as captured in the eCRF.

If the imputation of a partial start date of an AE leads to a start date prior to the date of first vaccination, it will be set to the date of first vaccination following the worst case principle.

3.3.2 Assignment of AEs to Vaccination Period

Each AE will be assigned to a vaccination period using date/time of vaccination and date/time of the start of the AE.

If start time is missing and start date of AE coincides with the date of a vaccination, the AE will be assigned to the vaccination period corresponding to the vaccination on this date.

Each AE starting at or after any vaccination not matching the definition of a solicited AE is defined as an unsolicited AE. If a solicited AE begins outside of the 8-day window following the previous vaccination it will be considered an unsolicited AE regardless of the preferred term. If start time is missing and start date coincides with date of any vaccination, it will be regarded as a treatment emergent adverse event (TEAE). If the start date is (partially) missing the AE will be regarded as a TEAE following the worst case principle.

If the AE cannot be assigned to a vaccination period because of a (partially) missing start date then it will be assigned to the overall vaccination period. Hence it is possible for the overall vaccination period to include more events than the sum of the individual vaccination periods.

AEs with onset after the active trial phase will be considered to fall within the FU phase. AEs with onset after the active trial phase but at or before the FU 1 visit will belong to FU 1 period. AEs with onset date after FU 1 but before FU 2 visit will belong to the FU 2 period.

3.3.3 General Considerations for AEs

MedDRA version 17.1 will be used for coding of AEs.

Duration of an AE is calculated as follows:

Unsolicited AE: expressed in [days]

- End date of AE – start date of AE + 1
- In case of (partially) missing start date or (partially) missing end date imputed dates will be used in the calculation.
- In case the AE is ongoing at the end date of the AE, the duration will not be calculated

Solicited AEs: expressed in [days]

end date of AE – start date of AE + 1

where

end date is the last day the symptom is defined as an AE
start date is the first day symptom is defined as an AE
(no matter if the AE occurred at every day between first day and last day).

- In case the AE is ongoing at the end date of the AE, the duration will not be calculated

Time interval between vaccination and start of AE are calculated as follows:

Relative day of start of AE is calculated as follows:

Unsolicited AEs: expressed in [days]

- Start date of AE – corresponding vaccination date
- In case of (partially) missing start date no calculation will be done.

Solicited AEs: expressed in [days]

- Start date of AE – corresponding vaccination date
- Where start date is the first day a symptom is defined as an AE, and vaccination day corresponds to Day 0.

Local and General Unsolicited AEs

Any unsolicited AE which is recorded with the preferred term including the text "injection site" or "vaccination site" will be considered as a local reaction. Any other preferred terms which are considered as local events will be documented in the DRM minutes. Any unsolicited AE not classified as a local AE will be classified as a General AE.

3.4 Analysis Variables

3.4.1 Demographic and Other Baseline Characteristics

Demographics

- Age
- Sex
- Race (American Indian or Alaskan Native, Oriental/Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White/Caucasian, Other)
- Ethnicity (Hispanic or Latino, or Non-Hispanic or Latino)
- Height [cm]
- Body weight [kg]
- Body Mass Index (BMI)

Other Baseline characteristics

- History of smallpox vaccination or vaccination with other pox-virus based vaccine
- Medical history (including cardiac risk assessment, but excluding HIV/AIDS specific conditions)

- Non-treatment emergent AEs

HIV specific characteristics

- History of HIV infection
  - Circumstances [categories] of HIV infection
  - Year of diagnosis [Year] of HIV infection
  - Lowest CD4 count [cells/mL] previously documented
  - Lowest CD4 count [cells/mL] previously measured (nadir)
  - CD4 count [cells/mL] at Screening
  - Highest Viral Load [copies/mL] during up to six months ago
  - Viral Load [copies/mL] at Screening
- HIV related illnesses
- AIDS defining conditions

3.4.2 Safety Variables

Physical examination (complete examinations at Visit SCR and targeted physical examination at all other visits).
Only abnormal physical examination results will be listed.

Vital signs (at each visit)

- Heart rate [beats per minute]
- Systolic and diastolic blood pressure [mmHg]
- Body temperature [°C]

12-lead Electrocardiogram (ECG) (at SCR and Visit 2)

(Additional ECGs will be performed and reported if clinically indicated [e.g. Visit 4 or Visit 7], or in case of any clinically significant cardiac events are present)

- Investigator's overall interpretation (normal, abnormal)
- Clinical significance

Safety laboratory data (at Visit SCR, Visit 2, Visit 4 and Visit 7)

(Additional safety laboratory data will be obtained and reported if clinically indicated [e.g. FU 1 or 2]).

