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

18-NOV-2014

NCT02038881

1 General Information

1.1 Investigator Signature Page

Herewith I agree that I have read and fully understand this protocol:

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.

This protocol describes necessary information to conduct the trial. I agree that I will conduct the trial according to the instructions given within this protocol. Furthermore, I agree that I will conduct this trial according to International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the 2013 version of the Declaration of Helsinki, as well as applicable local legal and regulatory requirements in the respective countries. I agree that all information revealed in this protocol is handled strictly confidentially.

Additionally, I will permit trial related monitoring, audits, Institutional Review Board (IRB) / Independent Ethics Committee (IEC) review and regulatory inspections, providing direct access to source data/documents.

_____ _____

Date [name]
Principal Investigator (PI), [site]

_____

_____

_____
[clinical trial site address]

1.2 Coordinating Investigator Signature Page

Herewith I agree that I have read and fully understand this protocol:
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.
I agree, that the protocol was written according to international ethical and scientific quality standards (ICH-GCP), in compliance with the 2013 version of the Declaration of Helsinki and applicable local legal and regulatory requirements in the respective countries.

1.3 Sponsor Signature Page

By signing the protocol:

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.

The undersigned parties agree, that the protocol was written according to international ethical and scientific quality standards (ICH-GCP), in compliance with the 2013 version of the Declaration of Helsinki and applicable local legal and regulatory requirements in the respective countries.

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1.4 Responsibilities

Trial Number	POX-MVA-037
Title	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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List of Abbreviations

AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
BN	Bavarian Nordic
CD	Cluster of Differentiation
CDISC	Clinical Data Interchange Standards Consortium
CrCl	Creatinine Clearance
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CTS	Clinical Trial Site
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
DS	Drug Safety
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF(s)	Electronic Case Report Form(s)
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
HDL	High-density Lipoprotein
GMT	Geometric Mean Titer
HCG	Human Choriogonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem Cell Transplant
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LDL	Low-density Lipoprotein
LF	Liquid frozen

LLN	Lower Limit of Normal
LV	Left Ventricular
MCH	Mean Corpuscular/cellular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular/cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMWR	Morbidity and Mortality Weekly Report
MP	Medicinal Product
MPXV	Monkeypox Virus
MVA	Modified Vaccinia Ankara Strain
MVA-BN®	Modified Vaccinia Ankara – Bavarian Nordic also named IMVAMUNE® or IMVANEX®
N/A	Not Applicable
n/N	Number
NHP	Non-Human Primates
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NYCBH	New York City Board of Health
ODM	Operational Data Modeling
PCR	Polymerase Chain Reaction
PEI	Paul Ehrlich Institut
PI	Principal Investigator
PPS	Per Protocol Set
PRNT	Plaque Reduction Neutralization Test
PVC	Premature Ventricular Contractions
RDW	Red Blood Cell Distribution Width
RNA	Ribonucleic Acid
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SCR	Screening
SD	Standard Deviation
SOP	Standard Operating Procedure
$TCID_{50}$	Tissue Culture Infectious Dose 50%
ULN	Upper Limit of Normal
US(A)	United States (of America)
V	Visit
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VACV	Vaccinia Virus
WBC	White Blood Cell Count
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1.5 Protocol Synopsis

Title	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
Clinical phase	Phase II
Sponsor	Bavarian Nordic A/S (b) (1) (A) [redacted]
Coordinating Investigator	(b) (1) (A) [redacted]
Number of sites and Country/ies	Up to 10 sites in the USA
Vaccination dose and schedule	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 week 12 (booster regimen)

Route of administration	Each MVA-BN® vaccination is administered subcutaneously (s.c.) in the upper arm.
Trial duration	Up to 75 weeks per subject
Sample size	90 (30 subjects per group)
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
Secondary objectives	To compare the immunogenicity and safety of three different vaccination strategies of MVA-BN® smallpox vaccine
Primary endpoint	Occurrence, relationship and intensity of any serious and / or unexpected Adverse Event at any time during the trial.
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) possibly, probably 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 7 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 7 days) after each vaccination.

Change in CD4 T cell counts in Human Immunodeficiency Virus (HIV)-infected subjects two weeks after each vaccination.

Trial design

Multicenter, randomized

Groups	N	Dose ($TCID_{50}$) per injection (0.5 ml)	Number of Injections	Vaccinations (Weeks)
1	30	at least 1 x 10^8/ml	Standard regime	0 - 4
2	30	at least 1 x 10^8/ml	Two injections at each time point	0 - 4
3	30	at least 1 x 10^8/ml	Standard regime + additional boost	0 - 4 - 12

Visit Schedule:

Visit (V)	Day	Target Week	Vaccination
SCR	Day -28 to -1	-4	
V1	Day 0	0	X
V2	V1 + 12 to 16 days	2	
V3	V1 + 28 to 35 days	4	X
V4	V3 + 12 to 16 days	6	
V5	V3 + 28 to 35 days	8	
V6*	V1+ 84 to 96 days	12	X*
V7*	V6 + 12 to 16 days	14	
V8*	V6 + 28 to 35 days	16	
FU 1	V3 (V6*) +182 to 210 days	30 (38*)	
FU 2	V3 (V6*) +364 to 392 days	56 (64*)	
*only Group 3			

Subject entry criteria

Inclusion criteria

1. Male and female subjects aged between 18-45 years, vaccinia-naïve.
2. HIV-1 infection documented by ELISA and confirmed by Western blot at any time prior to study entry. HIV-1 deoxyribonucleic acid (DNA) polymerase chain reaction (PCR), plasma HIV-1 ribonucleic acid (RNA), or a second antibody test other than ELISA is acceptable as an alternative confirmatory test at any time prior to trial entry. If an original of the test result cannot be obtained anymore but the subject was diagnosed as

described and details on how and when the subject was diagnosed are documented in the subjects source data/medical records by a current or previous physician or the PI, this is sufficient and the subject can be enrolled in the trial.

3. On stable antiretroviral therapy (ART) i.e. Combination ART for at least three months prior to screening visit in this clinical trial with no change to the therapy during these three months.
4. Screening HIV-1 RNA < 200 copies/ml
5. Screening CD4 counts ≥ 100 cells/µl and ≤ 500 cells/µl.
6. Documented nadir CD4 count < 200 cells/µl at any time prior to screening visit. If nadir is not documented lowest documented CD4 count < 200 cells/µl at any time prior to screening visit.
7. Hemoglobin ≥ 9.0 g/dl for female subjects, ≥ 10.0 g/dl for male subjects.
8. Platelets ≥ 100,000/mm^3.
9. Ability and willingness of subject to provide written informed consent.
10. Body Mass Index (BMI) ≥ 18.5 and < 35 kg/m^2.
11. Women of childbearing potential (WOCBP) must have used an acceptable method of contraception for 30 days prior to the first vaccination, must agree to use an acceptable method of contraception during the trial, and must avoid becoming pregnant for at least 28 days after the last vaccination. A woman is considered of childbearing potential unless post-menopausal (defined as ≥ 12 months without a menstrual period) or surgically sterilized. Acceptable contraception methods are restricted to abstinence, barrier contraceptives, intrauterine contraceptive devices or licensed hormonal products.
12. WOCBP must have a negative serum pregnancy test at screening (SCR) and a negative urine pregnancy test within 24 hours prior to each vaccination.
13. Absolute neutrophil cell count ≥ 750/mm^3.
14. Adequate renal function defined as a calculated Creatinine Clearance (CrCl) > 60 ml/min as estimated by the Cockcroft-Gault equation.

a) For men: (140 – age in years) x (body weight in kg) ÷ (serum creatinine in mg/dl x 72) = CrCl (ml/min)
b) For women: multiply the result for men by 0.85 = CrCl (ml/min).

15. Adequate hepatic function defined as: Total bilirubin ≤ 2 x upper limit normal (ULN) in the absence of other evidence of significant liver disease. Subjects with elevated bilirubin due to an Atazanavir therapy can be enrolled. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase ≤ 2.5 x ULN.
16. Screening Troponin I < 2 x ULN .

17. Electrocardiogram (ECG) without clinically significant findings (e.g. any kind of atrioventricular or intraventricular conditions or blocks such as complete left or right bundle branch block, AV node block, QTc or PR prolongation, premature atrial contractions or other atrial arrhythmia, sustained ventricular arrhythmia, two premature ventricular contractions (PVC) in a row, ST elevation consistent with ischemia).

Exclusion criteria

1. Pregnant or breast-feeding women.
2. Typical vaccinia scar.
3. Known or suspected history of smallpox vaccination.
4. History of vaccination with any poxvirus-based vaccine.
5. Uncontrolled serious infection, i.e. not responding to antimicrobial therapy.
6. History of any serious medical condition, which in the opinion of the investigator would compromise the safety of the subject or would limit the subject's ability to complete the trial including uncontrolled diabetes as according to the 'Division of Acquired Immune Deficiency Syndrome (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events' Version 1.0, December 2004, Clarification August 2009.
7. History of or active autoimmune disease. Persons with vitiligo or thyroid disease taking thyroid replacement are not excluded.
8. Known or suspected impairment of immunologic function except those defined in the inclusion criteria, including, but not limited to clinically significant liver disease, diabetes mellitus type I and moderate to severe kidney impairment.
9. History of malignancy other than squamous cell or basal cell skin cancer, unless there has been surgical excision that is considered to have achieved cure. Subjects with history of skin cancer must not be vaccinated at the previous tumor site. Subjects with a history of Kaposi sarcoma who did not have a surgical excision, are clinically stable and are in remission are not excluded.
10. History or clinical manifestation of clinically significant and severe hematological, pulmonary, central nervous, cardiovascular or gastrointestinal disorders (except HIV infection, chronic or active Hepatitis-B-Virus or Hepatitis-C-Virus infection).
11. Clinically significant psychiatric disorder not adequately controlled by medical treatment.
12. History of coronary heart disease, myocardial infarction, angina pectoris, congestive heart failure, cardiomyopathy, stroke or transient ischemic attack, uncontrolled high blood pressure, or any other heart condition under the care of a doctor.
13. Known history of an immediate family member (father, mother, brother, or sister) who has had onset of ischemic heart disease before age 50 years.

14. Ten percent or greater risk of developing a myocardial infarction or coronary death within the next 10 years using the National Cholesterol Education Program's risk assessment tool (http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof). NOTE: This criterion applies only to subjects 20 years of age and older.
15. Current alcohol abuse (40 g/day for at least six months) and/or intravenous and/or intranasal drug abuse (within the past six months).
16. Known allergy to MVA-BN® vaccine or any of its constituents, e.g. tris (hydroxymethyl)-amino methane, including known allergy to egg or aminoglycosides.
17. History of anaphylaxis or severe allergic reaction to any vaccine.
18. Acute disease (illness with or without a fever) at the time of screening or at any time of vaccine administration.
19. Body temperature ≥100.4°F (≥38.0°C) at the time of screening or at any time of vaccine administration.
20. Having received any vaccinations or planned vaccinations with a live vaccine within 30 days prior to or after trial vaccination.
21. Having received any vaccinations or planned vaccinations with a killed vaccine within 14 days prior to or after trial vaccination.
22. Use of immunosuppressant or immunomodulatory agents including systemic glucocorticoids (excluding nasal or inhaled steroids), tacrolimus, sirolimus, rapamycin, mycophenolate, cyclosporine, TNF-alpha blockers or antagonists, azathioprine, interferon or growth factors, or intravenous immunoglobulin in the 60 days prior to screening in this clinical trial.
23. Post organ and/or stem cell transplant subjects whether or not receiving chronic immunosuppressive therapy.
24. Administration or planned administration of immunoglobulins and/or any blood products during a period starting from three months prior to administration of the vaccine and ending at last physical trial visit.
25. Use of any investigational or non-registered drug or vaccine other than the trial vaccine within 30 days preceding the first dose of the trial vaccine, or planned administration of such a product during the trial period.
26. Trial personnel.

1.6 Trial Procedure Schedule

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		
Obtaining blood for safety lab[4]	X		X		X			X		(X)[1]	(X)[1]

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*)**
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			
Blood volume											
Appr. blood volume drawn (ml)[4,5]	13	9	13	9	18	0	9	18	2	11	11
Cumulative blood volume drawn (ml)[4]	13	22	35	44	62	62	71	89	91	102	113

*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] Approximate amounts of single blood draws: Safety lab including all tests: 7 ml; immunogenicity testing: 9 ml; viral load: 4ml; /CD4 count: 2 ml.

[6] Review of acceptable contraceptive methods and recent menstrual history with 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 FU2.

2 Background Information and Scientific Rationale

2.1 Introduction

Despite the fact that the World Health Organization (WHO) officially declared successful global eradication of smallpox in 1980, the existence of variola stockpiles and the threat of bioterrorism demands to maintain immunity to smallpox through vaccination. After the events of September 11th, 2001, concern over the use of bioweapons as agents of terrorism increased (McCurdy, 2004). As mass vaccination programs halted more than 30 years ago, it is estimated that the majority of the world population has no existing immunity to smallpox, and as such, the release of this highly contagious virus would have devastating effects. As a consequence, there is an urgent need for a safe and efficacious vaccine to protect the public against smallpox including also the immunocompromised population.

Bavarian Nordic A/S (BN), an international biopharmaceutical company, is developing a proprietary strain of Modified Vaccinia Ankara (MVA [MVA BN®, trade name IMVAMUNE® outside the European Union {EU}, invented name IMVANEX® in the EU]) for use as a prophylactic vaccine protecting against smallpox infection. For IMVANEX® a marketing authorization under exceptional circumstances was granted on 31 July 2013. BN filed a New Drug Submission with Health Canada in 2011 under the invented name IMVAMUNE®. A marketing authorization for IMVAMUNE® was granted in November 2013.

2.2 First Generation Smallpox Vaccines

The original smallpox vaccines were based on a number of different Vaccinia Virus (VACV) strains, e.g. Lister-Elstree strain recommended by the WHO and used primarily in Europe or the New York City Board of Health (NYCBH, Dryvax®) strain used in the United States of America (USA). While these proved to be highly effective immunizing agents making the eradication of smallpox possible, they also showed considerable side effects. Besides local reactions with scab development and scarring, general symptoms observed frequently after smallpox vaccination have been pyrexia, weakness, muscular pain, headache, swelling and soreness of local lymph nodes and rashes. Apart from less dramatic and transient side effects like erythematous or urticarial rashes, severe and potentially fatal cutaneous complications of VACV vaccination include eczema vaccinatum and progressive vaccinia. Most feared are complications of the central nervous system, especially post-vaccinal encephalitis, which lead to death in 15-25% of cases and in 25% to neurologic sequelae (Goldstein, 1975; Lane, 1969; Lane, 1970). Even though some countries such as the USA excluded high-risk individuals from vaccination, an average of seven persons per year still died from complications due to smallpox vaccination during the eradication campaign (McElwain, 1972).

Replication competent smallpox vaccines could be lethal if given to immune compromised individuals and are therefore contraindicated for e.g. persons who have received organ transplantation, persons with cancer, Atopic Dermatitis (AD) or HIV infection. A trial published in 1991 (Guillaume, 1991) reported two cases of HIV-infected, immunocompromised patients who experienced necrotic skin lesions due to generalized vaccinia infections that led to death.

However, complications following vaccinations with vaccinia can also occur in HIV-infected individuals with T cell counts in the normal range and who are otherwise healthy (Redfield, 1987).

Traditionally, successful vaccination with a smallpox vaccine was assessed based on the formation of a vesicle ("take") at the inoculation site seven to nine days after vaccination. Recent clinical trials using Dryvax® confirmed a success rate by vesicle formation in vaccinia-naïve volunteers of 95 to 99% (Frey, 2002; ACAM2000 Vaccines and Related Biological Products Advisory Committee [VRBPAC] Briefing Document, 2007).

2.3 Second Generation Smallpox Vaccines

Second generation smallpox vaccines are derived from first generation VACV strains by plaque purification and manufactured in cell cultures according to modern Good Manufacturing Practice standards (Monath, 2004). Vaccination of individuals with these vaccines is performed in the same way as with first generation smallpox vaccines, namely by intradermal administration (scarification) of a single dose.

ACAM2000® developed by Acambis Inc. is based on the Dryvax® NYCBH strain (Monath, 2004). In preparation of a Biologics License Application at the FDA, two pivotal Phase III clinical trials were conducted enrolling either vaccinia-naïve or vaccinia-experienced populations. The trials were designed to compare the safety, tolerability and efficacy of ACAM2000® and Dryvax®. In total, the ratio of individuals in these trials receiving ACAM2000® and Dryvax® was 3:1 (ACAM2000 Vaccines and Related Biological Products Advisory Committee [VRBPAC] Briefing Document, 2007).

