RSV-MVA-002

A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine

Clinical Trial Protocol, Edition 4.0

26-Apr-2018

NCT02873286

1 General Information

1.1 Investigator Signature Page

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

A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine.

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.

Function

(Date) (Signature) [Name, Department]

1.2 Coordinating Investigator Signature Page

A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine.

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 local legal and regulatory requirements applicable in the respective countries.

Function [redacted]

1.3 Sponsor Signature Page

By signing the protocol:

A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine

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 local legal and regulatory requirements applicable in the respective countries.

Coordinating Author	[redacted]
Medical Monitor	
Manager Immunology Laboratory	
Biostatistician	
Sr. Vice President Clinical Development	

1.4 Responsibilities

Trial Number	RSV-MVA-002
Title	A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine.
Coordinating Investigator Phone Fax E-mail	[redacted]
Sponsor and Product Supply MVA-BN-RSV vaccine Phone Fax	
Project Leader Phone Fax E-mail	
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ECG	
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Drug Depot

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List of Abbreviations

AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BFU	Booster Follow-Up
BFU1	Booster Follow-Up Visit 1
BFU2	Booster Follow-Up Visit 2
BFU3	Booster Follow-Up Visit 3
BMI	Body Mass Index
BN	Bavarian Nordic
BV	Booster Visit
CDISC	Clinical Data Interchange Standards Consortium
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CTS	Clinical Trial Site
DNA	Deoxyribonucleic Acid
DS	Drug Safety
EAP	End of Active Trial Phase
ECG	Electrocardiogram
eCRF(s)	Electronic Case Report Form(s)
ELISA	Enzyme-linked Immunosorbent Assay
ELISPOT	Enzyme-linked Immuno Spot Technique
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FI	Formalin Inactivated
FU	Follow-Up
FU1	Follow-Up Visit 1
FU2	Follow-Up Visit 2
GCP	Good Clinical Practice
GH-RH	Growth-Hormone Releasing Hormone
GMT	Geometric Mean Titer
GMFI	Geometric Mean Fold Increase
HbA1c	Glycated hemoglobin
HBsAG	Hepatitis B Surface Antigen
HCG	Human Choriogonadotropin

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IAS	Immunogenicity Analysis Set
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IM	Intramuscular
IL-4	Interleukin 4
IMP	Investigational Medicinal Product
Inf.U	Infectious Units
IRB	Institutional Review Board
LF	Liquid Frozen
LLN	Lower Limit of Normal
LRTI	Lower Respiratory Tract Infection
MCH	Mean Corpuscular/Cellular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular/Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MP	Medicinal Product
MVA	Modified Vaccinia Ankara Strain
MVA-BN	Modified Vaccinia Ankara – Bavarian Nordic also named IMVAMUNE or IMVANEX
n/N	Number
NIH	National Institutes of Health
ODM	Operational Data Modeling
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PEI	Paul Ehrlich Institute
PI	Principal Investigator
PPS	Per Protocol Set
PRNT	Plaque Reduction Neutralization Test
PV	Pharmacovigilance
PVC	Premature Ventricular Contractions
RDW	Red Blood Cell Distribution Width
RSV	Respiratory Syncytial Virus
RVP	Respiratory Viral Panel
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SC	Subcutaneous
SCR	Screening
SD	Standard Deviation
SFU	Spot Forming Unit
SMC	Safety Monitoring Committee
SMT	Safety Monitoring Team
SOP	Standard Operating Procedure
TBS	Tris-buffered Saline
$TCID_{50}$	Tissue Culture Infectious Dose 50 %
TEAE	Treatment-emergent Adverse Event
Th1/Th2	T-Helper Cells, Type 1/Type 2
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infection
V	Visit
VACV	Vaccinia Virus
VS	Staggering Visit
WBC	White Blood Cell Count
WOCBP	Women of Childbearing Potential