Clinical chemistry (serum)

- Total bilirubin
- Alkaline phosphatase (AP)
- Aspartate Aminotransferase (SGOT/AST)
- Alanine Aminotransferase (SGPT/ALT)
- Serum creatinine
- Low Density Lipoprotein (LDL) (only at Visit SCR)
- High Density Lipoprotein (HDL) (only at Visit SCR)
- Total cholesterol (only at Visit SCR)
- Sodium
- Potassium
- Calcium
- Troponin I

Hematology (whole blood)

- Red blood cell count
- Hemoglobin
- Total and differential WBC (Eosinophils, Basophils, Neutrophils - % and absolute, Lymphocytes, Monocytes)
- Platelet count
- Hematocrit, mean corpuscular/cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and red blood cell distribution width (RDW)

HIV Related

- Viral Load (only at Visit SCR and Visit 2)
- CD4 count (at Visit SCR, Visit 2, Visit 4, Visit 7, Visit 8 and FU 1 and FU 2)

Pregnancy test (serum β-HCG pregnancy test at SCR and urine β-HCG pregnancy test within 24 hours prior to each vaccination and at last active trial phase visit for women of childbearing potential).

Information on all pregnancy tests will be listed.

<u>Solicited local AEs reported in the subject memory aid (on days of vaccination and during the following seven days)</u>

- Injection Site Erythema (Redness)

- Injection Site Swelling
- Injection Site Pain
- Injection Site Induration
- Injection Site Pruritus (Itching)

Solicited general AEs reported in the subject memory aid (on days of vaccination and during the following seven days)

- Body Temperature (Fever)
- Headache
- Myalgia (Muscle pain)
- Chills
- Nausea
- Fatigue

Unsolicited AEs reported (on days of vaccination and during the following 28 days)

- Other, unsolicited local and general adverse events following vaccination

SAEs

AESIs

In case an AESI is also an SAE it will be treated and reported as an SAE.

Prior and Concomitant medication

3.4.3 Immunogenicity Variables

Seropositivity (yes/no) at Visits 1, 3, 4, 6, 7 and FU 1 and FU 2

- Vaccinia-specific neutralizing antibodies (PRNT)
- Total vaccinia-specific antibodies (ELISA)

Seroconversion (yes/no) at Visits 3, 4, 6, 7 and FU 1 and FU 2

- Vaccinia-specific neutralizing antibodies (PRNT)
- Total vaccinia-specific antibodies (ELISA)

Antibody titers at Visits 1, 3, 4, 6, 7 and FU 1 and FU 2

- Vaccinia-specific neutralizing antibodies (PRNT)
- Total vaccinia-specific antibodies (ELISA)

3.4.4 Pharmacokinetic Variables

Not applicable

3.4.5 Pharmacodynamic Variables

Not applicable

3.5 Analysis and Presentation Methods

3.5.1 Listings and Descriptive Statistics

All individual data entered in the eCRF and derived data will be listed as measured in the Individual Subject Data Listing.

For ELISA and PRNT titers descriptive statistics will be based on Geometric Means and confidence intervals (CI). Other, continuous measurements will be summarized by means of descriptive statistics (i.e. number of observations (N), mean, SD, minimum (Min), median, maximum (Max)) and categorical data will be summarized by means of frequency tables (i.e. count and percentages) and CI, if not stated otherwise.

All tables and listings will be sorted by scheduled visit (and subject, if appropriate).

All tables will be presented split by treatment groups (Groups 1 - 3).

Repeat assessments/measurements and unscheduled assessments/measurements will be included in the Individual Subject Data Listing. In case of any repeats of safety laboratory values, the repeat values will be used for the before-treatment assessment and the original value for the post-trial assessment. All other repeat values will be listed in a separate listing.

3.5.2 Software

All statistical summaries and analyses of safety and efficacy data will be performed using SAS® 9.2 or higher (Statistical Analysis System, SAS-Institute, Cary, NC, USA) for Windows XP.

3.5.3 Primary Endpoint

Occurrence, relationship and intensity of any serious and / or unexpected Adverse Events at any time during the trial.

All SAEs with onset from first injection of trial vaccine to FU 2 will be listed. An additional listing will also be prepared for the AESIs.