Safety information available from these trials suggests that non-serious adverse reactions were typical for vaccines administered by injection or scarification. The majority (99% and 97% respectively) of subjects experienced at least one treatment-emergent AE after vaccination. The AEs most commonly reported fell into four distinct categories: reactions at the vaccination site, lymphadenitis, constitutional "flu-like" symptoms and minor gastrointestinal symptoms. Of special interest, however, were a total of 10 serious cases of myo-/pericarditis that were reported within the ACAM2000® development program. In a vaccinia-naïve population of 1,675 subjects, these events occurred in seven subjects treated with ACAM2000® (5.73 events per thousand vaccinations) and in three subjects having received Dryvax® (10.38 events per thousand vaccinations for a combined calculated incidence of 5.97 cases of myo-/pericarditis per thousand vaccinations (95% confidence interval of 2.87 to 10.95 cases per thousand). These figures represent quite a high rate of potentially life-threatening serious AE following vaccination with a prophylactic vaccine.

Vaccine efficacy data were collected to demonstrate non-inferiority compared to Dryvax® based on the efficacy parameters of major cutaneous reaction ("take") rates and neutralizing antibody titers against VACV using a PRNT in both trials. Enrolling vaccinia-naïve subjects in one of the two trials, non-inferiority against Dryvax® could be shown for take rates, but not for antibody titers. On the contrary, for the trial population of vaccinia-experienced subjects enrolled in the second Phase III trial, non-inferiority against Dryvax® could be determined for neutralizing

antibody titers, but not for take rates. Taken together, two of the four targeted efficacy measures were met in these trials.

Based on the safety and efficacy data collected in these pivotal Phase III trials, the FDA approved ACAM2000® in September 2007 for use in vaccinia-naïve as well as vaccinia-experienced healthy populations, issuing a black box warning on the prescribing information for the special risks of this conventional second generation smallpox vaccine.

2.4 Origin and Characteristics of MVA-BN® Smallpox Vaccine

VACV is considered the best known member of the poxvirus family and the prototype of a live viral smallpox vaccine. VACV replicates in the cytoplasm of the host cell, its DNA does not integrate into the host cell genome and it is non-oncogenic.

MVA was derived from the serial passage of Chorioallantois Vaccinia Ankara, a VACV strain used during the smallpox eradication program. During this passaging, MVA suffered a multitude of mutations within its genome, including six major deletions, resulting in the loss of 15% (31kbp) of original genetic information (Antoine, 1998). The deletions affected a number of virulence and host range genes (Antoine, 1998; Rosel, 1986; Meyer, 1991) and as a consequence, MVA exhibits a severely restricted host range in most mammalian cell types (Sutter, 1992; Carroll, 1997; Blanchard, 1998; Drexler, 1998). Although MVA exhibits a strongly attenuated replication in these cell types, its genes are efficiently transcribed with the block in viral replication being at the level of virus assembly and egress (Sutter, 1992; Carroll, 1997).

MVA-BN® vaccine has been derived from MVA-572 and is a highly attenuated, purified live vaccine produced under serum-free conditions in chicken embryo fibroblasts cells. In contrast to the first and second generation smallpox vaccines MVA-BN® is not administered by scarification. The standard route and schedule of MVA-BN® are two subcutaneous injections administered four weeks apart. Since MVA-BN® is non-replicating in human cells it does not form vesicles (“takes”) (Mayr, 1975).

For further details on MVA-BN®, please refer to the relevant sections in the Investigator’s Brochure.

2.5 Summary of Nonclinical Studies with MVA-BN® Smallpox Vaccine

An extensive nonclinical development program has demonstrated the safety, efficacy and bio-equivalence of MVA-BN® compared to other traditional smallpox vaccines.

The studies conducted demonstrated the superior attenuation profile of MVA-BN® compared to traditional smallpox vaccines (e.g. ACAM2000®, Dryvax®) as well as other MVA strains. MVA-BN® does not replicate in any of the human cell lines tested (Chaplin, 2002) and is not lethal for severely immunocompromised animals (Suter, 2009). Repeated administrations (s.c. or intra-muscular) of MVA-BN® resulted in injection site irritations and some lymphoid changes; however, these effects were minimal and self-limited and are therefore not considered to be dose-limiting.

Two developmental toxicity studies in rats and rabbits demonstrated that none of the tested doses of MVA-BN® vaccine (1×10^7 $TCID_{50}$ or 1×10^8 $TCID_{50}$) were teratogenic or caused intrauterine toxicity to the fetuses. In a peri- and postnatal study in rats MVA-BN® did not have any effect on the dams or the intrauterine development of the embryos. Furthermore, it did not have any effect on the lactating females or their developing offspring.

Non-clinical studies on immunogenicity and efficacy demonstrated that MVA-BN® smallpox vaccine induces a comparable immune response (antibodies and T cells) as traditional smallpox vaccines (ACAM2000®, Dryvax® and Elstree) in both mice and non-human primates (NHP) (Stittelaar, 2005). A linear correlation between vaccine dose and antibody responses (total and neutralizing antibodies) induced by MVA-BN® could be demonstrated in mice and NHP (and in human subjects). This correlation translated into a vaccine dose related protection of NHP from lethal challenge with monkeypox virus (MPXV), indicating that antibodies are good predictive correlates for protection, reasonably likely to predict clinical efficacy. Indeed, the correlation of the fit between PRNT titers (induced by MVA-BN®) and the probability of survival from a lethal MPXV challenge was 0.9992, demonstrating a highly significant correlation between neutralizing antibodies and protection ($p = 0.00076$). Similarly, the correlation of the fit between ELISA titers (induced by MVA-BN®) and the probability of survival from a lethal MPXV challenge was 0.9966, demonstrating a highly significant correlation between total antibodies and protection ($p = 0.00336$).

For more detailed information on preclinical data please refer to the respective sections of the Investigator's Brochure.

2.6 Clinical Profile of MVA-BN® Smallpox Vaccine

To date, 16 clinical trials (11 sponsored by BN, thereof seven under Investigational New Drug (IND) 11596; five sponsored by the Division of Microbiology and Infectious Diseases (DMID), NIAID, NIH under IND 11229) evaluating the safety and immunogenicity of MVA-BN® have been completed. Currently five clinical trials are ongoing - four sponsored by BN under IND 11596 and IND 15316, respectively; one sponsored by the DMID (NIAID, NIH) under IND 11229). As of September 1, 2013 3,452 subjects have been vaccinated with MVA-BN® in

completed clinical trials, including risk groups with contraindications to conventional smallpox vaccines, such as HIV- infected patients and patients with AD.

2.6.1 Safety Overview of MVA-BN®

In all completed and ongoing clinical trials, vaccinations with MVA-BN® have shown to be generally safe and well tolerated. No cases of death, assessed as being even possibly related, have been reported for a subject in a clinical trial using MVA-BN®.

Serious Suspected Adverse Drug Reactions

A total of eight (8 out of 7,428 vaccinated subjects = 0.11%) serious suspected Adverse Drug Reactions (ADRs) have been reported for MVA-BN® smallpox vaccine so far (see Table 2). All of them have been thoroughly reviewed by BN and the trial specific Data Safety Monitoring Board (DSMB), who concluded that the continued use of MVA-BN® in a clinical setting presented no special risks to the subjects. No pattern regarding Serious ADRs (SADRs) could be detected.

In the ongoing clinical trial POX-MVA-013, in which 4,005 subjects have been recruited until September 1, 2013, one serious ADR is reported (see Table 2). As the trial is not unblinded yet, it is unknown whether the case occurred in the Placebo or in the MVA-BN® group.

Adverse Drug Reactions

Suspected ADRs were reported in completed clinical trials POX-MVA-001, -002, -004, -005, -007, -008, -009, -010, -011, -023, -024, -028, -029 -030, HIV-NEF-004 and HIV-POL-002 (N = 3,445) as following (see Table 1):

Table 1 Frequency of Adverse Drug Reactions

MedDRA* System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare+ (≥1/10,000 to <1/1,000)
Infections and Infestations	-	-	Nasopharyngitis Influenza Upper respiratory tract infection	Sinusitis Conjunctivitis
Blood and Lymphatic System Disorders	-	-	Lymphadenopathy	-
Metabolism and Nutrition Disorders	-	Appetite disorder	-	-
Psychiatric Disorders	-	-	Sleep disorder	-
Nervous System Disorders	Headache	Dizziness	Paraesthesia	Peripheral sensory neuropathy
Ear and Labyrinth Disorders	-	-	Vertigo	-
Cardiac Disorders	-	-	-	Tachycardia
Respiratory, Thoracic and Mediastinal	-	-	Pharyngolaryngeal pain	-

MedDRA* System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare+ (≥1/10,000 to <1/1,000)
Disorders			Rhinitis Cough	
Gastrointestinal Disorders	Nausea	-	Diarrhoea Vomiting Dry mouth Abdominal Pain	-
Skin and Subcutaneous Tissue Disorders	-	-	Rash Pruritus Dermatitis Skin discolouration Ecchymosis Hyperhidrosis Urticaria	Night sweats Angioedema
Musculoskeletal and Connective Tissue Disorders	Myalgia	Pain in extremity Arthralgia	Back pain Neck pain Musculoskeletal stiffness Muscle spasms	Musculoskeletal pain Muscular weakness
General Disorders and Administration Site Conditions	Injection site pain Injection site erythema Injection site induration Injection site swelling Injection site pruritus Fatigue	Injection site discolouration Injection site nodule Injection site haematoma Injection site warmth Chills Underarm swelling	Injection site irritation Injection site haemorrhage Injection site exfoliation Injection site paraesthesia Injection site inflammation Injection site reaction Injection site rash Injection site movement impairment Application site anesthesia Flushing Axillary pain Chest pain Asthenia Malaise	Oedema peripheral
Investigations	-	Body temperature increased Troponin I increased Pyrexia	Hepatic enzyme increased White blood cell count decreased Mean platelet volume decreased White blood cell count increased	-
Injury, Poisoning and Procedural Complications	-	-	Contusion	-

* Medical Dictionary for Regulatory Activities (MedDRA)
+ Rare for which 3 events were recorded

Looking only at the events that were reported by at least 1% of subject, the majority of ADRs represented local vaccination site reactions as well as common systemic reactions typical for modern injectable vaccines and were classified as being mild to moderate. Overall, the ADRs reported to date following multiple administrations with MVA-BN® in healthy or various special populations, be it vaccinia-experienced or vaccinia-naïve, are comparable in frequency and have not identified any particular safety risks for the vaccine.

The current Investigator's Brochure provides more details on frequencies of suspected ADRs according to System of Organ Class and Preferred Term reported in completed clinical trials and a comparison of suspected ADRs reported by ≥1% of immunocompromised subjects vaccinated with MVA-BN®.

Cardiac Signs and Symptoms

Based on observations with first and second generation smallpox vaccines (see Sections 2.2 and 2.3), particular attention has been placed on monitoring for cardiac signs and symptoms in all clinical trials using MVA-BN®. Despite close cardiac monitoring, no event indicating a case of myo-/pericarditis has been observed in any completed MVA-BN® trial.

Table 2 Serious Suspected ADRs (SAEs Assessed by the Investigator to be at Least Possibly Related to MVA-BN®)

Trial	Age/ Gender	Days After Vaccination	Event	Outcome	Underlying Diseases/ Circumstances	Investigator Assessment	BN Opinion
POX-MVA-005	30/Male	70 days after 2nd vaccination	Sarcoidosis	Stable and asymptomatic	Urinary tract infection with Chlamydia trachomatis at time of first symptoms (arthralgia)	Possibly related	Possibly related
POX-MVA-005	31/Female	26 months after 2nd vaccination	Crohn's disease	Stable and asymptomatic under therapy	Abnormal lab results (elevated alkaline phosphatase, absolute neutrophils and platelet counts) at screening for 2-year follow-up study POX-MVA-023 (excluded)	Possibly related	Possibly related
POX-MVA-008	28/Female	8 days after 2nd vaccination	Transitory ocular muscle paresis	Resolved without sequelae	No relevant medical history	Probably related	Possibly related
POX-MVA-010	30/Female	133 days after 2nd vaccination	Congestive heart failure due to cardiomyopathy	Stable under cardiac medications	Surgery for ventricular septal defect as child. HIV infection. Concomitant (denied, therefore previously unknown to BN) participation in a Growth-Hormone Releasing Hormone study; event also assessed as possibly related to Growth-Hormone Releasing Hormone	Possibly related	Unlikely related
POX-MVA-011	39/Female	1 day after 2nd vaccination	Simple pneumonia and pleurisy	Resolved without sequelae	HIV infection (CD4 count four weeks prior to second vaccination was 299 cells/µl). History of chronic obstructive pulmonary disease. Acute sinusitis and nasal congestion due to swimmer's ear which triggered hospital admittance.	Possibly related	Unlikely related
POX-MVA-013*	24/Male	5 days after 1st vaccination	Seizure	Resolved without sequelae	The subject has a family history as well as a previous history of grand mal seizures in childhood, which is considered to be a risk factor for the re-emergence of seizure episodes.	Possibly related	Unlikely related
POX-MVA-036	27/Female	0 days after 2nd vaccination	Throat tightness and other hypersensitivity symptoms such as hives, pruritus, tender vaccination site, swollen axilla, angioedema of forearms	Resolved without sequelae	The subject received her second dose of MVA-BN 21 days after the first dose and after 2 hours developed symptoms such as skin reactions and throat tightness which was responsive to epinephrine treatment. She had no wheezing and was not hypotensive. Symptoms subsided after several days under prednisone and diphenhydramine treatment. She has a family history of allergies and a	Possibly related	Possibly related

Trial	Age/ Gender	Days After Vaccination	Event	Outcome	Underlying Diseases/ Circumstances	Investigator Assessment	BN Opinion
					medical history of shingles. She has received multiple vaccines before but never had previous hives or other problems with vaccines.		
POX-MVA-036	30/Male	117 days after 1st vaccination	Non ST segment elevation myocardial infarction	Resolved without sequelae	Positive family history for cardiovascular diseases (both grandfathers had myocardial infarctions in their 50ies, father had blood clots), as well as overweight with a BMI above 33. A few days before event onset, subject returned from a trip to India with diarrhoea and was started on ciprofloxacine treatment (which per US prescribing information is associated with angina pectoris and myocardial infarction). He showed chest pain and increased troponin I, but no ST segment changes in the ECG and no coronary artery disease in cardiac catheterization. A post-infectious myocarditis (published case reports exist for campylobacter, shigella, salmonella) was considered as alternative etiology for the reported event.	Possibly related	Unlikely related

* This trial is still blinded, vaccination wither either MVA-BN® or Placebo.

2.6.2 Safety of MVA-BN® Smallpox Vaccine Given in High Dose

A single high dose of MVA-BN® (5 x 10^8 $TCID_{50}$) has been tested in 45 subjects in a NIH sponsored trial. The occurrence of serious and non-serious adverse events associated with vaccination and the local and systemic reactogenicity were compared to that elicited by the standard dose regimen of MVA-BN®. No significant difference in the number or severity of solicited or unsolicited adverse events or the number of events associated with vaccine between the high dose group and the standard dose group were observed. The only severe events that occurred in the study were reactogenicity (i.e. solicited) events. No serious events or severe unsolicited adverse events were reported. This study has shown that the safety profile of a high dose of MVA-BN® is comparable to that of the standard dose (see further details in the Investigator's Brochure).

2.6.3 Safety Profile of MVA-BN® Smallpox Vaccine in Healthy Compared to Special Populations

MVA-BN® smallpox vaccine has been tested in nearly 1,000 subjects with contraindications to conventional smallpox vaccines, i.e. individuals diagnosed with HIV infection or AD and hematopoietic stem cell transplant recipients (Walsh, 2013). In two separate Phase II trials (POX-MVA-010 [Greenberg, 2013] and POX-MVA-011) the safety of MVA-BN® smallpox vaccine in healthy subjects and subjects infected with HIV has been directly compared. When comparing the frequencies of overall ADRs the results from both trials revealed a comparable safety profile for healthy and HIV-infected subjects following vaccinations with MVA-BN® smallpox vaccine.

The POX-MVA-011 trial was designed to evaluate safety and immunogenicity in HIV-infected subjects after vaccination with the MVA-BN® smallpox vaccine compared to healthy subjects. The trial population in the full analysis set (FAS) consisted of 97 healthy, vaccinia-naive and vaccinia-experienced subjects as a control group compared to 482 vaccinia-naïve and experienced HIV-infected subjects. Their CD4 counts at time of trial enrollment ranged from 200-750 cells/µl which was split in three subgroups based on their CD4 counts (Table 3) for further analysis. A substantial proportion of HIV-infected trial population (38%) had a documented nadir of below 200 cells/µl in their medical history.