Definitions

Active trial phase	The trial phase starting with and including (Booster) Visit 1 and ending with and including (B)EAP (End of active trial phase) (V3/BV1 + 28-35 days; for details see Section 1.6 and Section 1.7).
Booster Baseline	Immune reponses measured at BV0
Booster Substudy	Administration of a single (booster) dose of MVA-BN-RSV vaccine approximately one year after the first MVA-BN-RSV vaccination in subjects previously vaccinated with MVA-BN-RSV in the main trial.
Dose 1	Represents the nominal titer of 1 x 10^8 Infectious Unit (Inf.U) per 0.5 mL.
Dose 2	Represents the nominal titer of 5 x10^8 Inf.U per 0.5 mL.
End of active trial phase ([B]EAP)	The last visit of the active trial phase (for details see Section 1.6 and Section 1.7).
Fold increase	The fold increase is defined as a subject's post-baseline titer at Visit X, divided by the baseline titer
Main Trial	In the main trial subjects receive two administrations 4 weeks apart consisting of MVA-BN-RSV Dose 1 (1 x 10^8 Inf.U), MVA-BN-RSV Dose 2 (5 x 10^8 Inf.U) or Placebo (TBS).
Nominal titer	The MVA-BN-RSV (Respiratory Syncytial Virus) vaccine is formulated at a nominal titer of 5 x 10^8 Inf.U per dose (0.5 mL). The actual titer will be evaluated by stability data.
Staggering visit (VS)	A visit only required by subjects enrolled into the sentinel and safety cohort in the main trial.
Subgroup	The subgroup consists of 20 subjects per treatment group in the main trial who have peripheral blood mononuclear cells (PBMC) collection as well as an additional serum and nasal swab sample collection time point one week post each vaccination. Out of this subgroup, approximately 13 subjects per treatment group will be recruited into the booster substudy.
Treatment group	Subjects are recruited into one of five treatment groups receiving different investigational medicinal product (IMP) doses and schedules.
Vaccination	Intramuscular administration of active MVA-BN-RSV vaccine or Tris-buffered saline (TBS)

1.5 Protocol Synopsis

Title	A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine
Clinical phase	Phase II
Sponsor	Bavarian Nordic A/S Hejreskovvej 10A, 3490 Kvistgård, Denmark
Coordinating Investigator	[redacted]
Number of sites and Country/ies	up to 16 sites in the USA
Vaccination dose and schedule	Liquid frozen (LF) suspension of MVA-mBN294B (common name MVA-BN-RSV vaccine), containing a nominal titer of 5 x 10^8 Inf.U per 0.5 mL. In total 400 subjects will be recruited into this trial. Subjects will receive two administrations 4 weeks apart which will consist of MVA-BN-RSV Dose 1 (1 x 10^8 Inf.U), MVA-BN-RSV Dose 2 (5 x 10^8 Inf.U) or Placebo (TBS). To obtain Dose 1 the MVA-BN- RSV vaccine will be diluted in MVA-BN formulation buffer (TBS) according to the study specific administration instructions. Following the main trial, two subgroups will be identified, which will continue in the booster substudy. The selection is based on safety and immunogenicity data obtained in the main trial. 86 subjects from 2 treatment groups (43 per treatment group) are supposed to receive one (booster) dose of MVA-BN-RSV vaccine approximately one year after their first vaccination. In this booster substudy, eligible subjects will receive the same dose they received during the main trial. For details on the treatment groups see Table 1

Route of administration	MVA-BN-RSV vaccine/TBS is administered intramuscularly (IM) into the deltoid muscle of the upper arm (preferably the non-dominant arm).
Trial duration	Up to 39 weeks per subject in the main trial and up to additional 56 weeks per subject enrolled in the booster substudy.
Sample size main trial	A total of 400 subjects will be recruited into 5 treatment groups à 80 subjects. PBMC collection will be performed in a subgroup of 20 subjects in each treatment group (total of 100 subjects). This subgroup will also have an additional serum and nasal swab sample collection time point one week post each vaccination in addition to the serum and nasal swab sample collection time points scheduled for all subjects.
Sample size booster substudy	From two treatment groups selected based on immunogenicity/safety parameters following primary vaccination (as determined by the sponsor), 43 subjects will be recruited into the booster substudy (86 subjects in total). Out of these, in total approximately 26 subjects will be recruited from the PBMC subgroup, approximately 13 subjects for each of the two selected treatment groups. Subjects will receive a single booster vaccination approximately 1 year after the first vaccine administration with the same dose they received during the main trial.
Primary objective	To assess the optimal dose and schedule of the MVA-BN-RSV vaccine in adult and elderly subjects in terms of immunogenicity.
Secondary objectives	To assess safety and reactogenicity of the MVA-BN-RSV vaccine in adult/elderly subjects To assess the RSV-specific humoral immune responses (in all subjects) and cellular immune responses (in a subgroup population of each group) against the MVA-BN-RSV vaccine in adult/elderly subjects.

	To explore a potential correlation of the RSV-specific immune response to RSV related respiratory disease symptoms. To assess the RSV-specific immune responses (in subjects of the selected treatment groups) one year after the last vaccination in the main trial in adult/elderly subjects. To assess the RSV-specific humoral immune responses (in subjects of the selected treatment groups) and cellular immune responses (in the respective subgroup population of the selected treatment groups) following a one year booster MVA-BN-RSV vaccination in adult/elderly subjects. To identify further potential differences in durability and/or boostability of immune responses in the two chosen MVA-BN-RSV dose regimens. To assess safety and reactogenicity of the MVA-BN-RSV vaccine following the booster vaccination in adult/elderly subjects.
Primary endpoint	Geometric Mean Titers (GMTs) after one or two MVA-BN-RSV vaccinations or placebo measured by Plaque Reduction Neutralization Test (PRNT; against strain A) 2 weeks post last vaccination
Secondary endpoints	**Safety** Occurrence, relationship to the trial vaccine and intensity of any serious adverse event (SAE). Occurrence of any Grade 3 or higher adverse events (AE) possibly, probably or definitely related to the trial vaccine within 4 weeks after each vaccination. Occurrence, intensity and duration of solicited local AEs 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 during the 8-day period (day of vaccination and the following 7 days) after each vaccination.