3.5.4 Disposition of Subjects

All subjects screened will be accounted for. For the active trial phase a summary table will be presented specifying:

- The number of subjects screened
- The number of subjects randomized to each group
- The number of subjects completing the active trial phase of the trial
- The number of subjects included in each analysis set
- The number of subjects withdrawn from the second vaccination
- The number of subjects within Group 3 withdrawn from the third vaccination
- The number of subjects prematurely discontinuing the trial (as well as the frequency of primary reasons for withdrawal/premature discontinuation)
- The number of subjects completing the respective FU 1 and FU 2 Visits.

A listing will present all randomized subjects, time and date of completion or discontinuation with date of last dose of trial medication, date of discontinuation, reason for discontinuation and primary reason for withdrawal from any vaccination, if applicable.

All screening failures (subjects not eligible for the trial) will be listed including the reason why not eligible. Listings will also be presented for all violations in inclusion criteria and all exclusion criteria fulfilled.

3.5.5 Demographic and Other Baseline Data

All listings will be based on the screened subjects with screen failures and subjects randomized but not treated considered as two separate trial groups. However tables of the descriptive statistics for the demographics will only be produced for the FAS and PPS.

Descriptive statistics will be presented for the continuous demographic variables, age, height, and body weight. Note that the value obtained on the date of the actual Screening Visit is used for age, height and body weight calculations (hence also for BMI) and not the date of any partial Re-screening Visit.

Age is calculated using the following formula:

AGE = Year of Screening Visit – Year of Birth;
if Month of Screening Visit < Month of Birth then AGE → AGE – 1;
if Month of Screening Visit = Month of Birth
and Day of Screening Visit < Day of Birth then AGE → AGE – 1

Frequencies and percentages of subjects will be tabulated for the categorical variables sex, race and ethnicity in the same table by treatment group and overall. Percentages will be based on the total number of subjects in the relevant population.

Descriptive statistics for the demographic data will be produced by treatment group.

A summary of medical history by Preferred Term (PT) and System Organ Class (SOC) will be produced for each treatment group.

Non-treatment emergent AEs will be listed by body system and preferred term. Relative day of onset and duration of non-treatment emergent AEs will be calculated as described in Section 3.3.3. Pre-treatment Adverse Events are defined as AEs with start date after the subject was screened for the trial but before the first injection was received. These events are to be reported.

Frequency summaries of the history of HIV infection, AIDS defining conditions, circumstances of HIV infection, and HIV related illness will be produced by treatment group.

Summary statistics of the historical viral load and CD4 statistics (year of diagnosis, lowest CD4 count previously documented, CD4 nadir, CD4 count at screening, highest viral load during up to six months ago, viral load at screening) will also be presented stratified by treatment group.

3.5.6 Prior and Concomitant Medication

All prior medication will be summarized by Anatomical-Therapeutical-Chemical (ATC) class and Generic name according to the 2014/Q3 version of the World Health Organization Drug Dictionary (WHO-DD). All concomitant medication will be summarized by ATC class and Generic name for all subjects in the FAS.

The table/listing "Prior medication" includes the medication data where end date is before date of first injection of trial vaccine. The table/listing "Concomitant medication" includes ongoing medication or medication with missing end date or with end date after date of first injection of trial vaccine.

All listings will display the original dates as captured in the eCRF.

3.5.7 Compliance

Compliance will be evaluated with respect to the number vaccinations received and the number of memory aids completed.

3.5.8 Immunogenicity Analysis

All immunogenicity results will be listed. Tables and figures will be prepared for the PPS and the FAS. All of the following analyses will be performed for results generated using both the PRNT and ELISA.

Seropositivity rates

Vaccinia-specific seropositivity rates will be presented by treatment group for Visits 1, 3, 4, 6, 7, FU 1 and FU 2 along with the Clopper-Pearson 95% confidence intervals (CIs) of the seropositivity rates.

Seroconversion rates

Vaccinia-specific seroconversion rates measured by ELISA and PRNT will be presented by treatment group for Visits 3, 4, 6, 7, FU 1 and FU 2 (and for combined groups as indicated) along with the Clopper-Pearson 95% CIs of the seroconversion rates.

In addition, the difference in seroconversion rates of Group 2 at Visit 4 will be compared to the combined Group 1 / Group 3 seroconversion rates and will be calculated as

Difference in seroconversion rates =

{ Group 2 seroconversion rate } – { combined Group 1 and Group 3 seroconversion rate }

along with an exact 95% CI calculated following the "Invert two one-sided tests" method of Chan and Zhang (Chan, 1999).