Table 3 Demographic Data of HIV-infected Subjects Enrolled in the Clinical Trial POX-MVA-011 (FAS, N = 482)

Variable	Vaccinia Status	HIV Overall	CD4 200-349 cells/µl	CD4 350-500 cells/µl	CD4 501-750 cells/µl
Sample size [n]	naïve	351	89	163	99
	experienced	131	24	61	46

CD = cluster of differentiation; FAS = full analysis set; n = number of subjects
Data source: Clinical Study Report (CSR) of POX-MVA-011; Synopsis and Section 15, Table 3.2

Almost a quarter of the HIV-infected trial population (23%) reported at least one AIDS defining condition in their medical history and more than a third (36%) of the HIV-infected subjects

presented with a history of at least one infection indicative of severe immunosuppression and clinical AIDS.

The safety of MVA-BN® smallpox vaccine was still comparable to that observed in healthy subjects. Of note is the even lower incidence of solicited local AEs in HIV-infected subjects compared to healthy subjects which was observed already in the previous Phase II trial and may be at least partly attributed to the possible underreporting expected in HIV-infected subjects given expected lower reactogenicity in an immunocompromised population.

The safety data collected from these special populations are of particular importance, as they demonstrate that MVA-BN® smallpox vaccine is well tolerated even by subjects with impaired immune systems, which are known to be at risk of developing severe and/or serious adverse reactions to conventional replicating smallpox vaccines.

2.6.4 Immunogenicity Overview of MVA-BN®

In three Phase I and II dose finding trials MVA-BN® was tested for safety and immunogenicity among healthy volunteers (Vollmar, 2006, Frey, 2007, Von Krempelhuber, 2010). Across these trials a linear dose relationship was observed between the vaccine doses for both ELISA and PRNT titers. Maximum ELISA seroconversion rates and peak titers were reached two weeks after the second vaccination, with 100% seroconversion after the second dose for all dose groups receiving at least 2 x 10^7 $TCID_{50}$ of MVA-BN® or higher. Statistical analysis indicated lower doses to be inferior to a nominal titer of 1 x 10^8 $TCID_{50}$ tested throughout all dose ranging studies, whereas the highest dose tested (nominal titer of 1 x 10^8 $TCID_{50}$, which means an end of shelf-life titer of no less than 5 x 10^7 $TCID_{50}$) achieved ELISA seroconversion rates between 81 and 100% already after the first dose. For the PRNT, the same trend was observed with 71-96% seroconversion rates two weeks after the second MVA-BN® administration in all groups receiving the highest dose.

The early onset of seroconversion and the higher titers of total and neutralizing antibodies combined with an excellent safety profile qualified the dose of no less than 5 x 10^7 $TCID_{50}$ (nominal titer of 1 x 10^8 $TCID_{50}$) as the most suitable human dose. Therefore, based on the results of dose ranging studies, coupled with the animal immunogenicity and efficacy studies, the final optimal (standard) dose and schedule for the general population was decided to be two doses of no less than 5 x 10^7 $TCID_{50}$ MVA-BN® administered (s.c.) four weeks apart.

Although antibody responses measured by ELISA in HIV-infected subjects tend to be lower compared to GMTs in healthy and AD subjects four weeks after the first and second vaccinations with MVA-BN®, GMTs measured by PRNT were comparable in HIV-infected compared to healthy and AD populations. The ability of the second MVA-BN® vaccination to significantly boost the immune response in immunocompromised populations to high titer levels is as robust as in the healthy population.

In NIH sponsored trials POX-MVA-002 (DMID 02-017; Frey, 2007) and POX-MVA-009 (DMID 06-0012) the immune responses induced by MVA-BN® were compared to the conventional smallpox vaccine Dryvax®. In total 97.8% of subjects vaccinated with a single

administration of the standard dose of MVA-BN® seroconverted by ELISA either at Day 14 or Day 28 post vaccination (29/29 in POX-MVA-002 and 61/63 in POX-MVA-009). 100% of subjects in the Dryvax® group had seroconverted 28 days after scarification (13/13 and 8/8 respectively). A second vaccination with MVA-BN® significantly increased the titers measured two weeks later so that the GMTs two weeks after the second vaccination with MVA-BN® were comparable to those four weeks after a single vaccination with Dryvax®. Furthermore, the majority of study participants (n = 54) received MVA-BN® prior to challenge (vaccination) with Dryvax®. In these subjects, MVA-BN® priming resulted in a significant reduction of viral replication at the site of Dryvax® inoculation and either prevented take development or resulted in a diminished take coupled with an accelerated healing time; factors which are associated with people previously vaccinated with traditional smallpox vaccines or infected with variola virus. Partial attenuation of primary takes in some vaccinia-experienced individuals receiving vaccination has also been well documented in previous studies (Stickl, 1974; Cherry, 1977; McIntosh, 1977; Orr, 2004).

Analysis of sera derived from MVA-BN® vaccinees compared to sera from Dryvax® recipients demonstrated that subjects vaccinated with MVA-BN® had a significantly higher in vitro variola virus neutralization capacity (titer) compared to subjects vaccinated with Dryvax® (Damon, 2009). This result supports a comparable efficacy afforded by MVA-BN® and conventional smallpox vaccines against smallpox in people.

In addition, MVA-BN® and Dryvax® induced similar levels of T cell immunity with most subjects having detectable T cell responses 26-30 days following vaccinations among vaccinia-naïve volunteers. Data on cellular immune responses, analyzed in various trials using intracellular cytokine staining for detection of vaccinia-specific Interferon-γ producing CD4 T cells showed a strong dose-dependency. In vaccinia-experienced subjects, MVA-BN® was able to stimulate the memory T and B cell responses induced by a previous smallpox vaccination with conventional vaccines.

Additional detailed information on the clinical development of MVA-BN® is provided in the Investigator's Brochure.

2.7 Rationale

BN received marketing authorization for MVA-BN® smallpox vaccine (IMVANEX®) from the European Medicines Agency (EMA) on 31 July 2013. The dossier included clinical data from trials in healthy adults and populations contraindicated to receive live smallpox vaccines, namely HIV-infected or subjects diagnosed with AD. MVA-BN® has shown to be safe and well tolerated in all tested populations.

Data obtained in clinical trials enrolling HIV-infected subjects have consistently shown that the collective (PRNT and ELISA) seroconversion rates and induction of a sufficient magnitude of GMTs after a standard dose regimen of MVA-BN® supports the proposed vaccination strategy in this population. The finding that GMTs were lower in the HIV-infected compared to the healthy subjects indicates that these individuals in general had a suppressed immune response due to their

HIV infection. However, antibody titers were still at high levels, clearly justifying the conclusion that a strong immune response had been induced in this immunocompromised population.

As part of the post authorization obligations further clinical trial data are requested to explore the safety of MVA-BN® in a highly immunocompromised population.

Immunodeficiency is characterized by a compromised or even absent ability of the immune system to cope effectively with infectious pathogens. A well characterized state of immunodeficiency is the result of the infection with HIV. Other immunodeficiency states include those secondarily caused by immunosuppressive drugs, e.g. chemotherapy or glucocorticoids, for treatment of autoimmune diseases or to prevent solid organ rejection in transplant patients. In addition, some diseases directly or indirectly can cause immunosuppression, e.g. cancer, or renal failure requiring long-term hemodialysis, as well as chronic infections.

MVA-BN® smallpox vaccine has been tested in nearly 1,000 subjects with contraindications to conventional smallpox vaccines, i.e. individuals diagnosed with HIV infection or AD and hematopoietic stem cell transplant (HSCT) recipients. Data obtained in patients with a history of HSCT showed that MVA-BN® was safe and generally well tolerated in this immunosuppressed population (Walsh, 2013). The placebo controlled clinical trial was conducted by the US Division of Microbiology and Infectious Diseases of the National Institutes of Health (NIH/DMID) who used a low and standard dose for vaccination in this patient population with a history of HSCT. Vaccination with traditional, replication-competent smallpox vaccines is contraindicated in persons with a history of HSCT (Wharton, 2003).

Several trials in HIV-infected subjects suggest that MVA-BN® is safe and immunogenic in immunocompromised subjects (Harrer, 2005, Greenberg, 2013). In the POX-MVA-011 trial safety and immunogenicity was evaluated in HIV-infected compared to healthy subjects. In this trial, the CD4 count of the HIV-infected study population prior to enrollment into the study ranged from 200-750 cells/µl. Based on their medical history, a substantial proportion of these subjects (38%) had a documented nadir of CD4 cells below 200 cells/µl, 23% had reported at least one AIDS defining condition and more than a third (36%) had previously presented with a history of at least one infection indicative of severe immunosuppression and clinical AIDS. Safety analysis demonstrated that this trial population could receive MVA-BN® without any safety concerns.

More than 34 Million people are HIV infected and a considerable part is classified as having Aquired Immunodeficiency Syndrome (AIDS). The classification system for HIV infection which includes AIDS was simplified in 2008 retaining the 26 AIDS defining conditions besides three CD4 T-lymphocyte categories: stage 1 to 3 (with stage 3 being classified as AIDS). This case definition underlines the role of CD4 T-lymphocyte counts which are regarded as an objective measure of immune suppression. The severity of immunodeficiency increases with HIV disease progression – once a patient is classified into the stage 3 – AIDS – e.g. nadir < 200 cells/µl, they cannot be reclassified into a less severe stage (Morbidity and Mortality Weekly Report (MMWR) Dec 5, 2008). Hence even sub-clinically HIV infected subjects with reasonably restored CD4 counts under ART still have an impaired immune system with severe abnormalities in T and B cells (Miedema, 1988). Immunodeficiency is the hallmark of AIDS. Since HIV

directly infects T helper cells, and also indirectly impairs other immune system responses, HIV infection can be considered as representing a particularly severe form of immunodeficiency. Since HIV-infected subjects constitute a significant proportion of immunocompromised people in the general population and are engaged in care at large outpatient clinics they are considered excellent candidates to represent the highly immunocompromised population for enrollment in this trial.

The targeted population will be HIV-infected subjects with a current CD4 count between 100 and 500 cells/µl combined with a nadir CD4 cell count category 3 (documented CD4 count < 200 cells/µl at any time prior to enrollment). To account for the expected impact on the immune response to vaccination in this population, the trial will evaluate whether increasing the number of doses can improve the immune response to MVA-BN® compared to the standard dose regimen in highly immunocompromised individuals, while still being comparably safe and well tolerated. MVA-BN® will be administered either by simultaneous administration of two standard doses to achieve a higher total dose, or in a three dose schedule by adding a third standard dose as early booster 12 weeks after the first vaccination. Durability of immune response in this population will be evaluated at the six months FU visit - which is comparable to the accepted follow-up period in already completed clinical trials in healthy and HIV populations vaccinated with MVA-BN® smallpox vaccine.

This trial will generate important additional data in a highly immunocompromised population.

2.8 Trial Population

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.

2.9 Risk/Benefit Assessment

2.9.1 Potential Risks

Blood drawing may cause discomfort, bruising or light-headedness. Rarely, a blood draw may result in infection at the site where the blood is taken.

Preclinical data with MVA-BN® in rats and rabbits have revealed no special hazard for humans based on conventional studies of safety.

Based on the available data for MVA-BN® as well as for MVA-based vaccines in healthy and immunocompromised subjects, adverse reactions in this trial setting are expected to be comparable to adverse reactions previously reported for MVA-BN® and/or those typically seen with other modern vaccines. Main risks involve the development of local reactions at the injection site, e.g. erythema, pain swelling and induration.

As with all injectable vaccines, there is a risk of an allergic reaction or an anaphylactic event. Trial site staff will watch subjects for at least 30 minutes after each vaccination and in the event

that a severe allergic reaction might occur, appropriate medical treatment and supervision will be readily available.

The severe and life-threatening adverse reactions such as progressive vaccinia, eczema vaccinatum, generalized vaccinia and inadvertent inoculation that have been observed after the administration of conventional smallpox vaccines are due to the replication of these vaccinia strains. MVA-BN® is replication incompetent in human cells and consequently has a better safety and tolerability profile. It is essentially impossible that MVA-BN® could induce the severe side effects listed above associated with replication competent vaccinia viruses. Apart from the better safety profile with regard to severe reactions, the available clinical experience with MVA-BN® shows that it is generally better tolerated, for example with regard to local reactions, than conventional smallpox vaccines.

2.9.2 Benefits

There will be no direct benefit to the trial participants. Trial participants will contribute significantly to the development of a safer smallpox vaccine which is a benefit for society in view of a potential threat following deliberate release of smallpox virus. Based on the current immunogenicity and efficacy data collected in non-clinical and clinical studies, participants in clinical trials are expected to acquire protection against smallpox infection.

Analysis of the samples collected will not directly benefit the subject. BN may learn more about smallpox and other diseases: how to prevent them, how to treat them, or how to cure them.

3 Objectives

Please refer to trial protocol synopsis Section 1.5.

4 Trial Design

4.1 Experimental Design

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, 90 vaccinia-naïve subjects will be enrolled in this trial (see Table 4). All subjects will be randomly assigned (1:1:1) to Group 1, Group 2 or Group 3. Group 1 will receive the standard regime – two vaccinations at Day 0 and Day 28. Group 2 will receive two injections at each vaccination day in the standard schedule and Group 3 will receive the standard regime and an additional early boost 12 weeks after the first dose of the standard vaccination schedule with MVA-BN® smallpox vaccine.

Table 4 Distribution of the Three Treatment Groups

Groups	N	Dose ($TCID_{50}$) per Injection (0.5 ml)	Number of Injections	Vaccinations (Weeks)
1	30	at least 1 x 10^8/ml	Standard regime	0 - 4
2	30	at least 1 x 10^8/ml	Two injections at each time point	0 - 4
3	30	at least 1 x 10^8/ml	Standard regime + additional boost	0 - 4 - 12

4.2 Description of Trial Procedures

The trial procedures will be conducted according to the trial procedure schedule (Section 1.6) and as described on the following pages. Visits must be scheduled within the intervals / visit windows given below.

4.2.1 Screening Phase

All subjects must be thoroughly informed of all aspects of the trial (e.g. trial visit schedule, required evaluations and procedures, risks and benefits) as described in the informed consent form (ICF). The ICF and the statement about the Health Insurance Portability and Accountability Act (HIPAA) must be reviewed with the subject and signed and dated by the subject and the Investigator, or person designated by the investigator, who conducted the informed consent discussion before proceeding with any evaluations or procedures required by this protocol.

After ICF has been collected, subjects will enter a screening period of up to 28 days before the first vaccination.

Screening Visit (Days -28 to -1)

The following tasks will be performed

- Subject to read, sign and date ICF and HIPAA
- Check inclusion/exclusion criteria
- Obtaining medical history
- Obtaining HIV specific medical history
- Check vaccination history (previous smallpox vaccination or vaccination with a pox-virus-based vaccine) and absence of smallpox vaccination scar
- Complete physical examination including auscultation of heart and lungs and measurement of body weight and height
- Evaluation of vital signs
- Cardiac assessment (Section 8.2.7)
  - Calculation of the individual cardiac risk factor (after receipt of lab results for cholesterol)
  - Evaluation of family cardiac risk factors
  - Perform baseline ECG
- Recording of AEs/SAEs/AESIs
- Recording of prior and concomitant medication

- Counseling on avoidance of pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP
- Blood draw (2 ml) for CD4 count
- Blood Draw (4 ml) for viral load
- Blood draw for safety laboratory (7 ml) including
  - Serum pregnancy test (WOCBP only)
  - Hematology & serum chemistry
  - Troponin I
  - Total cholesterol, High-density Lipoprotein (HDL) and Low-density Lipoprotein (LDL)

If a subject is screened and cannot be enrolled, because of a certain transient condition (e.g. abnormal lab value due to an acute condition or a missing lab evaluation due to mishandling of the sample), then the subject can be re-screened on one further occasion only and the respective test(s) should be repeated as a "partial" re-screening rather than a full re-screening. The re-screening visit must be within the 28 day window started by the first screening visit and the window -28 to -1 before first vaccination must not be exceeded. A "partial" re-screening visit is indicated by filling out only the respective re-screening sections in the electronic Case Report Form (eCRF).

If a subject cannot be enrolled due to other circumstances (e.g. completion of a wash-out period for a medication or vaccine not allowed during the trial) or the 28 day period is exceeded, a complete re-screening assessment including physical examination, lab examination, and ECG must be performed. The clock then re-starts at the re-screening visit with Day -28 before the first vaccination.

4.2.2 Active Trial Phase

After successfully passing the screening evaluations, the eligible volunteers can enter the active trial phase (Visit 1 to Visit 5 for Group 1 and Group 2 / Visit 1 to Visit 8 for Group 3) starting with Visit 1.

At Visit 1 subjects will be assigned randomly to Group 1, Group 2 or Group 3 after re-confirmation of the subject's eligibility. The randomization scheme is 1:1:1 (Group 1, 2, 3). An automated randomization system will be used. The detailed process will be described in a trial specific procedure.