Occurrence, relationship to the trial vaccine and intensity of unsolicited non-serious AEs within 4 weeks after each vaccination.

Immunogenicity

RSV-specific antibody response rate measured by Immunoglobulin G (IgG) Enzyme-linked Immunosorbent Assay (ELISA) (total RSV, G protein A strain, G protein B strain) at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers (separately for main trial and booster substudy of the clinical trial).

RSV-specific GMT measured by IgG ELISA at all immunogenicity serum sampling time points and based on the individual peak titers (separately for main trial and booster substudy of the clinical trial).

RSV-specific antibody response rate measured by Immunoglobulin A (IgA) ELISA at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers (separately for main trial and booster substudy of the clinical trial).

RSV-specific GMT measured by IgA ELISA at all immunogenicity serum sampling time points and based on the individual peak titers (separately for main trial and booster substudy of the clinical trial).

RSV-specific antibody response rate measured by PRNT (RSV strain A) at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers (separately for main trial and booster substudy of the clinical trial).

RSV-specific GMT measured by PRNT (RSV strain A) at all immunogenicity serum sampling time points and based on the individual peak titers (separately for main trial and booster substudy of the clinical trial).

RSV-specific antibody response rate measured by PRNT (RSV strain B) at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers

	(separately for main trial and booster substudy of the clinical trial). RSV-specific GMT measured by PRNT (RSV strain B) at all immunogenicity serum sampling time points and based on the individual peak titers (separately for main trial and booster substudy of the clinical trial). RSV-specific antibody response rate measured by IgA ELISA at all post vaccination nasal swab sampling time points (mucosal IgA) and based on the individual peak titers (separately for main trial and booster substudy of the clinical trial). RSV-specific GMT measured by IgA ELISA at all nasal swab sampling time points (mucosal IgA) and based on the individual peak titers (separately for main trial and booster substudy of the clinical trial). RSV-specific response and responder rates measured by Interferon gamma (IFN-γ) and Interleukin 4 (IL-4) Enzyme-linked Immuno Spot Technique (ELISPOT) at all post vaccination PBMC sampling time points until EAP and until BEAP. RSV-specific median and geometric mean Spot Forming Units (SFU) measured by IFN-γ / IL-4 ELISPOT at all PBMC sampling time points until EAP and until BEAP. RSV-specific memory B cells measured at FU1 and FU2 as well as Booster Follow Up Visit 1 (BFU1) and Booster Follow Up Visit 2 (BFU2). Incidence of RSV-specific disease and correlation with immunogenicity readouts.
Trial design main trial	Randomized, single-blind, placebo controlled, dose-ranging **Table 1 Treatment Groups**

Group	N	Age [years]	Volume per dose [mL]	1st vaccination Day 0 [Inf.U]	2nd vaccination Day 28 [Inf.U]	Route
1	80	≥ 55	0.5	1×10^8	Placebo	IM

2	80	≥ 55	0.5	1×10^8	1×10^8	IM
3	80	≥ 55	0.5	5×10^8	Placebo	IM
4	80	≥ 55	0.5	5×10^8	5×10^8	IM
5	80	≥ 55	0.5	Placebo	Placebo	IM
Total	**400**					

Subjects will be stratified by age into two groups: 55 < 70 and ≥ 70 years of age. In order to have the highest power to detect differences between the strata recruitment will be aimed for equal distribution across the age strata; a minimum of 20 subjects per treatment group in the age stratum ≥ 70 years are required.

Recruitment into the trial will be performed in a staggered manner. The staggering process will be performed at one clinical trial site. The trial will start with a sentinel cohort with 2 subjects, of whom one subject will be recruited into Group 2 and the other subject into Group 4 (i.e. 1:1 subjects receiving Dose 1 and Dose 2). Each subject will receive a priming vaccination followed 4 weeks later by a boosting vaccination of the same dose. Safety will be assessed prior to and 3 days post first vaccination. Safety assessments will be based on solicited and unsolicited adverse event data evaluated by the Safety Monitoring Team (SMT) comprising of the national co-ordinating investigator, investigator and the medical monitors (BN and CRO). Following a positive safety assessment after the first vaccination in both subjects recruited into the sentinel cohort, recruitment in the safety cohort will start.