Similarly, the difference between the seroconversion rate at Visit 7 for Group 3 and the seroconversion rates at Visit 4 for Group 1 and Group 2 (separately) will also be calculated along with the exact 95% confidence interval.

For both the FU Visits (FU 1 and FU 2) the difference of the seroconversion rate for Group 3 will be compared to the seroconversion rate of Group 1 and Group 2 separately.

Lastly, the difference of the seroconversion rates for Group 1 will be compared to the seroconversion rates of Group 2 and Group 3 separately at Visit 3, Visit 4, FU 1 and FU 2.

A bar chart will be presented showing the seroconversion rates measured by ELISA and PRNT per treatment group for each visit for the PPS and the FAS.

Geometric Mean Titers (GMTs)

GMTs measured by ELISA and PRNT will be calculated at Visits 1, 3, 4, 6, 7, FU 1 and FU 2 for each treatment group and for combined groups as indicated.

Descriptive statistics will be derived by visit including number of observations available at each visit (n) and GMT with 95% CI (derived by the antilogarithm of the 95% CI of the $\log_{10}$ titer transformations). GMTs and upper and lower confidence limits will be displayed to one decimal place.

The ratio of the GMTs will be presented between Group 2 and the combined Group 1 / Group 3 at Visit 4 along with the 95% CI. Similarly, the ratio of the GMTs will be presented between

Group 3 at Visit 7 and Group 1 / Group 2 separately at Visit 4, and at the FU Visits (FU 1 and FU 2) the ratios of the GMTs will be presented between Group 3 and Group 1 / Group 2 separately. Lastly, the ratios of the GMTs at Visit 1, 3, 4, FU 1 and FU 2 will be presented between Group 1 and Group 2 / Group 3 separately.

A line chart will be presented showing the GMTs measured by ELISA and PRNT per treatment group for each visit for the PPS and the FAS.

3.5.9 Adverse Events

For the treatment phase analysis a summary table will be presented of the number (and percentage) per vaccination period both per subject and for the number of events for the following events:

- Any AEs
- Any TEAEs
- ADRs (Adverse Drug Reactions)
- Treatment emergent ADRs; note that all local solicited AEs are automatically considered ADRs
- Severe TEAEs (Grade 3 or higher, for grading please refer to the CTP)
- Severe ADRs (ADR graded 3 or higher, for grading please refer to the CTP)
- SAEs
- AESIs
- AEs leading to withdrawal from vaccination
- Deaths

In addition, the incidence of AEs will be calculated (i.e. the number of subjects developing a treatment emergent AE divided by the number of subjects at the time of the vaccination) with corresponding 95% Clopper-Pearson CI. The incidence of any AE will also be calculated for each vaccination period, overall vaccination period and per subject.

For analysis of the treatment phase the information will be based on the data provided from Visit 1 to Visit 5, and additionally Visit 6 to Visit 8 for Group 3.

For the treatment phase, all AEs will be listed by subject, including demographic information, SOC and PT. Any AE with onset later than 28 days after the previous vaccination will not be included in summary tables but will be included in the listing and will be flagged accordingly as non-treatment emergent.

According to the CTP no new AEs should be reported during the FU phase, except SAEs and AESIs, but if any are reported then they will be listed but considered non-treatment emergent.

The number of subjects with at least one treatment emergent AE during the treatment phase will be descriptively compared between the treatment groups, and between vaccination periods within Group 3.

Serious Adverse Events

The number of subjects with at least one SAE during the trial will be descriptively compared between the treatment groups, and between vaccination periods within Group 3.

SAEs reported will be listed in the same manner as for AEs.

The number of subjects with at least one Treatment Emergent SAEs will be descriptively compared between the treatment groups, and between vaccination periods within Group 3.

Adverse Events of Special Interest

AESIs will be reported separately but in the same way as SAEs.

Solicited Local AEs

Solicited local AEs will be summarized by PT after each vaccination visit, and broken down by maximum intensity.

In addition, the incidence will be calculated by severity (i.e. the number of subjects developing a particular local solicited AE during the 8-day period after each vaccination divided by the number of subjects actually receiving this vaccination) with corresponding 95% Clopper-Pearson CI. The incidence will also be calculated for any solicited local AE for each vaccination period and per subject.

The duration of the AEs will be included in the listing. The duration of the AEs will also be summarized using the mean, SD, median, minimum and maximum.

Solicited General AEs

Solicited general AEs will be summarized in the same manner as solicited local AEs.