The procedures performed at Visit 1 and all following visits are listed below. **Blood draws and all other examinations listed above the vaccination events must always be performed prior to vaccination.**

At Visit 1 / Day 0, subjects will receive the first s.c. vaccination with 0.5 ml of MVA-BN® in the upper arm.

Following each vaccination subjects will be kept under close observation at the clinical trial site (CTS) for at least 30 minutes, with appropriate medical treatment readily available in case of a

rare anaphylactic reaction following the administration of vaccines. Any AEs that occur during or after vaccination will be recorded.

Reactogenicity and AEs will be collected on a subject memory aid by having the subject record local and general symptoms for an 8-day period (Days 0-7), beginning with the day of vaccination. The memory aid will be returned to the clinic staff at the following visit. If symptoms persist at Day 7, daily symptoms and temperature will continue to be measured each day until resolved and the last day of symptoms and maximum intensity is recorded on the memory aid. Unsolicited AEs will be assessed at all visits except FU 1 and FU 2 (Screening to Visit 5 for Group 1 and 2 / Screening to Visit 8 for Group 3).

Visit 1 (Day 0)
Tasks to be performed prior to randomization and vaccination • Confirmation of inclusion / exclusion criteria • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of AEs/SAEs/AESIs • Recording of concomitant medications • Counseling on avoidance of pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP • Urine pregnancy test (WOCBP only) • Blood draw (9 ml; serum collection) for immunogenicity testing (baseline) **If the subject is still eligible for participation in this trial the subject will be randomized. The following tasks will be performed after randomization:** • Administration of first MVA-BN® vaccination • Subject observation by CTS staff for at least 30 minutes after vaccination • Recording of immediate AEs/AESIs/SAEs • Handout of memory aid for first vaccination, ruler and thermometer <u>Temporary deferral of vaccination:</u> If an acute illness is present the subject may be vaccinated at a later date within the accepted time window. The vaccine can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection, or any other mild condition with or without low-grade febrile illness, i.e. oral temperature < 100.4°F (< 38.0°C).

Visit 2 (V1 + 12-16 days)

The following tasks will be performed
• Targeted physical examination including auscultation of the heart and lungs
• Evaluation of vital signs
• Performing of ECG
• Recording of concomitant medication
• Recording of AEs/SAEs/AESIs
• Blood draw (2 ml) for CD4 count
• Blood Draw (4 ml) for viral load
• Blood draw (7 ml) for safety laboratory including
  ○ Troponin I
  ○ Hematology & serum chemistry
• Collection of the memory aid handed out at Visit 1, review with subject
• Examination of the vaccination site(s)

Visit 3 (V1 + 28-35 days)
Tasks to be performed prior vaccination • Check withdrawal criteria (see Section 4.2.5) • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medications • Counseling on avoidance of pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP • Recording of AEs/SAEs/AESIs • Urine pregnancy test (WOCBP only) • Blood draw (9 ml; serum collection) for immunogenicity testing **If the subject is still eligible to receive the second vaccination the following tasks will be performed** • Administration of second MVA-BN® vaccination • Subject observation by CTS staff for at least 30 minutes after vaccination • Recording and documentation of immediate AEs/SAEs/AESIs • Handout of the memory aid for second vaccination Temporary deferral of second vaccination: If an acute illness is present the subject may be vaccinated at a later date within the accepted time window. The vaccine can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection, or any other mild condition with or without low-grade febrile illness, i.e. oral temperature < 100.4°F (< 38.0°C).

Visit 4 (V3 + 12-16 days)

The following tasks will be performed
• Targeted physical examination including auscultation of the heart and lungs
• Evaluation of vital signs
• Recording of concomitant medication
• Recording of AEs/SAEs/AESIs
• Blood draw (2 ml) for CD4 count
• Blood draw (7 ml) for safety laboratory including
  ○ Hematology & serum chemistry
  ○ Troponin I
• Blood draw (9 ml; serum collection) for immunogenicity testing
• Collection of the memory aid handed out at Visit 3, review with subject
• Examination of the vaccination site(s)
•
Only if clinically indicated
• Perform ECG reading

Visit 5 (V3 + 28-35 days)
The following tasks will be performed • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medication • Recording of AEs/SAEs/AESIs • Urine pregnancy test (WOCBP)

Group 3 only: Visit 6 (V1 + 84-96 days)
Tasks to be performed prior to vaccination • Check withdrawal criteria (see Section 4.2.5) • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medications • Counseling on avoidance of pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP • Recording of AEs/SAEs/AESIs • Urine pregnancy test (WOCBP only) • Blood draw (9 ml; serum collection) for immunogenicity testing **If the subject is still eligible to receive the booster vaccination the following tasks will be**

performed

- Administration of booster MVA-BN® vaccination
- Subject observation by CTS staff for at least 30 minutes after vaccination
- Recording and documentation of immediate AEs/SAEs/AESIs
- Handout of the memory aid for booster vaccination

Temporary deferral of booster vaccination: If an acute illness is present the subject may be vaccinated at a later date within the accepted time window. The vaccine can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection, or any other mild condition with or without low-grade febrile illness, i.e. oral temperature < 100.4°F (< 38.0°C).

Group 3 only: Visit 7 (V6 + 12-16 days)

The following tasks will be performed

- Targeted physical examination including auscultation of the heart and lungs
- Evaluation of vital signs
- Recording of concomitant medication
- Recording of AEs/SAEs/AESIs
- Blood draw (2 ml) for CD4 count
- Blood draw (7 ml) for safety laboratory including
  - Hematology & serum chemistry
  - Troponin I
- Blood draw (9 ml; serum collection) for immunogenicity testing
- Collection of the memory aid handed out at Visit 6, review with subject
- Examination of the vaccination site

Only if clinically indicated

- Perform ECG reading

Group 3 only: Visit 8 (V6 + 28-35 days)

The following tasks will be performed

- Targeted physical examination including auscultation of the heart and lungs
- Evaluation of vital signs
- Recording of concomitant medication
- Recording of AEs/SAEs/AESIs
- Urine pregnancy test (WOCBP only)
- Blood draw (2 ml) for CD4 count

4.2.3 Follow-Up (FU) Phase

To monitor long-term safety, subjects will come six months (FU 1) after the last vaccination and 12 months after the last vaccination (FU 2) to the CTS. It will be checked if an SAE/AESI has occurred since the last trial visit and if there is any new information on SAEs/AESIs/AEs ongoing at last trial visit. A targeted physical examination, evaluation of vital signs and a blood draw for immunogenicity and CD4 count will be done.

4.2.3.1 FU 1

For subjects who were withdrawn from the second MVA-BN® vaccination, the FU 1 will be performed six months after the 1st vaccination and for subjects who were withdrawn from the booster MVA-BN® vaccination, the FU 1 will be performed six months after the 2nd vaccination (see Section 4.2.5).

FU 1 (V3 + 182-210 days for Group 1 and 2 / V6 + 182-210 days for Group 3)
The following tasks will be performed • Recording of SAEs/AESIs and AEs ongoing at last active trial visit (Visit 5 for Group 1 and 2, Visit 8 for Group 3). • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Blood draw (9 ml; serum collection) for immunogenicity testing • Blood draw (2 ml) for CD4 count **Only if clinically indicated** • Blood draw for safety laboratory (7 ml) • Other safety evaluations, if required

4.2.3.2 FU 2

For subjects who were withdrawn from the second MVA-BN® vaccination, the FU 2 will be performed 12 months after the 1st vaccination and for subjects who were withdrawn from the booster MVA-BN® vaccination, the FU 2 will be performed 12 months after the 2nd vaccination (see Section 4.2.5).

FU 2 (V3 + 364-392 days for Group 1 and 2 / V6 + 364-392 days for Group 3)
The following tasks will be performed • Subject to read, date and sign updated ICF (adding FU 2 to the original trial schedule) • Recording of SAEs/AESIs and AEs ongoing at last active trial visit. • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Blood draw (9 ml; serum collection) for immunogenicity testing • Blood draw (2 ml) for CD4 count **Only if clinically indicated** • Blood draw for safety laboratory (7 ml) • Other safety evaluations, if required

4.2.4 Unscheduled Visits

If clinically indicated, additional visits may be necessary between scheduled visits. Unscheduled visits may be performed to repeat laboratory testing or physical exams due to a new development. Examinations, performed at unscheduled visits will be documented in the source documents as well as in the respective eCRF sections for unscheduled visits.

4.2.5 Withdrawal from Second or Booster Vaccination

The decision not to administer the second/booster vaccination can be made by the investigator or by the subject.

Criteria:

The following criteria should be checked prior to second/booster vaccination. If any are applicable, the subject should not receive any further vaccination(s):

- Any clinically significant cardiac sign and symptom (i.e. AESI) defined in Section 8.1.2.3.
- An AE that, in the opinion of the investigator, makes it unsafe for the subject to receive a further vaccination. In this case, the appropriate measures will be taken.
- Anaphylactic reaction following the administration of any vaccine(s).
- Clinical need for concomitant or ancillary therapy not permitted in the trial, i.e.
    - Vaccination with any licensed live vaccine within 30 days prior or after trial vaccinations or any licensed killed vaccine within 14 days prior or after trial vaccinations
    - Start of chronic systemic administration (defined as more than 14 days) of > 5 mg prednisone (or equivalent) per day or any other systemic use of immune-modifying drugs.
    - Administration of immunoglobulins and/or any blood products.
- Use of any investigational or non-registered drug or vaccine other than the trial vaccine.
- Pregnancy
- Subject refuses to receive second vaccination.
- Any condition which contradicts administration of the second vaccination in the opinion of the investigator.

Procedure:

If a subject did not receive the second trial vaccination the reason for this decision must be recorded in the eCRF. Visit 3 and Visit 4 are not required and the procedures below should be followed:

- Visit 5 procedures have to be performed 28 to 35 days after last vaccination

- FU 1 procedures have to be performed 182 to 210 days after last vaccination
- FU 2 procedures have to be performed 364 to 392 days after last vaccination.

If a subject from treatment Group 3 did not receive the second or booster vaccination the reason for this decision must be recorded in the eCRF. Visits 6, 7 and 8 are not required and the procedures below should be followed:

- FU 1 procedures have to be performed 182 to 210 days after last vaccination.
- FU 2 procedures have to be performed 364 to 392 days after last vaccination.

4.2.6 Premature Discontinuation

The trial may be discontinued prematurely for a subject at any time. The decision to discontinue the trial for a subject prematurely can be made by the investigator or by the subject. Reasons for discontinuing the trial prematurely may include, but are not limited to the following:

Criteria:

- Subject's request to discontinue prematurely (withdrawal of informed consent).
- Subject unwilling or unable to comply with trial requirements.
- Discontinuation due to an AE.
- Any reason that, in the opinion of the investigator, precludes the subject's further participation in the trial.

Procedure:

If a subject discontinues prematurely, the reason for this decision must be recorded in the eCRF. If the subject is unable or not willing to attend all planned visits, every attempt should be made to perform at least a concluding safety visit. For WOCBP a pregnancy test should be performed during this safety visit. If the subject is not willing to undergo any further trial procedure (withdrawal of consent), "withdrawal of consent" needs to be documented as reason for premature discontinuation.

4.3 Trial Duration

The total duration of the trial for each subject including the screening period and Follow-up visits will be up to 75 weeks. The duration of the trial as a whole is dependent on the recruitment period.

4.4 Data Safety Monitoring Board

The DSMB is an independent board that oversees the safety of subjects participating in the trial. The members of the DSMB are independent, i.e. not involved as investigators in any MVA-BN® trials and have no direct or indirect financial interests in BN or the Contract Research

Organization (CRO) managing the trial. The primary responsibilities of the DSMB are to periodically review and evaluate the accumulated trial data for participant safety, trial conduct and progress, and make recommendations to BN and the Coordinating and PI(s) concerning the continuation, modification, or termination of the trial program. The DSMB considers trial specific data as well as relevant background knowledge about the disease, test agent, and subject population under trial. A separate charter describes in detail relevant operational procedures, communication pathways, roles and responsibilities of the DSMB.

If an event occurs which fulfills the trial halting rules the DSMB will review the event in a timely manner and give a recommendation to BN and the Coordinating Investigator and PI(s) to halt, resume or terminate the trial participation of the affected subject and/or the trial as a whole.

4.5 Trial Halting Rules

A temporary halting or termination for the trial as a whole can be decided by the DSMB in case of an occurrence of

- an SAE
- an unexpected Grade 3 or higher systemic reaction or lab toxicity (Section 16.1; Appendix I: Toxicity Scale for Laboratory Values)

with an at least reasonable possibility of a causal relationship to the administration of MVA-BN® smallpox vaccine, i.e. the relationship cannot be ruled out.

These parameters are not all-inclusive. Other AEs could occur that would trigger a DSMB review. Any member of the DSMB, any PI and/or the BN Drug Safety (DS) Officer could request a DSMB review based on any observation.

If an event fulfilling the trial halting criteria reaches the investigator's attention, the investigator has the liability to alert the responsible DS Department immediately (within 24 hours) and provide a comprehensive documentation of the event. Contact details of the responsible DS Department are provided in Section 8.3.1.

5 Selection of Subjects

Each investigator will keep a log of subjects screened for the trial, and provide the reason in case of exclusion. Information about every subject entering the trial will be documented in the eCRF.

5.1 Recruitment Procedure

Subjects will be recruited actively. Recruitment strategies, including IRB approved advertisements, will be evaluated by the Sponsor.

30 subjects will be enrolled in each group (90 in total).

After signing the ICF and HIPAA, subjects undergo screening procedures to check eligibility according to the inclusion/exclusion criteria. In the event of a screening failure secondary due to mild or limited acute illness or abnormal laboratory values, the subject may be re-screened after resolution of the event. Re-screening may require only an additional blood draw or a complete re-screening evaluation, depending on the circumstances of and the time interval from the initial screening failure (see also Section 4.2.1).

5.2 Inclusion Criteria

Please refer to trial protocol synopsis Section 1.5.

5.3 Exclusion Criteria

Please refer to trial protocol synopsis Section 1.5.

6 Investigational Medicinal Product

MVA-BN® smallpox vaccine is a highly attenuated live vaccinia virus which is administered subcutaneously. The packages and vials will be labeled according to the respective Product Specifications.

One vaccine dose has a virus titer of at least 1 x 10^8 $TCID_{50}$ /ml MVA BN® in 0.5 ml of the drug product.

For further details on MVA-BN® see current version of the Investigator's Brochure.

6.1 Production, Packaging and Labeling

The MVA-BN® bulk drug substance is produced at Bavarian Nordic A/S and the final drug product MVA-BN® is filled, formulated and labeled at the contract manufacturer (b) (1) (A) [redacted].

Addresses:

Bavarian Nordic A/S
(b) (1) (A) [redacted]

(b) (1) (A) [redacted]

The packages and vials of liquid frozen (LF) MVA-BN® smallpox vaccine will be labeled with US IND labels.

6.2 Shipment, Storage and Handling

MVA-BN® smallpox vaccine will be shipped temperature controlled to the warehouse and from the warehouse to the CTS. At the CTS, the package is handed over to the personnel in charge of

vaccine preparation, e.g. the pharmacist. After receipt of vaccine, the personnel are responsible for proper storage of vaccine.

MVA-BN® smallpox vaccine is shipped and stored at -4°F ± 9°F (-20°C ± 5°C) avoiding direct light. A vial should not be re-frozen once it has been thawed. Details on shipment, storage and handling of the LF formulation of MVA-BN® are provided in BN Standard Operating Procedure (SOP) (b) (1) (A) "Storage, Handling and Vaccination Procedures of Liquid Frozen MVA-BN® (IMVAMUNE) and Recombinant MVA-Based Vaccines in Clinical Trials" listed in Section 6.3.

6.3 Preparation, Administration and Dosage

Details on vaccine preparation, administration and dosage of MVA-BN® smallpox vaccine are provided in SOP (b) (1) (A) entitled "Storage, Handling and Vaccination Procedures of Liquid Frozen MVA-BN® (IMVAMUNE®) and Recombinant MVA-Based Vaccines in Clinical Trials".

6.4 Accountability and Disposal

After receipt of the investigational medicinal product (IMP), the CTS personnel have the ultimate responsibility for distribution, proper storage and drug accountability. Records of receipt, inventory, use by each subject, return or disposal and temperature control must be maintained in the pharmacy file.

Used and unused vials should be stored in a safe place and remain the property of BN. The personnel of the respective CTS are responsible for ensuring adequate accountability of all used and unused IMP. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition) and IMP accountability using an IMP inventory log. The IMP inventory log will document quantity of IMP received, quantity of IMP used for vaccination (including lot number, date dispensed, subject identification number and initials of the person dispensing the IMP) and quantity of IMP returned to BN or destroyed.