In addition a similar summary table will be produced for relationship of the AEs to trial vaccine. Also the incidences of AEs with reasonable possibility of vaccine contribution (i.e. relationship to vaccine documented as “possible”, “probable”, “definite” or missing), and those with Grade ≥ 3 and with reasonable possibility of vaccine contribution will be summarized per vaccination period and overall by subject.

Unsolicited AEs

Treatment emergent unsolicited AEs will be summarized by SOC and PT and vaccination period and by subject.

A summary of the number of AEs by intensity and by relationship to trial vaccination will also be presented.

The number of AEs with a reasonable possibility of being related to the vaccine will be presented in a separate listing and summarized in a table by SOC and PT and vaccination period and by subject.

Non-treatment emergent AEs will only be flagged and included in the listing, but will not be included in the tables.

3.5.10 Clinical Laboratory Variables (Hematology, Chemistry, HIV)

All measured hematology and chemistry values (and changes from baseline for continuous parameters) will be listed and summarized per visit using descriptive statistics.

Summary tables will be produced for the number of high and low laboratory values per visit by hematology and chemistry parameters.

In addition, all clinical laboratory values outside the normal range will be listed with screening number, demographic information and flagging of abnormal values (L=Below normal range, H=Above normal range) with their clinical significance.

'Shift tables' will be used to evaluate categorical changes from SCR to Visit 2 and SCR to Visit 4 (and SCR to Visit 7 in Group 3) with respect to normal ranges (below, within, above normal range) in hematology and chemistry parameters.

Measured CD4 count and viral load values and changes from Baseline will be summarized per visit using descriptive statistics. A plot of median CD4 counts per visit and per treatment group will be produced. All measured values will be listed.

3.5.11 Vital Signs and ECG

Measured vital signs values and changes from Baseline will be summarized at each time point using descriptive statistics. All measured values will be listed.

The investigator's overall interpretation of either normal, abnormal and if abnormal whether the ECG is clinically significant or not clinically significant, will be summarized at Screening and Visit 2. All ECGs including those clinically indicated and those not clinically indicated will be listed. In addition shift tables between SCR and Visit 2 will be produced to summarize the number of changes in ECG status.

3.5.12 Pregnancy Test

Results of pregnancy tests will be presented in an individual subject listing.

3.5.13 Physical Examination

Subjects with abnormal physical examinations will be listed.

3.6 Alterations in SAP from the Clinical Trial Protocol

None

4 References

Chan I and Zhang Z (1999) Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions. Biometrics 55(4): 1202-1209.

Clinical Trial Protocol POX-MVA-037: Randomized, open-label Phase II trial to assess the safety and immunogenicity of MVA-BN smallpox vaccine when increasing the number of injections compared to the standard regimen in immunocompromised subjects with HIV infection. Edition 5.0 dated 18 November 2014 Doc. No. 92000015

5 Index of Tables, Figures and Listings

5.1 Tables

15.1 Disposition and Demographics

15.1.5 Compliance
15.1.5.1 Compliance: Number of Subjects who Received Vaccinations – FAS

14.2 Immunogenicity Tables

15.2.1 Neutralizing Antibody Titers Measured by Vaccinia-specific PRNT
15.2.1.1.1 PRNT Seropositivity Rates – PPS
15.2.1.1.2 PRNT Seropositivity Rates – FAS

15.2.1.2.1 PRNT Seroconversion Rates – PPS
15.2.1.2.2 PRNT Seroconversion Rates – FAS

15.2.1.3.1 PRNT Geometric Mean Titers – PPS
15.2.1.3.2 PRNT Geometric Mean Titers – FAS

15.2.1.4.1 PRNT Comparison of Seroconversion Rates – PPS
15.2.1.4.2 PRNT Comparison of Seroconversion Rates – FAS
15.2.1.4.3 PRNT Comparison of Seroconversion Rates of Week 6 to Week 14 – PPS
15.2.1.4.4 PRNT Comparison of Seroconversion Rates of Week 6 to Week 14 – FAS

15.2.1.5.1 PRNT Comparison of GMTs – PPS
15.2.1.5.2 PRNT Comparison of GMTs – FAS
15.2.1.5.3 PRNT Comparison of GMTs of Week 6 to Week 14 – PPS
15.2.1.5.4 PRNT Comparison of GMTs of Week 6 to Week 14 – FAS

15.2.2 Antibody Titers Measured by Vaccinia-specific ELISA
15.2.2.1.1 ELISA Seropositivity Rates – PPS
15.2.2.1.2 ELISA Seropositivity Rates – FAS