Additionally, the quantity of IMP returned to BN or destroyed must be documented on an IMP return/destruction form. If destruction at the CTS is agreed upon, material should be autoclaved or incinerated and discarded according to local regulations.

Furthermore, used syringes should be autoclaved or incinerated and discarded at the CTS according to local regulations.

7 Assessment of Immunogenicity

The methods for collection, storage and handling of lab specimens for immunogenicity testing are specified in separate manuals, which will be provided to the investigators before enrollment commences. Additionally, training will be provided on the procedures during the investigator meeting and/or at the initiation visit.

7.1 Humoral Immunogenicity

Immunogenicity testing will be performed on samples obtained from subjects of all three groups on trial Visit 1, Visit 3, Visit 4, FU1 and FU 2. Further, immunogenicity testing will be performed on samples obtained from subjects of Group 3 on trial Visits 6 and 7. Blood samples obtained on vaccination visits (i.e., Visit 1, Visit 3 and Visit 6) will be drawn prior to vaccination.

Antibody responses to MVA-BN® smallpox vaccine will be measured using a vaccinia-specific ELISA and vaccinia-specific PRNT, both assays established and validated at BN. The immunogenicity analysis will be performed at BN. All personnel involved in immunogenicity testing will be blinded to subject randomization details.

The procedures for the analytical tests performed are outlined in Sections 7.1.1 and 7.1.2 below. The SOPs, effective at the time of testing will be filed in the electronic Trial Master File.

7.1.1 ELISA

Details on the ELISA procedure can be found in SOP (b) (1) (A) : "Automated ELISA for Detection of Vaccinia Specific Antibodies in Human Sera".

The ELISA GMT is calculated by taking the antilogarithm of the mean of the $\log_{10}$ titer transformations. Titers below the detection limit are assigned the arbitrary value of 1.

The seroconversion rate is defined as the percentage of seroconverted subjects based on the total number of subjects included. Seroconversion is defined for initially seronegative subjects as appearance of antibody titers ≥ detection limit. For subjects who are initially seropositive (i.e. with baseline [V1] antibody titers ≥ detection limit) at least a doubling of the titer is needed to fulfill the definition of seroconversion.

7.1.2 PRNT

Details on the PRNT procedure can be found in SOP BN0003536: "Human Plaque Reduction Neutralization Test Using Vaccinia Virus Western Reserve".

The PRNT GMT is calculated by taking the antilogarithm of the mean of the $\log_{10}$ titer transformations. Titers below the detection limit are assigned the arbitrary value of 1.

The seroconversion rate is defined as the percentage of seroconverted subjects based on the total number of subjects included. Seroconversion is defined for initially seronegative subjects as appearance of antibody titers ≥ detection limit. For subjects who are initially seropositive (i.e. with baseline [V1] antibody titers ≥ detection limit) at least a doubling of the titer is needed to fulfill the definition of seroconversion.

7.2 Future Use of Lab Specimen

Serum remaining after completion of all immunogenicity testing for the trial will be stored for future analysis supporting the licensure path of MVA-BN® smallpox vaccine. Future analysis will facilitate the bridging of trial results to animal immunogenicity results and/or to immune response data collected from subjects vaccinated with traditional smallpox vaccines. Subjects will be asked to consent to storage / future use of samples and will be informed about data protection measures. Specimens will be stored in BN's secured laboratory area or at an external storage facility in a coded, anonymized manner to ensure data protection. Genetic testing will not be performed.

8 Safety and Reactogenicity

Safety will be monitored by performing physical examinations including vital signs, routine laboratory measurements as well as by evaluating local and general solicited AEs and unsolicited AEs.

Using replication-competent vaccinia-based smallpox vaccines during smallpox vaccination programs in the US during the last years, cases of acute myocarditis and pericarditis were observed (Cassimatis, 2004). No confirmed cases of myo- or pericarditis have been observed for MVA-BN® smallpox vaccine. However, as a precautionary measure, special cardiac monitoring assessments will be performed.

8.1 Definitions

8.1.1 Medical History

Symptoms present before or at the screening visit will be documented in the medical history.

8.1.2 AEs

Any new signs, symptoms or changes in health starting after ICF signature are documented in the AE section of the eCRF. AEs are recorded based on unsolicited and solicited questioning (Section 8.1.2.1 and 8.1.2.2).

8.1.2.1 Unsolicited AEs

Unsolicited AEs are defined as any untoward (undesirable) occurrence of a medical event in a clinical trial subject temporally associated with the administration of an IMP or a medical product (MP) which does not necessarily have a causal relationship with this IMP/MP. For Group 1 and 2 up to Visit 5 (Week 8) and for Group 3 up to Visit 8 (Week 16) all AEs (e.g. feeling of ill-health, subjective symptoms and objective signs, intercurrent diseases, accidents, etc.) observed by the investigator and/or reported by the subject must be recorded in the eCRF regardless of the assessment of causality in relationship with the IMP/MP.

Abnormal laboratory values assessed as being clinically significant by the investigator are to be documented as AEs. In addition, abnormal laboratory values fulfilling the Grade 3 or Grade 4 criterion according to the toxicity scale (Section 16.1; Appendix I: Toxicity Scale for Laboratory Values) are to be documented as AE in the eCRF, regardless of whether they are considered clinically relevant or not. For lab values fulfilling the Grade 3 or 4 criterion, the decision to repeat the labs is left at the discretion of the PI. Toxicity grade and seriousness of an AE will be assessed separately, i.e. a Grade 3 or Grade 4 AE will not automatically be regarded as serious.

The investigator should ask the subject if they have experienced any AEs since their last visit. All intercurrent diseases reported by the subject, need to be recorded by the investigator in the appropriate section of the eCRF.

8.1.2.2 Solicited AEs

Within this clinical trial protocol solicited AEs are defined as all symptoms specifically listed in the memory aid provided to the subjects following each vaccination. The subjects are requested to monitor and record local symptoms (i.e. erythema, swelling, induration, pruritus and pain at the injection site) as well as general symptoms (i.e. body temperature, headache, chills, myalgia, nausea and fatigue) in the memory aid daily for the day of vaccination and the following seven days (Days 0-7, 8 day period).

8.1.2.3 AESIs

An AESI is defined in this trial as:

- Any cardiac sign or symptom developed since the first vaccination
- ECG changes determined to be clinically significant
- Cardiac enzyme troponin I $\geq$ 2 x ULN

8.1.2.4 SAEs

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death, if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- or is an otherwise important medical event, e.g. leads to suspicion of transmission of an infectious agent

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.2 Assessment

8.2.1 Relevant Medical History

Relevant medical history will be documented at SCR and will focus particularly on any important diseases and in case of infections or tumors, the pathogen involved or the pathological diagnosis, if available. Special attention should be given to history of prior allergic reactions, especially to vaccines.

Diagnosis of HIV and disease state has to be documented separately: date of diagnosis, nadir, CD4 count and highest viral load up to six months before SCR.

In addition, smallpox vaccination history must be checked (check for a smallpox vaccination scar and any documentation of previous smallpox vaccination, if available; Note: check also for smallpox vaccination programs during military service or for smallpox response teams or history of vaccination with a poxvirus-based vaccine e.g. in the course of a clinical trial).

8.2.2 Prior and Concomitant Medications

All concomitant (ongoing) medication except homeopathic substances and dietary supplements must be recorded in the eCRF and the subject's medical record including information about the indication, dosage regimen, and the onset and end of treatment.

The following medication, taken within three months prior to screening, will also be recorded in the eCRF and the subjects medical record: vaccines, corticosteroids (via any route of administration), other immune-modulating drugs, immunoglobulin and/or any blood products, investigational drugs and depot preparations which are still active at the date of SCR.

The antiretroviral medications, taken within six months prior to SCR, will also be recorded in the eCRF and the subject's medical record.

8.2.3 Physical Examination

Complete physical examination

A complete physical examination will be performed at the SCR. The examination includes a review of major organ systems as well as height and weight. The examination should be directed at finding evidence of any infections, tumors and lymphadenopathy (a grading scale for lymphadenopathy is included in Section 16.4; Appendix IV: Grading Scale for Lymphadenopathy). In addition, auscultation of the heart and lungs to check specifically for signs of any heart condition will be performed.

Targeted physical examination

A targeted physical examination, guided by any signs or symptoms previously identified or any new symptoms that the subject has experienced since the last visit, is required at all visits starting at Visit 1. In addition, auscultation of the heart and lungs will be performed.

8.2.4 Vital Signs

Blood pressure and pulse rate will be taken after the subject has been sitting for approximately two minutes. Body temperature will be measured orally.

8.2.5 Unsolicited AEs

All intercurrent diseases reported when the investigator actively inquires the subject will be documented in the source and all required details (e.g. start and stop date, severity) will be assessed. Unsolicited AEs will be reported in the respective section of the eCRF and the subject's medical record.

AEs for Group 1 and 2 will be assessed and documented at all visits except FU 1 and FU 2 (i.e. Screening to Visit 5) and if ongoing at Visit 5, followed until resolution or until the FU 2 at the latest.

AEs for Group 3 will be assessed and documented at all visits except FU 1 and FU 2 (i.e. Screening to Visit 8) and if ongoing at Visit 8, followed until resolution or until the FU 2 at the latest.

SAEs/AESIs will be assessed and documented at all trial visits, including the FU 1 and FU 2. Ongoing AESIs which occurred after at least one vaccination will be followed up until resolution or achievement of stable clinical conditions. SAEs will be followed up until resolution or achievement of stable clinical conditions.

Assessment of Intensity

For all unsolicited AEs not represented in the toxicity scale for Laboratory Values (Section 16.1; Appendix I: Toxicity Scale for Laboratory Values), the maximum intensity will be based on the following descriptions:

Grade 1 An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with daily activities.

Grade 2 An AE which is sufficiently discomforting to interfere with daily activities.

Grade 3 An AE which prevents daily activities. (Such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

Assessment of Causality

The relationship between the occurrence of an AE and the IMP will be assessed using the categories presented below. For expedited reporting and all other purposes, the categories "none" and "unlikely" will represent no evidence or argument to suggest a causal relationship, while "possible", "probable" and "definite" will be seen to convey that there is evidence or argument to suggest a causal relationship. Following worst case scenario all AEs without a causality assessment from the investigator will be classified as "possible".

None	The time interval between the administration of the IMP and the occurrence or worsening of the AE rules out a relationship, and/or another cause is established and there is no evidence of a (concomitant) causal connection with or worsening caused by the IMP.
Unlikely	The time interval between administration of the IMP and the occurrence or worsening of the AE makes a causal relationship unlikely, and/or the known effects of the IMP or substance class provide no indication of a (concomitant) causal connection with or worsening caused by the IMP and there is another cause which serves as an adequate explanation, and/or although the known effects of the IMP or substance class make it possible to derive a plausible causal chain with regard to a (concomitant) causal connection or worsening, however, another cause is considerably more likely, and/or another cause of the AE has been identified and a (concomitant) causal connection with or worsening caused by the IMP is unlikely.

Possible	A plausible causal chain with regard to a (concomitant) causal connection with / worsening of the AE can be derived from the pharmacological properties of the IMP or substance class. However, other approximately equally likely causes are known, or although the pharmacological properties of the IMP or substance class provide no indication of a (concomitant) causal connection with / worsening of the AE, there is no other known cause which provides an adequate explanation.
Probable	The pharmacological properties of the trial medication or substance class, and/or the course of the AE after discontinuation of the IMP and possible subsequent re-exposure, and/or specific findings (e.g. positive allergy test or antibodies against the IMP / metabolites) suggest a (concomitant) causal connection with / worsening of the AE resulting from the IMP, however another cause cannot completely be ruled out.
Definite	The pharmacological properties of the IMP or substance class and/or the course of the AE after discontinuation of the IMP and possible subsequent re-exposure, and/or specific findings (e.g. positive allergy test or antibodies against the IMP / metabolites) definitely indicate that there is a (concomitant) causal connection with / worsening of the AE resulting from the IMP and there are no indications of other causes.

8.2.6 Solicited AEs

After each vaccination subjects receive a memory aid to record solicited local and general AEs most likely to occur on the day of vaccination and the following seven days (Days 0-7; 8-day period).

All solicited symptoms observed after vaccination with details concerning the intensity and the course of the reaction should be documented there. The investigator will collect this information during the following scheduled visits and transfer it to the eCRF and the subject's medical record. Local and general reactions still ongoing after seven days will be measured or examined each day until resolution or until no further change can reasonably be expected, and the last day of symptoms and maximum intensity will be documented in the memory aid.

In case of severe and unexpected local and/or general reactions, the subject should be instructed to contact the trial physician outside of scheduled trial visits.

8.2.6.1 Solicited Local AEs

The solicited local symptoms erythema, swelling, induration, pruritus and pain at the injection site are to be documented in the memory aid by the subject.

To standardize procedures, uniform rulers will be handed out to all subjects for measurements of erythema, swelling and induration diameters, as will digital thermometers for oral measurements of body temperature.

Assessment of Intensity

Injection site erythema	size measured in diameter
Injection site swelling	size measured in diameter
Injection site induration	size measured in diameter

The maximum severity will be scored as follows:

0	=	0
1	=	< 30 mm
2	=	≥ 30 – <100 mm
3	=	≥ 100 mm

Injection site pruritus:

0	=	Absent
1	=	Mild
2	=	Moderate
3	=	Severe

Injection site pain:

0	=	Absent
1	=	Painful on touch
2	=	Painful when limb is moved
3	=	Spontaneously painful / prevents normal activity

Assessment of Causality

Solicited local AEs are defined as being related to the vaccine.

8.2.6.2 Solicited General AEs

The solicited general symptoms body temperature, headache, myalgia, nausea, chills and fatigue are to be documented in the memory aid by the subject.

Assessment of Intensity

Subjects are asked to document the solicited general AEs in the memory aid as described in Table 5 below. In the subject's memory aid, the grading of maximum symptom intensity is described in basic, easily understood language based on the following descriptions:

Table 5 Grading of General Symptoms from the Subject's Memory Aid

MedDRA coded Preferred Term General AEs	Grade	Maximum Severity
Body temperature*	0	< 99.5°F (< 37.5°C)
	1	≥ 99.5 – <100.4°F (≥ 37.5 – < 38.0°C)
	2	≥ 100.4 – <102.2°F (≥ 38.0 – < 39.0°C)
	3	≥ 102.2 – <104.0°F (≥ 39.0 – < 40.0°C)
	4	≥ 104.0°F (≥ 40.0°C)
Headache, Myalgia, Nausea, Chills and Fatigue	0	None
	1	Mild: easily tolerated, minimal discomfort and no interference with daily activity
	2	Moderate: Some interference with daily activity
	3	Severe: Prevents daily activity

*Pyrexia is defined as oral temperature ≥ 100.4°F (≥38.0°C).

Assessment of Causality

Causal relationship between solicited general AEs and the vaccine will be assessed by the investigator using the same categories as for unsolicited AEs (see Section 8.2.5).

8.2.7 Cardiac Assessment

To evaluate the cardiac profile of MVA-BN®, targeted physical exams including auscultation of the heart and lung will be performed (Section 8.2.3). Any kind of cardiac signs (i.e. discovered by the physician during examination of the patient) or symptom(s) (i.e. experienced and reported by the subject) detected during the trial such as but not limited to chest pain, dyspnea, arrhythmia or edema are recorded.

ECG

A standard 12-lead ECG will be taken at the SCR and at Visit 2. At Visit 4 and Visit 7 (Group 3 only) an ECG is only done if clinically indicated. ECGs will be evaluated by a central ECG reading center. The workflow and communication flow will be provided in a separate manual.

Cardiac Risk Factors

The individual cardiac risk factor is calculated at SCR (for subjects 20 years of age and older), using the National Cholesterol Education Program's risk assessment tool

(http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof). Subjects with a 10% or greater risk of developing a myocardial infarction or coronary death within the next 10 years are excluded from trial participation.

In addition, the family cardiac risk factor is evaluated at SCR. Subjects with an immediate family member (father, mother, brother, or sister), who has had onset of ischemic heart diseases before 50 years of age, are also excluded from trial participation.

Troponin I

Troponin I will be measured at SCR and on the following visits: Visit 2, Visit 4 and Visit 7 (Group 3 only).

Cardiac events fulfill the definition of an AESI as described in Section 8.1.2.3. The investigator will be asked to assess the clinical significance of the case.

Case definitions as published by the CDC (Morbidity and Mortality Weekly Report [MMWR] May 30, 2003) are provided in Section 16.2; Appendix II: Case Definitions Acute Myocarditis / Pericarditis in order to:

- help investigators to recognize possible events of acute myocarditis and/or pericarditis and
- distinguish from unspecific and isolated ECG changes without or with unclear clinical significance.

Subjects who develop any kind of cardiac signs or symptoms during the trial such as but not limited to chest pain, dyspnea, arrhythmia or edema are referred to a local cardiologist for cardiac evaluation such as (treadmill) ECG, measurement of cardiac enzyme and/or echocardiogram. Depending on the results of these evaluations, further diagnostic tests will be done as recommended by the cardiologist and subjects will be followed up at a frequency determined by the cardiologist. Any AESIs occurring after at least one vaccination will be followed up until complete resolution or until the sequelae are stable and considered to be permanent.

In any case of cardiac signs or symptoms, or increased laboratory results for Troponin I, the subject will be asked to attend for an unscheduled visit at the site, in order to perform or repeat Troponin I testing, to perform a physical examination for cardiac symptoms and to record an unscheduled ECG.

Further details regarding the follow-up of AESIs are described in the 'Investigator's Manual – Follow-up of Adverse Events of Special Interest'.

Figure 1 outlines the algorithm for assessment of cardiac events.

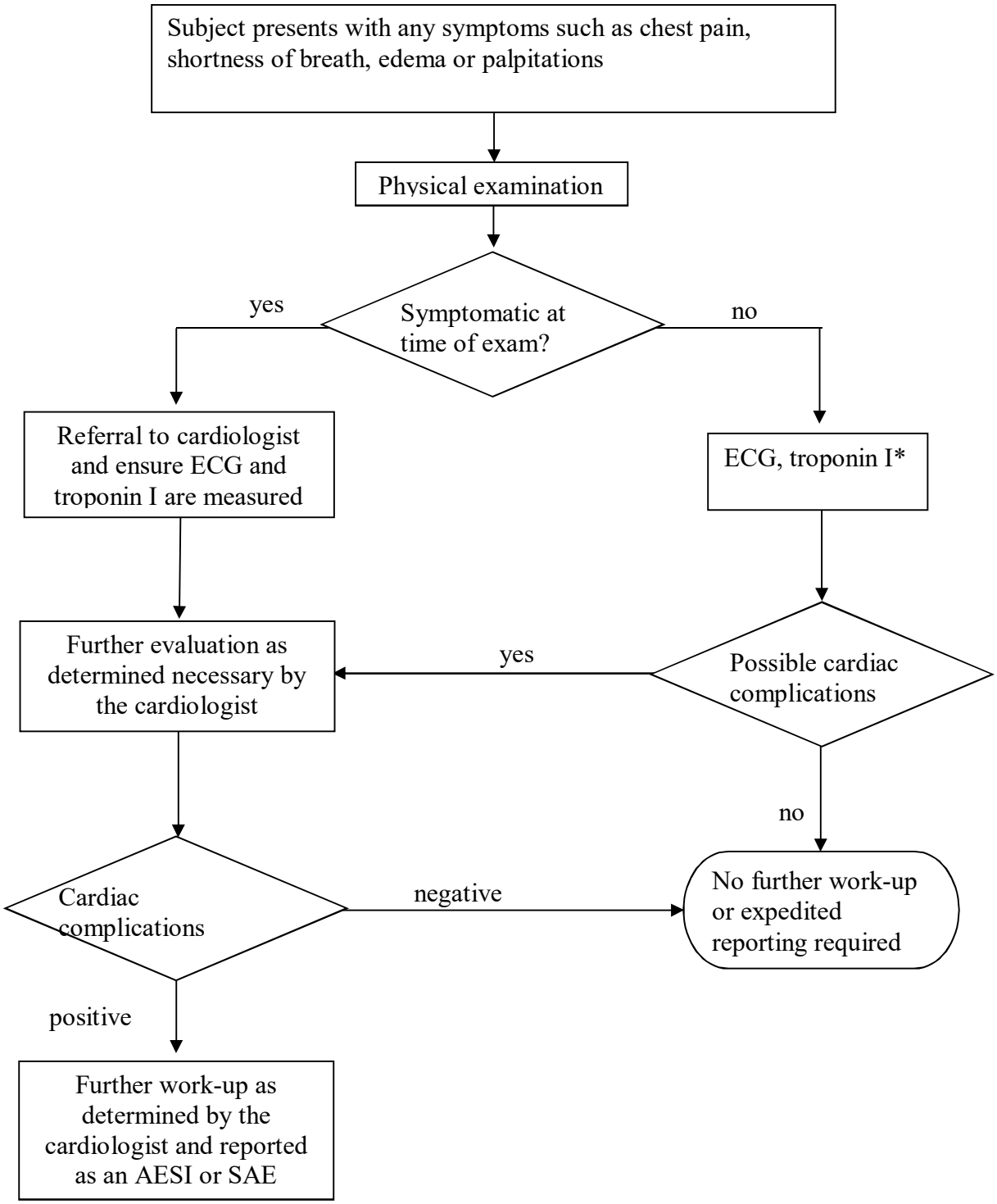

Figure 1 Algorithm for Assessment of Cardiac Events

*At any protocol-scheduled ECG and/or troponin I abnormality, the algorithm will begin at this point.

8.2.8 Safety Laboratory Measurements

The intensity of laboratory / systemic quantitatively measured toxicities will be graded according to the toxicity scale in Section 16.1; Appendix I: Toxicity Scale for Laboratory Values. These grading scales include the laboratory values determined with the routine safety parameters. In case of other laboratory values not included in the routine safety laboratory and not listed in Section 16.1; Appendix I: Toxicity Scale for Laboratory Values, the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004, Clarification August 2009 will be used for grading of laboratory toxicities.

Safety laboratory is determined at SCR, Visit 2, Visit 4, Visit 7 (Group 3 only) and at any other visit(s) if clinically indicated. The safety laboratory measurements are performed at a central laboratory. Laboratory normal ranges are provided by the central laboratory and filed in the Investigator File. Safety laboratory parameters to be evaluated are:

Hematology: Red blood cell count, hemoglobin, total and differential White Blood Cell count (WBC), platelet count (Hematocrit, mean corpuscular/cell volume (MCV), mean corpuscular/cellular hemoglobin (MCH) , mean corpuscular hemoglobin concentration (MCHC) and red blood cell distribution width (RDW) are routinely performed as part of the complete blood cell count and will be included in the laboratory report).

HIV specific parameters: CD4 count will be determined with every safety laboratory and at Visit 8 and FU 1 and FU 2. Viral load will be determined at SCR and at Visit 2. Viral load will be determined at any other visit if clinically indicated.

Serum chemistry:

Total bilirubin, AP, AST, ALT, serum creatinine (for calculation of CrCl at SCR), sodium, potassium, calcium, troponin I (troponin mandatory at SCR and in addition Visit 2, Visit 4 and Visit 7 (Group 3 only)).

Pregnancy test:

A β-human choriogonadotropin (HCG) pregnancy test will be conducted for all WOCBP at SCR, within 24 hours prior to each vaccination and at the individual last active trial phase visit (i.e. Visits 1, 3, 5 and Visits 6 and 8 for Group 3 respectively). At SCR a serum β-HCG pregnancy test will be performed; all other pregnancy tests will be conducted as urine β-HCG tests.

The following parameters will only be evaluated during the screening period for assessment of inclusion / exclusion criteria and at the following visits only if clinically indicated:

Cholesterol
Total, HDL and LDL

8.2.9 Pregnancy

As per inclusion criteria, women of childbearing potential must have a negative serum pregnancy test at SCR and a negative urine pregnancy test within 24 hours prior to each vaccination. In addition, they must have used an acceptable method of contraception for 30 days prior to the first vaccination, must agree to use an acceptable method of contraception during the trial, and must avoid becoming pregnant for at least 28 days after the last vaccination. Nevertheless, IMP exposed pregnancies cannot be excluded with certainty. Subjects who become pregnant prior to the first vaccination will be excluded from the trial and are regarded as screening failure. Subjects who become pregnant during the active trial period (up to and including one month [minimum 28 days] after receiving a dose of vaccine) must not receive additional doses of vaccine but may continue other trial procedures at the discretion of the investigator (see Section 4.2.5). All reports, where the embryo or foetus may have been exposed to the IMP (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up until delivery in order to collect information on the outcome of the pregnancy.

Subjects should be instructed to notify the investigator if it is determined – also after completion of the trial – that they became pregnant either during the trial or within one month (minimum 28 days) after receiving the last vaccine dose.

8.3 Reporting

8.3.1 Reporting of SAEs

All SAEs occurring throughout the entire course of the trial have to be reported to the CRO Drug Safety (DS) Department. The CTS has to send the completed SAE form by e-mail or fax to the CRO DS Department within 24 hours of becoming aware of the SAE.

If not reported via an eCRF, SAE reports should be faxed to the following number:

The investigator should not delay reporting because of missing information. Nonetheless, the report should be as complete as possible. This initial notification should include, as a minimum, sufficient information to permit identification of the following:

- the reporter (investigator's name and contact information)

- the subject
- involved trial medication
- AE(s)
- seriousness criterion and/or criterion for AESI
- date of onset

The CRO DS Department alerts BN DS Department of all SAEs and provides the available information within 24 hours to BN DS. BN is responsible for expedited as well as periodic reporting to the involved regulatory authorities (e.g. FDA, EMA, Paul Ehrlich Institut [PEI]) according to applicable laws and guidelines. Regulatory authorities will be notified as soon as possible but no later than seven days after first knowledge of fatal or life-threatening unexpected SAE with an at least possible relationship to the IMP (SADR) and no later than 15 days after knowledge of any other unexpected SADR. In addition BN will report the SAEs to the DSMB, while the investigator or the CRO is responsible for reporting to the Ethics Committees or Institutional Review Boards. Figure 2 outlines the reporting process and timelines for SAEs.

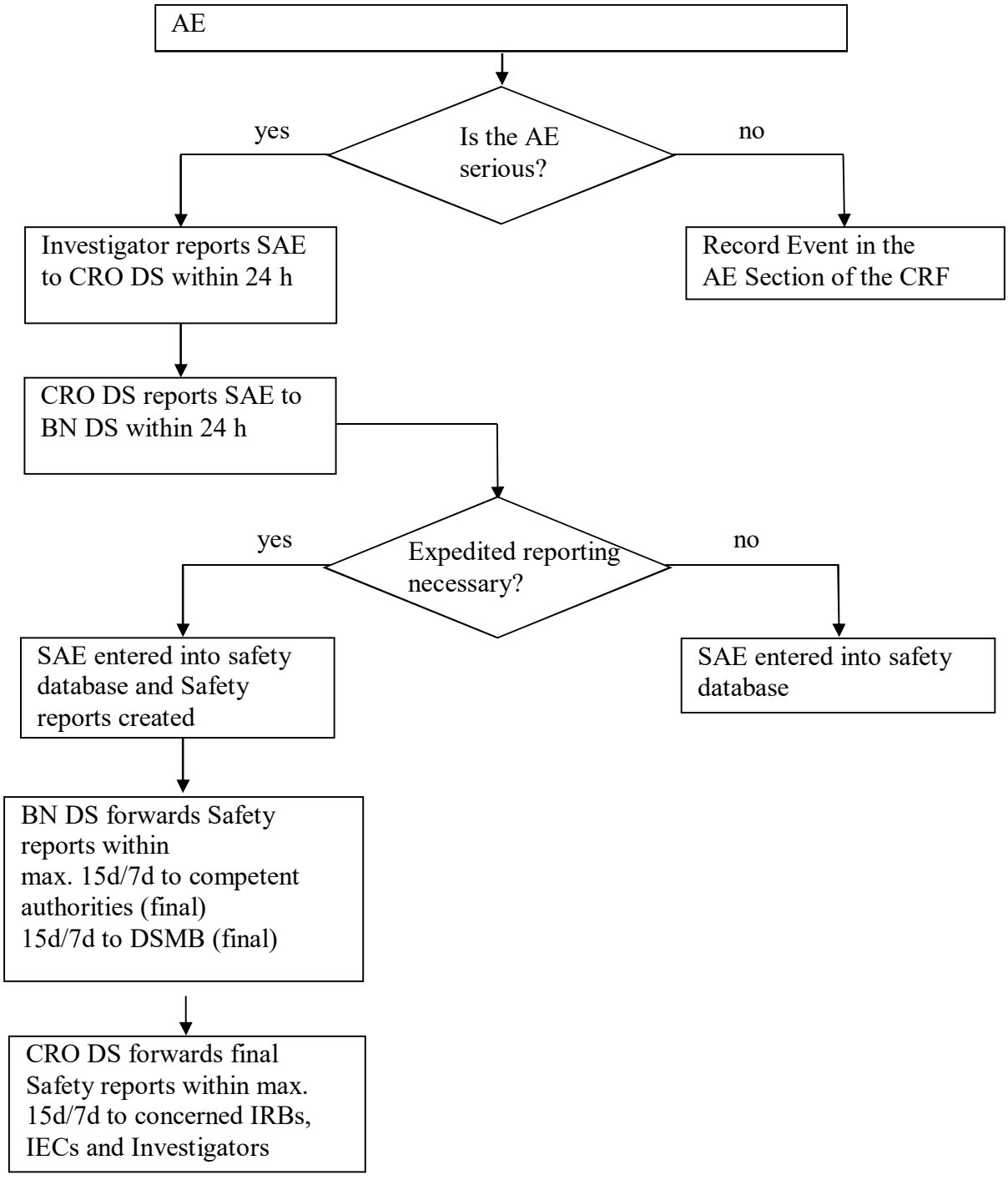

Figure 2 Algorithm for Reporting of SAEs

8.3.2 Reporting of AESIs

AESIs occurring throughout the entire course of the trial will be reported in the AE section of the eCRF by marking the appropriate tick box. AESIs have to be reported in the eCRF immediately after detection. An automatic email notification will be sent to the relevant project members as soon as an AESI was reported. A periodic report of AESIs will be provided from the CRO to BN Drug Safety.

Figure 3 outlines the reporting process and timelines for AESIs.

8.3.3 Reporting of Pregnancy

If a subject becomes pregnant during the active trial period (up to and including one month [minimum 28 days] after receiving a dose of vaccine) this must be reported to BN on a Pregnancy Report Form within 24 hours of the investigator's becoming aware of the event.

A pregnancy should be followed to term, any premature terminations reported, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to BN as soon as possible after delivery.

Any event during pregnancy fulfilling the criteria for an SAE will be reported as SAE to BN/CRO DS (see Section 8.3.1). However, hospitalization for delivery is a prospectively planned hospitalization and is not considered a SAE per se.

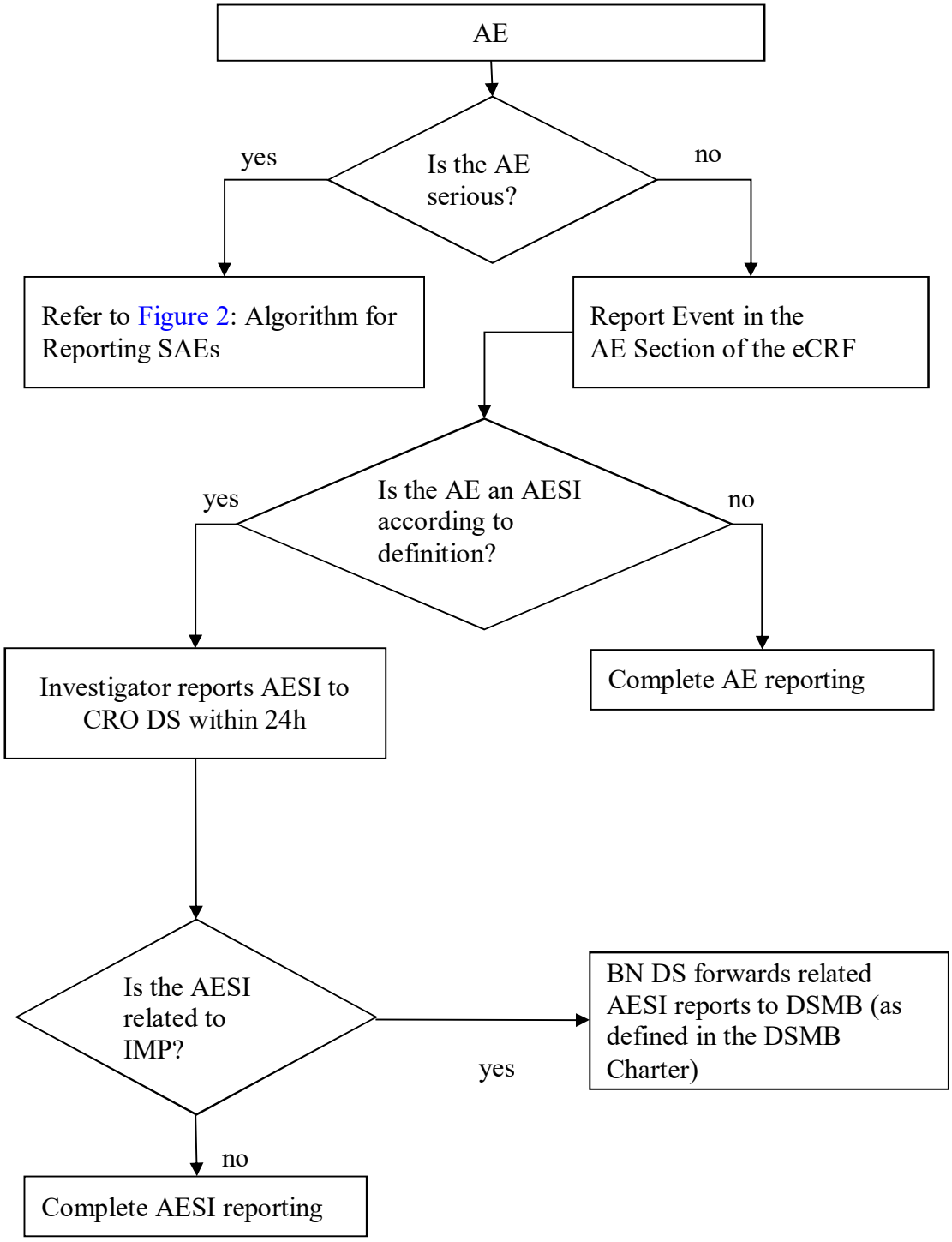

Figure 3 Algorithm for Reporting of AESIs

9 Statistical Considerations

The primary endpoint of this trial is to compare the occurrence, relationship and intensity of any serious and / or unexpected Adverse Event at any time during the trial. This analysis will be descriptive.