15.2.2.2.1 ELISA Seroconversion Rates – PPS
15.2.2.2.2 ELISA Seroconversion Rates – FAS

15.2.2.3.1 ELISA Geometric Mean Titers – PPS
15.2.2.3.2 ELISA Geometric Mean Titers – FAS

15.2.2.4.1 ELISA Comparison of Seroconversion Rates – PPS
15.2.2.4.2 ELISA Comparison of Seroconversion Rates – FAS
15.2.2.4.3 ELISA Comparison of Seroconversion Rates of Week 6 to Week 14 – PPS
15.2.2.4.4 ELISA Comparison of Seroconversion Rates of Week 6 to Week 14 – FAS

15.2.2.5.1 ELISA Comparison of GMTs – PPS
15.2.2.5.2 ELISA Comparison of GMTs – FAS
15.2.2.5.3 ELISA Comparison of GMTs of Week 6 to Week 14 – PPS
15.2.2.5.4 ELISA Comparison of GMTs of Week 6 to Week 14 – FAS

15.3 Safety

15.3.1 Adverse Events

15.3.1.1 Overview of Solicited and Unsolicited Adverse Events

15.3.1.1.1 Overview of Solicited and Unsolicited Adverse Events (Per Vaccination Period) – FAS

15.3.1.1.2 Overview of Solicited and Unsolicited Adverse Events (Per Subject) – FAS

15.3.1.1.3 Overview of Pooled Solicited and Unsolicited Adverse Events (Per Subject) by Gender – FAS

15.3.1.1.4 Overview of Pooled Solicited and Unsolicited Adverse Events (Per Subject) by Ethnicity – FAS

15.3.1.1.5 Overview of Pooled Solicited and Unsolicited Adverse Events (Per Subject) by Race – FAS

15.3.1.1.6 Overview of Pooled Solicited and Unsolicited Adverse Events (Per Subject) by Age Band – FAS

15.3.1.1.7 Treatment Emergent Solicited and Unsolicited Adverse Events (Per Vaccination Period) – FAS

15.3.1.1.8 Treatment Emergent Solicited and Unsolicited Adverse Events (Per Subject) – FAS

15.3.1.1.9 Treatment Emergent Solicited and Unsolicited Adverse Events (Per Vaccination Period): Overall Incidence – FAS

15.3.1.1.10 Treatment Emergent Solicited and Unsolicited Adverse Events (Per Subject): Overall Incidence – FAS

15.3.1.1.11 Pooled Solicited and Unsolicited Adverse Events: Incidence of Related Adverse Events by Preferred Term and System Organ Class (Per Subject) – FAS

15.3.1.1.12 Pooled Solicited and Unsolicited Adverse Events: Incidence of Related Adverse Events by Preferred Term and System Organ Class (Per Subject) by Gender – FAS

15.3.1.1.13 Pooled Solicited and Unsolicited Adverse Events: Incidence of Related Adverse Events by Preferred Term and System Organ Class (Per Subject) by Ethnicity – FAS

15.3.1.1.14 Pooled Solicited and Unsolicited Adverse Events: Incidence of Related Adverse Events by Preferred Term and System Organ Class (Per Subject) by Race – FAS

15.3.1.1.15 Pooled Solicited and Unsolicited Adverse Events: Incidence of Related Adverse Events by Preferred Term and System Organ Class (Per Subject) by Age Band – FAS

15.3.1.2 Solicited Local Adverse Events

15.3.1.2.1 Solicited Local Adverse Events (Per Vaccination Period): Summary of Maximum Intensity – FAS

15.3.1.2.2 Solicited Local Adverse Events (Per Subject): Summary of Maximum Intensity – FAS

15.3.1.2.3 Solicited Local Adverse Events (Per Vaccination Period): Incidence by Maximum

Intensity – FAS

15.3.1.2.4 Solicited Local Adverse Events (Per Subject): Incidence by Maximum Intensity – FAS

15.3.1.2.5 Solicited Local Adverse Events (Per Vaccination Period): Summary of Duration – FAS

15.3.1.2.6 Solicited Local Adverse Events (Per Subject): Summary of Duration – FAS

15.3.1.3 Solicited General Adverse Events

15.3.1.3.1 Solicited General Adverse Events (Per Vaccination Period: Summary of Maximum Intensity – FAS

15.3.1.3.2 Solicited General Adverse Events (Per Subject): Summary of Maximum Intensity – FAS

15.3.1.3.3 Solicited General Adverse Events (Per Vaccination Period): Incidence by Maximum Intensity – FAS

15.3.1.3.4 Solicited General Adverse Events (Per Subject): Incidence by Maximum Intensity – FAS

15.3.1.3.5 Solicited General Adverse Events (Per Vaccination Period): Summary of Duration – FAS

15.3.1.3.6 Solicited General Adverse Events (Per Subject): Summary of Duration – FAS

15.3.1.4 Unsolicited Adverse Events

15.3.1.4.1 Treatment Emergent Unsolicited Adverse Events (Per Vaccination Period): Incidence by Preferred Term and System Organ Class – FAS