9.1 Randomization Procedure

Randomized treatment assignments for the subjects will be done after confirmation of subject's eligibility. Subjects will be allocated randomly across the trial into Group 1, Group 2 or Group 3. Randomization will be stratified by CTS in a 1:1:1 ratio.

Please refer to trial protocol synopsis (see Section 1.5).

9.2 Sample Size Calculation

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

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 Δ / SD > 0.74. Taking into account the relative SD of 0.85 for the log10 PRNT titers the detection of a log10 PRNT difference of 0.629 can be detected (or a four-fold increase in titers on the original titer scale). For the ELISA where the log10 SD is at most 0.42 a difference of 0.31 can be detected, i.e. a two-fold increase in titers can be detected.

9.3 Trial Cohorts/Datasets to be Evaluated

Analysis of immunogenicity variables will be done on a valid case basis, i.e. for missing observations no imputation technique such as "Last observation carried forward" (LOCF) will be applied, since this could introduce an optimistic bias into the analysis.

Full Analysis Set (FAS):

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

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

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) 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 for the classification of subjects into the various subsets will be made on a case-by-case basis in a data review meeting prior to database lock.

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

9.4 Biometrical Evaluation

9.4.1 Main Analysis

As soon as the last subject has completed FU 2 and after any necessary settlement of queries etc. in the eCRFs a data review meeting will be held and the subjects will be assigned to the datasets as described in Section 9.3. After the data review meeting and necessary settlement of queries that may arise during the data review meeting, the database will be locked. The final analysis will then be performed and will include all immunogenicity and safety data up to and including FU 2. Results of the final analysis will be reported in the Clinical Study Report (CSR).

9.4.2 Presentation of Data

For biometrical analysis, data obtained in this trial and documented in the eCRFs will be listed. For parameters of interest, summary tables with descriptive group statistics for metrical variables will be prepared. For categorical / dichotomous variables summary tables showing the absolute and relative count in each category will be prepared.

Full details of the analyses will be defined in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the respective database lock. The CRO will be responsible for data management and statistical evaluation. Data will be analyzed using SAS®.

Antibody titers and derived parameters, e.g. GMTs and seroconversion rates, will be assessed by vaccinia-specific ELISA and vaccinia-specific PRNT methods as described in Section 7.1.

Clinical laboratory test results will be marked whether the result is below, within or above the respective reference range. The number of values outside of the corresponding reference range will be counted.

All ECGs will be evaluated by a centralized procedure as described in the ECG Assessment Plan. Detailed descriptive analysis of the reasons/category of ECG abnormalities will be performed.

The occurrence of solicited local and general AEs during the 8-day period post vaccination (Days 0–7) will be summarized on a per subject and per vaccination basis.

Unsolicited AEs will be coded using MedDRA coding terminology. The intensity of AEs will be graded according to Section 8.2.

AESIs will be separately listed and tabulated.

SAEs will be listed separately. Each SAE will be described individually in detail.

10 Ethical Aspects

10.1 Ethical and Legal Regulations

The PIs are to ensure that this clinical trial is conducted in complete accordance with the provisions of the 2013 version of the Declaration of Helsinki, the national laws and other guidelines for the conduct of clinical trials like the ICH GCP to guarantee the greatest possible subject protection.

10.2 Approval by an IEC / IRB

The clinical trial protocol must be reviewed by the competent IEC / IRB according to the national laws of the respective CTS before the first subject is included in this trial.

If one of the investigators is a member of one of these committees, he/she may not vote on any aspect of the review of this protocol.

The Sponsor will assure that the IEC / IRB is informed of any amendment to the protocol and any unanticipated problems involving risks to human subjects included in the trial. Such information will be provided to the IEC / IRB at intervals appropriate to the degree of subject risk involved, but not less than once a year. Copies of all correspondence between the investigator and the IEC / IRB must be forwarded immediately to the Sponsor. In case of withdrawal of IEC / IRB approval of the trial, the Sponsor has to be contacted immediately by facsimile, e-mail or telephone.

10.3 Confidentiality and Data Protection

The PI of the respective CTS is obliged to ensure anonymity of the subject. He/she has to make sure that all documents including eCRFs provided (e.g. in the course of a marketing authorization procedure) to third parties (in this case: to the manufacturer of MVA-BN® smallpox vaccine or to an authority) contain no subject names.

Only a subject and site number may identify subjects. Their name or clinic and subject's medical record number may not be used. The PI keeps separate confidential subject logs for trial enrollment which allows subject numbers to be matched with names and addresses of subjects at any time. Documents not meant to be passed on to third parties have to be stored securely by the PI.

Any information collected in the course of the trial may be made available only to persons directly involved in this trial (PI and his staff members, monitors, statisticians) or to authorized

persons by the Sponsor or the PI or authorities. The Sponsor of the trial will only receive pseudonymized data for analysis.

11 Informed Consent

No subject can participate in this trial without having given informed consent in writing after the investigator or his delegate has informed the subject clearly and completely, verbally and in writing, over the purpose, procedures, the potential future use of blood samples and potential benefits and risks of the trial prior to any trial specific procedure.

One signed copy of the Informed Consent including HIPAA must be given to each subject and one signed copy must remain in the Investigator Site File and be available for verification by the monitor, Sponsor/CRO auditor or competent regulatory authorities at any time.

Subjects must be informed unequivocally that they may refuse participation in the trial and that they may withdraw from the trial at any time and for whatever reason and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician.

Subjects also consent to authorize the monitor, quality assurance personnel and regulatory authorities to inspect source documents for data verification and quality assurance purposes. Such verifications will always be conducted at the CTS and under the ethical supervision of the investigator. All aspects of the confidentiality of the subject's data will be guaranteed.

The Informed Consent will be prepared in accordance with ICH GCP guidelines and must be approved by the appropriate IEC / IRB.

12 eCRFs and Retention of Records

12.1 eCRF

In this trial, the use of an eCRF is planned.

All eCRFs are to be filled out completely by the trial personnel, then reviewed and signed electronically by the PI to confirm their correctness in a timely manner. It is the PI's responsibility to ensure that all subject data entered including discontinuations or changes in trial or other medications in the eCRF are accurate and supported by the subject's medical records unless the eCRF has been declared as source documentation by BN. The eCRFs for any subject leaving the trial should be completed at the time of the final visit or shortly thereafter.

12.2 Retention of Records

Essential documents as listed in ICH GCP need to be archived according to ICH GCP or national law, whatever is longer.

To meet regulatory requirements, the original source data and an electronic copy of the eCRF data will be stored at the respective CTS. The eCRF data will be stored and archived according to the Clinical Data Interchange Standards Consortium (CDISC) Operational Data Modeling (ODM) (see www.cdisc.org for details). Since CDISC ODM is also the source for the Electronic Data Capture web-based system, no transcription of data is necessary. If needed, paper copies (file printouts) can be created from the ODM file.

12.3 Monitoring of the Trial

The CRO (contact information to be found in the "Responsibilities" section in the beginning of this protocol) will be contracted to perform monitoring services according to ICH GCP.

Monitoring will be conducted according to the monitoring plan which must be approved by BN and the CRO. The monitoring plan will specify in detail the items for source data verification and other tasks, to be performed by the Clinical Research Associate (CRA) during the CTS visit.

The CRA is responsible for obtaining an overview of the course of the trial in co-operation with the investigators, checking if the clinical trial protocol is being observed, and helping the investigators to solve any problems which may arise. All documents in the context with this clinical trial will be handled confidentially at all times.

The PI has agreed to give the CRA access to relevant hospital or clinical records to confirm their consistency with the eCRF entries and to obtain an adequate overview of the course of the trial. The CRA verifies that the entries in the eCRF are complete, accurate and supported by source documents. In addition the CRA will verify that all required data documented in the source were transferred accurately in the eCRF. This will be done under preservation of data protection.

The source data verification must be performed by direct insight in the subject's record. If a subject refuses to consent to this procedure, he/she may not be enrolled in the trial. The CTS will provide direct access to all trial related data for the purpose of monitoring and inspection by local and regulatory authorities. The PI (or a representative) has further agreed to support the monitor in solving any problems he/she discovers during his/her visits.

13 Audits and Inspections

Audits and inspections may be carried out by the quality assurance department (BN and/or CRO), local authorities, or authorities to whom information on this trial has been submitted. All documents pertinent to the trial must be made available for such audits / inspections. Informed consent of subjects participating in this trial has to include the consent in this access to source documents.

14 Responsibilities of the PI

The PI agrees to carry out the trial in accordance with the guidelines and procedures outlined in this clinical trial protocol. The PI especially consents to strictly adhere to the ethical principles (see Section 10 of this protocol).

Changes to the protocol require written "Amendments to the protocol" and written approval by the IEC/IRB, the Coordinating Investigator and the PI of the respective CTS. Changes are allowed only if the trial value is not reduced and if they are ethically justifiable. The amendment must be passed on to all participating investigators with the obligation to adhere to its provisions. If warranted, the subject information has to be changed accordingly.

It is within the responsibility of the investigator that the eCRF has to be completed in a timely manner after each subject visit and electronically signed after the subject has finished the trial for each subject participating in the trial.

At the conclusion of the trial, the investigator will return all partly used, unused and empty drug containers to the Sponsor or the drug containers will be destroyed at the CTS according to local legal requirements.

The investigator may ask to terminate participation in the trial due to administrative or other reasons. If this should be the case, appropriate measures which safeguard the interests of the participating subjects must be taken after verification and consultation with the PI.

Each investigator will maintain appropriate medical and research records for this trial, in compliance with ICH E6 (R1) Guideline for GCP, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. He/she will permit authorized representatives of the Sponsor and regulatory agencies to review (and, when required by applicable law, to copy) clinical records for the purposes of quality reviews, audits/inspections, and evaluation of the trial safety and progress.

The PI agrees to follow the detailed publication policy included in the clinical trial agreement.

By signing this protocol, the PI confirms that he/she has read the entire clinical trial protocol, agrees to its procedures, and will comply strictly with the formulated guidelines.

15 References

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16 Appendices

16.1 Appendix I: Toxicity Scale for Laboratory Values

Grade 1 or Grade 2 toxicity is only graded according to Table 6 and Table 7, if the value is outside of the institutional normal range applicable for this trial. Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded. The values provided in Table 6 and Table 7 are based on the 'Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events' Version 1.0, December 2004, Clarification August 2009.

Estimating severity grade
For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

Grade 1	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with daily activities.
Grade 2	An AE which is sufficiently discomforting to interfere with daily activities.
Grade 3	An AE which prevents daily activities. Such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.
Grade 4	Life-threatening or disabling.

Serious or life-threatening AEs
ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a Grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: Seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

Table 6 Toxicity Scale for Serum Chemistry

Lab Value	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium – Hyponatremia mmol/L	130 - 135	125 - 129	121 - 124	≤ 120
Sodium – Hypernatremia mmol/L	146 - 150	151 - 154	155 - 159	≥ 160
Potassium – Hyperkalemia mmol/L	5.6 - 6.0	6.1 - 6.5	6.6 - 7.0	> 7.0
Potassium – Hypokalemia mmol/L	3.0 - 3.4	2.5 - 2.9	2.0 - 2.4	< 2.0
Calcium – Hypercalcaemia mmol/L	2.65 - 2.88	2.89 - 3.13	3.14 - 3.38	> 3.38
Calcium- Hypocalcaemia mmol/L	1.95 - 2.10	1.75 - 1.94	1.53 - 1.74	< 1.53
Serum creatinine mg/dl	1.1 - 1.3 x ULN	1.4 - 1.8 x ULN	1.9 - 3.4 x ULN	≥ 3.5 x ULN
Alkaline Phosphatase increase by factor	1.25 - 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 10 x ULN	> 10 x ULN
ALT (SGPT) and AST (SGOT) increase by factor	1.25 - 2.5 x ULN	2.6 - 5.0 x ULN	5.1 - 10 x ULN	> 10 x ULN
Total Bilirubin increase by factor	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5.0 x ULN	> 5.0 x ULN
Cardiac troponin I increase by factor	N/A	N/A	N/A	Levels consistent with myocardial infarction or unstable angina
Total Cholesterol (fasting) mg/dl	200 - 239	240 - 300	> 300	N/A

Table 7 Toxicity Scale for Hematology

Lab Value	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (HIV positive) g/dl	8.5 - 10	7.5 - 8.4	6.5 - 7.4	< 6.5
WBC Increase cell/mm^3	> ULN - < 15,000	≥ 15,000 - < 20,000	≥ 20,000	N/A
WBC Decrease cell/mm^3	2,000 - 2,500	1,500 - 1,999	1,000 - 1,499	< 1,000
Lymphocytes Decrease cell/mm^3	600 - 650	500 - 599	350 - 499	< 350
Neutrophils Decrease cell/mm^3	1,000 - 1,300	750 - 999	500 - 749	< 500
Platelets Decreased cell/mm^3	100,000 - 124,999	50,000 - 99,999	25,000 - 49,999	< 25,000

16.2 Appendix II: Case Definitions Acute Myocarditis / Pericarditis

16.2.1 Case Definition for Acute Myocarditis

A possible case of acute myocarditis is defined by the following criteria and the absence of evidence of any other likely cause of symptoms:

Presence of dyspnea, palpitations, or chest pain of probable cardiac origin in a subject with either one of the following:

- ECG abnormalities beyond normal variants, not documented previously, including
- ST-segment or T-wave abnormalities,
- Paroxysmal or sustained atrial or ventricular arrhythmias,
- AV nodal conduction delays or intraventricular conduction defects, or
- Continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy, or
- Evidence of focal or diffuse depressed left-ventricular (LV) function of indeterminate age identified by an imaging trial (e.g., echocardiography or radionuclide ventriculography).

A probable case of acute myocarditis, in addition to the above symptoms and in the absence of evidence of any other likely cause of symptoms, has one of the following:

- Elevated cardiac enzymes, specifically, abnormal levels of cardiac troponin I, troponin T, or creatine kinase myocardial band (a troponin test is preferred);
- Evidence of focal or diffuse depressed LV function identified by an imaging trial (e.g., echocardiography or radionuclide ventriculography) that is documented to be of new onset or of increased degree of severity (in the absence of a previous trial, findings of depressed LV function are considered of new onset if, on FU studies, these findings resolve, improve, or worsen); or
- Abnormal result of cardiac radionuclide imaging (e.g., cardiac magnetic resonance imaging with gadolinium or gallium-67 imaging) indicating myocardial inflammation.

A case of acute myocarditis is confirmed if histopathologic evidence of myocardial inflammation is found at endomyocardial biopsy or autopsy.

16.2.2 Case Definition for Acute Pericarditis

A possible case of acute pericarditis is defined by the presence of

- Typical chest pain (i.e., pain made worse by lying down and relieved by sitting up and/or leaning forward) and no evidence of any other likely cause of such chest pain.

A probable case of acute pericarditis is a possible case of pericarditis, or a case in a person with pleuritic or other chest pain not characteristic of any other disease, that, in addition, has one or more of the following:

- Pericardial rub, an auscultatory sign with one to three components per beat,
- ECG with diffuse ST-segment elevations or PR depressions without reciprocal ST depressions that are not previously documented, or
- Echocardiogram indicating the presence of an abnormal collection of pericardial fluid (e.g., anterior and posterior pericardial effusion or a large posterior pericardial effusion alone).

A case of acute pericarditis is confirmed if histopathologic evidence of pericardial inflammation is evident from pericardial tissue obtained at surgery or autopsy.

16.3 Appendix III: Interpretation Support for Assessment of Screening ECGs

For a clearer and mutual understanding of inclusion criterion #17, the following provides clarifying explanations and examples pertaining to eligibility for enrollment.

Examples of subjects eligible for enrollment:

- Non-specific ST and T wave changes are not considered clinically significant and subject can be enrolled.
- Sinus bradycardia which does not require clinical intervention is not considered clinically significant and subject can be enrolled.
- Subjects who present with atrial disease which do not require clinical intervention, e.g. a pacemaker or drug treatment, are allowed to be enrolled, as these can be considered not clinically significant. Examples are premature atrial contractions or ectopic atrial beats.
- Occasional PVCs which do not require clinical intervention are not considered clinically significant and subject can be enrolled.
- First degree atrioventricular block or PR interval prolongations are also acceptable as long as they do not require clinical intervention, i.e. do not represent an indication for a pacemaker, and therefore the condition can be classified as not clinically significant.
- Right or left axis deviation which does not require clinical intervention is not considered clinically significant and subject can be enrolled.
- QTc prolongations < 500 ms which do not require clinical intervention are not considered clinically significant and subject can be enrolled. QTc prolongations > 500 ms which do not require clinical intervention should be discussed with the Medical Monitor before enrollment.

Examples of subjects NOT eligible for enrollment:

- Second or third degree atrioventricular block could represent significant heart disease and subject should not be enrolled.
- Incomplete left bundle branch blocks could represent significant heart disease and subject should not be enrolled.
- Significant ventricular disease represented by complete intraventricular conduction defects (complete left or right bundle branch block) must be considered clinically significant and subjects presenting with any such condition should not be enrolled. Left anterior or posterior intraventricular fascicular blocks or hemiblock could represent ventricular disease and subject should not be enrolled.
- ST elevation consistent with ischemia, subject should not be enrolled.
- Two PVCs in a row, subject should not be enrolled.

16.4 Appendix IV: Grading Scale for Lymphadenopathy

A grading scale for lymphadenopathy would apply as follows:

Grade 0 (normal finding):	No palpable lymph nodes or lymph nodes up to a diameter of 1 cm, soft, non-tender
Grade 1 (mild):	Slightly palpable lymph nodes or lymph nodes up to a diameter of 1 cm, bilaterally enlarged lymph nodes, signs of tenderness
Grade 2 (moderate):	Markedly palpable lymph nodes or lymph node diameter exceeds 2 cm, bilaterally enlarged lymph nodes, pain, skin redness, warmth, limiting instrumental daily life activities
Grade 3 (severe):	Markedly palpable lymph nodes or lymph node diameter exceeds 2 cm, generalized enlargement of lymph nodes, severe pain, general symptoms like fever and sweating limiting self-care daily activities

16.5 Appendix V: Amendment #4

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

Amendment # 4 to Clinical Trial Protocol Edition 4.0 dated 20-Aug-2014

Date of Amendment 4: 18-Nov-2014

1 Rationale

With the objective to collect long term safety and immunogenicity data a one year follow up visit (FU 2) has been added to the visit schedule.

As a result from the first DSMB meeting conducted on October 30th, 2014 the procedure for following up on adverse event of special interest was adapted in accordance with the DSMB recommendation.

Communication with clinical trial site made it obvious that the term 'enrollment' is ambiguous and can be understood in different ways. Triggered by this discussions the inclusion/exclusion criteria have been reworded for clarity in accordance with the information provided to the clinical trial sites.

A discrepancy between laboratory measurements as described in the protocol versus actual trial processes was detected recently and corrected throughout the protocol.

Changes are outlined in the section 2 below.

2 Changes

General Changes:

- A one year follow-up visit (FU2) was added to the Trial Procedure Schedule (Section 1.6) and Section 4.2.3 Follow-Up Phase. For practical reasons this additions are not shown in the detailed table of changes below. Please refer to respective paragraphs to review the additions.
- The protocol (Section 8.2.8) states that CD3 count will be determined in addition to CD4 counts. However, only CD4 counts are determined and reported in course of the safety laboratory measurements. Section 8.2.8 has been revised accordingly and all references to CD3 counts have been removed throughout the protocol. Not every single change in this regard is listed in the table of changes below.
- Section 2.6 was reviewed to reflect the status in accordance with current IB. Only safety relevant changes are shown in table of changes below.
- During preparation of this amendment the whole protocol has been reviewed and updated for formal consistency. Formatting and/or stylistic changes are not listed in the table of changes below.

Relevant changes are listed in detail in the table of changes below.

Changes / added terms are highlighted in **bold** letters in the text below, removed terms are in *italic* letters.

Clinical Trial Protocol Edition #4.0, dated 20-Aug-2014 Previously written:	**Revised Clinical Trial Protocol Edition #5.0, dated 18-Nov-2014 Changed to:**
Page 15, 1.5 Protocol Synopsis, Number of sites	**Page 15, 1.5 Protocol Synopsis Number of sites**
Up to *8* sites in the USA	Up to **10** sites in the USA **Reason for change:** Additional sites needed to meet enrollment goal.
Page 16, 1.5 Protocol Synopsis, Trial Duration	**Page 16, 1.5 Protocol Synopsis, Trial Duration**
Up to *48* weeks per subject	Up to **75** weeks per subject **Reason for change:** Addition of one year follow up.
Page 16 & 17, 1. 5 Protocol Synopsis, Secondary Endpoints	**Page 16 and 17, 1. 5 Protocol Synopsis, Secondary Endpoints**
GMTs after vaccination with MVA-BN® smallpox vaccine measured by ELISA and PRNT at 6 months Follow-up (FU) Visit of Group 3 compared to respective FU Visit of Group 1 and Group 2 (separately). Seroconversion after vaccination with MVA-BN® smallpox vaccine measured by ELISA and PRNT at 6 months FU Visit of Group 3 compared to respective FU Visit 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, FU) of Group 2 and 3 (separately) compared to Group 1.	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 Visit**s** 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 Visit**s** 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. **Reason for change:** Addition of one year follow up.

Clinical Trial Protocol Edition #4.0, dated 20-Aug-2014 Previously written:	**Revised Clinical Trial Protocol Edition #5.0, dated 18-Nov-2014 Changed to:**
Page 18, 1. 5 Protocol Synopsis, Trial Design, Visit Schedule	**Page 18, 1. 5 Protocol Synopsis, Trial Design, Visit Schedule**
Visit (V) Day Target Week FU V3 (V6*) +182 to 210 days 30 (38*)	Visit (V) Day Target Week FU **1** V3 (V6*) +182 to 210 days 30 (38*) **FU 2 V3 (V6*) +364 to 392 days 56 (64*)** **Reason for change:** Addition of one year follow up
Page 19 & 20, 1. 5 Protocol Synopsis, Inclusion Criteria 3, 5, 6, 16	**Page 19, 1. 5 Protocol Synopsis, Inclusion Criteria 3, 5, 6, 16**
3. On stable antiretroviral therapy (ART) i.e. Combination ART for at least 3 months prior to *enrollment* visit in this clinical trial with no change to the therapy during these 3 months. 5. *Current* CD4 counts ≥ 100 cells/µl ≤ 500 cells/µl. 6. Documented nadir CD4 count < 200 cells/µl at any time prior to *enrollment*. If nadir is not documented lowest documented CD4 count < 200 cells/µl at any time prior to *enrollment*. 16. Troponin I < 2 x ULN .	3. On stable antiretroviral therapy (ART) i.e. Combination ART for at least three months prior **to screening visit** in this clinical trial with no change to the therapy during these three months. 5. **Screening** CD4 counts ≥ 100 cells/µl **and** ≤ 500 cells/µl. 6. Documented nadir CD4 count < 200 cells/µl at any time prior to **screening visit**. If nadir is not documented lowest documented CD4 count < 200 cells/µl at any time prior to **screening visit.** 16. **Screening** Troponin I < 2 x ULN. **Reason for change:** Modified for clarity**.**
Page 21, 1.5 Protocol Synopsis, Exclusion Criteria 18, 19, 22	**Page 21, 1.5 Protocol Synopsis, Exclusion Criteria 18, 19, 22**
18. Acute disease (illness with or without a fever) at the time of *enrollment*. 19. Body temperature ≥100.4°F (≥38.0°C) at the time *enrollment*. 22. Use of immunosuppressant or immunomodulatory agents including systemic glucocorticoids (excluding nasal or inhaled	18. Acute disease (illness with or without a fever) at the time of **screening or at any time of vaccine administration.** 19. Body temperature ≥100.4°F (≥38.0°C) at the time **of screening or at any time of vaccine administration.** 22. Use of immunosuppressant or

Clinical Trial Protocol Edition #4.0, dated 20-Aug-2014 Previously written:	**Revised Clinical Trial Protocol Edition #5.0, dated 18-Nov-2014 Changed to:**
steroids), tacrolimus, sirolimus, rapamycin, mycophenolate, cyclosporine, TNF-alpha blockers or antagonists, azathioprine, interferon or growth factors, or intravenous immunoglobulin in the 60 days prior to *enrollment* in this clinical trial.	immunomodulatory agents including systemic glucocorticoids (excluding nasal or inhaled steroids), tacrolimus, sirolimus, rapamycin, mycophenolate, cyclosporine, TNF-alpha blockers or antagonists, azathioprine, interferon or growth factors, or intravenous immunoglobulin in the 60 days prior to **screening** in this clinical trial. **Reason for change**: Modified for clarity.
Page 29, 2.6.1 Safety Overview of MVA-BN®, Table 1	**Page 29, 2.6.1 Safety Overview of MVA-BN®, Table 1**
Skin and Subcutaneous Tissue Disorders Rare(≥1/10,000 to <1/1,000) Night sweats	Skin and Subcutaneous Tissue Disorders Rare(≥1/10,000 to <1/1,000) Night sweats **Angioedema** **Reason for change**: Updated with respect to the latest MVA-BN® Smallpox Vaccine Investigator's Brochure.
Page 47, 4.2.5. Withdrawal from Second or Booster vaccination	**Page 46, 4.2.5. Withdrawal from Second or Booster vaccination**
Start of chronic administration (defined as more than 14 days) of > 5 mg prednisone (or equivalent) per day or any other immune-modifying drugs.	Start of chronic **systemic** administration (defined as more than 14 days) of > 5 mg prednisone (or equivalent) per day or any other **systemic use of** immune-modifying drugs. **Reason for change:** Modified for clarity.
Page 47, 4.2.5. Withdrawal from Second or Booster Vaccination	**Page 47, 4.2.5. Withdrawal from Second or Booster Vaccination**
<u>Procedure:</u> If a subject did not receive the second trial vaccination the reason for this decision must	<u>Procedure:</u> If a subject did not receive the second trial vaccination the reason for this decision must

Clinical Trial Protocol Edition #4.0, dated 20-Aug-2014 Previously written:	**Revised Clinical Trial Protocol Edition #5.0, dated 18-Nov-2014 Changed to:**
be recorded in the eCRF. Visit 3 and Visit 4 are not required and the procedures below should be followed: • Visit 5 procedures have to be performed 28 to 35 days after last vaccination • FU *Visit* procedures have to be performed 182 to 210 days after last vaccination If a subject from treatment Group 3 did not receive the second or booster vaccination the reason for this decision must be recorded in the eCRF. Visits 6, 7 and 8 are not required and the procedures below should be followed: • FU *Visit* procedures have to be performed 182 to 210 days after last vaccination *visit*.	be recorded in the eCRF. Visit 3 and Visit 4 are not required and the procedures below should be followed: • Visit 5 procedures have to be performed 28 to 35 days after last vaccination • **FU 1** procedures have to be performed 182 to 210 days after last vaccination • **FU 2 procedures have to be performed 364 to 392 days after last vaccination.** If a subject from treatment Group 3 did not receive the second or booster vaccination the reason for this decision must be recorded in the eCRF. Visits 6, 7 and 8 are not required and the procedures below should be followed: • **FU 1** procedures have to be performed 182 to 210 days after last vaccination. • **FU 2 procedures have to be performed 364 to 392 days after last vaccination.** • **Reason for change:** Addition of one year follow up.
Page 48, 4.3. Trial Duration	**Page 47, 4.3. Trial Duration**
The total duration of the trial for each subject including the screening period and Follow-up visit will be up to *48* weeks.	The total duration of the trial for each subject including the screening period and Follow-up visits will be up to **75** weeks. **Reason for change:** Addition of one year follow up.
Page 51, 7.1. Humoral Immunogenicity	**Page 51, 7.1. Humoral Immunogenicity**
Immunogenicity testing will be performed on samples obtained from subjects of all three groups on trial Visit 1, Visit 3, Visit 4 and FU.	Immunogenicity testing will be performed on samples obtained from subjects of all three groups on trial Visit 1, Visit 3, Visit 4, FU1

Clinical Trial Protocol Edition #4.0, dated 20-Aug-2014 Previously written:	**Revised Clinical Trial Protocol Edition #5.0, dated 18-Nov-2014 Changed to:**
Further, immunogenicity testing will be performed on samples obtained from subjects of Group 3 on trial Visits 6 and 7. *Baseline* (i.e., Visit 1, Visit 3 and Visit 6) *blood samples* will be drawn prior to vaccination.	and FU 2. Further, immunogenicity testing will be performed on samples obtained from subjects of Group 3 on trial Visits 6 and 7. **Blood samples obtained on vaccination visits** (i.e., Visit 1, Visit 3 and Visit 6) will be drawn prior to vaccination. **Reason for change:** Addition of one year follow up and modification for clarity.
Page 54, 8.2.1. Relevant Medical History	**Page 54, 8.2.1. Relevant Medical History**
Diagnosis of HIV and disease state has to be documented separately: date of diagnosis, *disease stage*, nadir, viral load and CD4 count during *the last year* before SCR.	Diagnosis of HIV and disease state has to be documented separately: date of diagnosis, nadir, CD4 count and highest viral load **up to six months** before SCR. **Reason for change:** Modified to match procedures performed.
Page 55 & 56, 8.2.5. Unsolicited AEs	**Page 55, 8.2.5. Unsolicited AEs**
AEs for Group 1 and 2 will be assessed and documented at all visits except FU *visit* (Screening to Visit 5) and if ongoing at Visit 5, followed until resolution or until the FU *Visit* at the latest. AEs for Group 3 will be assessed and documented at all visits except FU *Visit* (i.e. Screening to Visit 8) and if ongoing at Visit 8, followed until resolution or until the FU *Visit* at the latest. SAEs/AESIs will be assessed and documented at all trial visits, including the FU *Visit*. Ongoing AESIs which occurred after at least one vaccination will be followed up until resolution or achievement of stable clinical	AEs for Group 1 and 2 will be assessed and documented at all visits except FU **1 and FU 2** (i.e. Screening to Visit 5) and if ongoing at Visit 5, followed until resolution or until the FU **2** at the latest. AEs for Group 3 will be assessed and documented at all visits except FU **1 and FU 2** (i.e. Screening to Visit 8) and if ongoing at Visit 8, followed until resolution or until the FU **2** at the latest. SAEs/AESIs will be assessed and documented at all trial visits, including the FU **1 and FU 2**. Ongoing AESIs which occurred after at least one vaccination will be followed up until resolution or achievement of stable clinical

Clinical Trial Protocol Edition #4.0, dated 20-Aug-2014 Previously written:	**Revised Clinical Trial Protocol Edition #5.0, dated 18-Nov-2014 Changed to:**
conditions. SAEs will be followed up until resolution or achievement of stable clinical conditions.	conditions. SAEs will be followed up until resolution or achievement of stable clinical conditions. **Reason for change:** Addition of one year follow up.
Page 59 & 60, 8.2.7. Cardiac Assessment	**Page 59 & 60, 8.2.7. Cardiac Assessment**
No changes to original test, only addition.	**In any case of cardiac signs or symptoms, or increased laboratory results for Troponin I, the subject will be asked to attend for an unscheduled visit at the site, in order to perform or repeat Troponin I testing, to perform a physical examination for cardiac symptoms and to record an unscheduled ECG.** **Further details regarding the follow-up of AESIs are described in the 'Investigator's Manual – Follow-up of Adverse Events of Special Interest'.** **Reason for change:** Implementation of DSMB recommendation.
Page 62 8.2.8. Safety Laboratory Measurements	**Page 62 8.2.8. Safety Laboratory Measurements**
HIV specific parameters: CD4 count *(as well as CD3 count, which is a standard part of the CD4 lab panel)* will be determined with every safety laboratory and at Visit 8 and FU *Visit*.	HIV specific parameters: CD4 count will be determined with every safety laboratory and at Visit 8 and FU **1 and FU 2.** **Reason for change:** Modified to match procedures performed and addition of one year follow up.