15.3.1.4.2 Treatment Emergent Unsolicited Adverse Events (Per Subject): Incidence by Preferred Term and System Organ Class – FAS

15.3.1.4.3 Treatment Emergent Unsolicited Adverse Drug Reactions (Per Vaccination Period): Incidence by Preferred Term and System Organ Class – FAS

15.3.1.4.4 Treatment Emergent Unsolicited Adverse Drug Reactions (Per Subject): Incidence by Preferred Term and System Organ Class – FAS

15.3.1.4.5 Treatment Emergent Unsolicited Adverse Events (Per Vaccination Period): Summary of Intensity and Relationship to Trial Vaccination – FAS

15.3.1.4.6 Treatment Emergent Unsolicited Adverse Events (Per Subject): Summary of Intensity and Relationship to Trial Vaccination – FAS

15.3.1.4.7 Unsolicited Adverse Events: Incidence of Related Adverse Events by Preferred Term and System Organ Class (Per Subject) by Gender – FAS

15.3.1.4.8 Unsolicited Adverse Events: Incidence of Related Adverse Events by Preferred Term and System Organ Class (Per Subject) by Ethnicity – FAS

15.3.1.4.9 Unsolicited Adverse Events: Incidence of Related Adverse Events by Preferred Term and System Organ Class (Per Subject) by Race – FAS

15.3.1.4.10 Unsolicited Adverse Events: Incidence of Related Adverse Events by Preferred Term and System Organ Class (Per Subject) by Age Band – FAS

15.3.2 Serious Adverse Events/Adverse Events of Special Interest

15.3.2.1 Serious Adverse Events (Per Vaccination Period): Incidence by Preferred Term and System Organ Class – FAS

15.3.2.2 Adverse Events of Special Interest (Per Vaccination Period): Incidence by Preferred Term and System Organ Class – FAS

15.3.3 Laboratory Results
15.3.3.1 Laboratory Data (Mean Values): Hematology – FAS
15.3.3.2 Laboratory Data (Mean Values): Biochemistry – FAS
15.3.3.3 Laboratory Data (Mean Values): CD4 – FAS
15.3.3.4 Laboratory Data (Mean Values): Viral Load – FAS
15.3.3.5 Laboratory Data (Shift Table): Hematology – FAS
15.3.3.6 Laboratory Data (Shift Table): Biochemistry – FAS
15.3.3.7 Laboratory Data (Shift Table): CD4 – FAS

15.3.4 Vital Signs and ECG Data
15.3.4.1 Vital Signs – FAS
15.3.4.2 ECG Data: Global Information – FAS
15.3.4.3 ECG Data (Shift Table): Global Information – FAS
15.3.4.4 ECG Data: Investigator Assessment – FAS

5.2 Listings

16.2.1 Disposition and Demographics
16.2.1.1 Disposition
16.2.1.1.1 Eligibility for Trial Participation - Subjects not Eligible for the Trial – All Subjects
16.2.1.1.2 Violation of Inclusion Criteria – All Subjects
16.2.1.1.3 Exclusion Criteria Fulfilled – All Subjects
16.2.1.1.4 Overall Assessment – FAS
16.2.1.1.5 Booster Vaccination – FAS
16.2.1.1.6 Disposition – FAS
16.2.1.1.7 Protocol Deviations – FAS
16.2.1.1.8 Sample Handling Deviations – FAS

16.2.1.2 Demographics
16.2.1.2.1 Demographic Data – All Subjects
16.2.1.2.2 History of HIV Infection – All Subjects
16.2.1.2.3 Cardiac Risk and Smallpox Vaccination History – All Subjects

16.2.1.3 Medical History
16.2.1.3.1 Medical History – FAS
16.2.1.3.2 Pre-treatment Adverse Events – FAS
16.2.1.3.3 Pre-treatment Serious Adverse Events - FAS
16.2.1.3.4 Pre-treatment Adverse Events of Special Interests - FAS
16.2.1.3.5 Abnormal Physical Examination at Screening – FAS
16.2.1.3.6 HIV-Related Illnesses – FAS
16.2.1.3.7 AIDS Defining Conditions – FAS

16.2.1.4 Prior and Concomitant Medication
16.2.1.4.1 Prior Medication – FAS
16.2.1.4.2 Concomitant Medication – FAS
16.2.1.4.3 Concomitant HIV-Related Medication – FAS

16.2.1.5 Compliance
16.2.1.5.1 Dates of Visits, Blood Sampling and Visit Intervals – FAS
16.2.1.5.2 Investigational Product Administration – FAS

16.2.2 Immunogenicity Listings
16.2.2.1 PRNT Titers, Seropositivity and Seroconversion – FAS
16.2.2.2 ELISA Titers, Seropositivity and Seroconversion – FAS

16.2.3 Safety Listings
16.2.3.1 Adverse Events
16.2.3.1.1 Unsolicited Adverse Events
16.2.3.1.1.1 Unsolicited Adverse Events – FAS
16.2.3.1.1.2 Unsolicited Adverse Drug Reactions – FAS
16.2.3.1.1.3 Grade ≥ 3 Unsolicited Adverse Events – FAS
16.2.3.1.1.4 Grade ≥ 3 Unsolicited Adverse Drug Reactions – FAS

16.2.3.1.2 Solicited Local Adverse Events
16.2.3.1.2.1 Injection Site Pain – FAS
16.2.3.1.2.2 Injection Site Erythema – FAS
16.2.3.1.2.3 Injection Site Swelling – FAS
16.2.3.1.2.4 Injection Site Induration – FAS
16.2.3.1.2.5 Injection Site Pruritus – FAS

16.2.3.1.3 Solicited General Adverse Events
16.2.3.1.3.1 Body Temperature Increased – FAS
16.2.3.1.3.2 Headache – FAS
16.2.3.1.3.3 Myalgia – FAS
16.2.3.1.3.4 Chills – FAS
16.2.3.1.3.5 Nausea – FAS
16.2.3.1.3.6 Fatigue – FAS

16.2.3.1.3.7 Related Body Temperature Increased – FAS
16.2.3.1.3.8 Related Headache – FAS
16.2.3.1.3.9 Related Myalgia – FAS
16.2.3.1.3.10 Related Chills – FAS
16.2.3.1.3.11 Related Nausea – FAS
16.2.3.1.3.12 Related Fatigue – FAS

16.2.3.2 Serious Adverse Events/Adverse Events of Special Interest
16.2.3.2.1 Serious Adverse Events – FAS

16.2.3.2.2 Adverse Events of Special Interest– FAS
16.2.3.2.3 Adverse Events of Special Interest: Cardiac Follow-up – FAS

16.2.3.3 Laboratory Data
16.2.3.3.1 Laboratory Data: Hematology – FAS
16.2.3.3.2 Laboratory Data: Hematology – Abnormal Values - FAS
16.2.3.3.3 Laboratory Data: Biochemistry – FAS
16.2.3.3.4 Laboratory Data: Biochemistry – Abnormal Values - FAS
16.2.3.3.5 Laboratory Data: HIV – FAS
16.2.3.3.6 Laboratory Data: Pregnancy Test Results (Female Subjects Only) – FAS
16.2.3.3.7 Laboratory Data: Laboratory Normal Ranges - FAS
16.2.3.3.8 Laboratory Data: Laboratory Comments – FAS

16.2.3.4 Vital Signs and ECG data
16.2.3.4.1 Vital Signs – FAS
16.2.3.4.2 ECG Data: Investigator and Central Assessment – FAS
16.2.3.4.3 Targeted Physical Examination – FAS

5.3 Figures

Figure 1.1.1: ELISA GMTs at all Visits – PPS
Figure 1.1.2: ELISA GMTs at all Visits – FAS
Figure 1.2.1: PRNT GMTs at all Visits – PPS
Figure 1.2.2: PRNT GMTs at all Visits – FAS
Figure 1.3.1: ELISA Seroconversion Rates at all Visits – PPS
Figure 1.3.2: ELISA Seroconversion Rates at all Visits – FAS
Figure 1.4.1: PRNT Seroconversion Rates at all Visits – PPS
Figure 1.4.2: PRNT Seroconversion Rates at all Visits – FAS

Figure 2.1: Median CD4 counts by Visit – FAS