The safety cohort will include a total of 10 subjects: 5 subjects will be recruited each into Groups 2 and 4 (i.e. 5:5 subjects receiving Dose 1 and Dose 2). Following a positive safety assessment by the SMT based upon solicited and unsolicited adverse event data 3 days post first vaccination recruitment in all groups for the remaining subjects will be opened.

In addition, after completion of the staggering steps, an independent Safety Monitoring Committee (see Section 4.4.2) will oversee the clinical trial evaluating safety data on a regular basis.

Trial Design

booster substudy

From each of the two treatment groups chosen for the booster substudy, 43 subjects will be recruited to receive a booster vaccination approximately one year after their first vaccination in the main trial. Subjects will receive the same dose as in the main trial. All 86 subjects will be followed up for 12 months after their last vaccination.

Table 2 Treatment Groups Booster Substudy

Group	N	Age [years]	Volume per dose [mL]	Booster vaccination Day 0	Route
1	43	≥ 55	0.5	Same dose as defined in main trial	IM
2	43	≥ 55	0.5	Same dose as defined in main trial	IM
Total	**86***				

*at least 40 evaluable subjects from the two chosen treatment groups

Reports

Final Clinical Study Report (including safety and immunogenicity data until 3 months follow-up visit)

Clinical Study Report Addendum 1 (including additional immunogenicity data not yet included in the Final Clinical Study Report and 6 months follow-up data for safety and immunogenicity)

Clinical Study Report Addendum 2 (including safety and immunogenicity data of thebooster substudy and additional immunogenicity data not yet included in the Final Clinical Study Report or Addendum 1)

Main Trial - Subject entry criteria

Inclusion criteria

1. Male and female subjects, ≥ 55 years of age.
2. Prior to performance of any trial specific procedures, the subject has read, signed and dated an informed consent form, having been advised of the risks and benefits of the trial in a language understood by the subject, and has signed the Health Insurance Portability and Accountability Act (HIPAA) authorization form.
3. Subjects without symptomatic cardiopulmonary and/or metabolic disease. Note that subjects who have any active

symptoms related to cardiac and/or pulmonary and/or metabolic disease (including e.g. uncontrolled asthma, angina pectoris, hyperglycaemia or other episodic symptoms), or who receive ongoing therapy to control current, active symptoms, are not eligible. Subjects on stable treatment (no change in ≥ 1 month) for previous and controlled symptoms or conditions are eligible. The following are examples of subjects who may bear cardiopulmonary or metabolic diagnoses but who would remain eligible:

- Subjects on stable (no change in ≥ 1 month) therapy for findings (e.g. hypertension, hyperlipidemia) which are not associated with current symptoms or disability.
- Subjects with type II diabetes mellitus are considered eligible as long as they are stable on oral antidiabetics and have either a documented glycated hemoglobin (HbA1c) of ≤ 8 % within three months prior to trial participation or confirmation of controlled blood glucose level must be obtained at the SCR (screening) visit by a lab test.
- Subjects who receive short term treatment for temporary conditions.
- Other clinically insignificant findings not deemed to be associated with increased risk for respiratory viral infections as determined by the investigator.

4. Able to comply with trial requirements; including access to transportation for trial visits.
5. Body mass index (BMI) ≥ 18.5 and ≤ 39.9

   BMI formula for pounds and inches:

$$\textbf{BMI} = \frac{(\text{bodyweight in pounds}) * 703}{(\text{bodyheight in inches})^2}$$

6. Women of childbearing potential (WOCBP) must have used an acceptable method of contraception for at least 30 days prior to the first vaccination, must agree to use an acceptable method of contraception (as defined in Section 8.2.11) during the trial, and must avoid becoming pregnant for at least 28 days after the last vaccination. WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to each vaccination

7. Not clinically significant laboratory values as defined in the protocol, excluding any Grade ≥ 3 toxicity.
8. Negative human immunodeficiency virus antibody test (anti-HIV), negative hepatitis B surface antigen (HBsAG) and negative antibody test to hepatitis C virus.
9. Electrocardiogram (ECG) without clinically significant acute findings (e.g. findings suggestive of current ischemia, ventricular arrhythmias, congestive heart failure and ventricular hypertrophy).

Exclusion criteria

1. Pregnant or breast-feeding women.
2. Uncontrolled serious infection, i.e. not responding to antimicrobial therapy.
3. History or current clinical manifestation 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.
   - History of cerebrovascular disorders, including stroke. Patients with history of transient ischaemic attack (TIA) ≥ 1 year prior to trial participation remain eligible.
   - History of myocardial infarction within ≤ 1 year prior to trial participation, current clinical manifestation of angina pectoris, current clinical manifestation of congestive heart failure ≥ New York Heart Association (NYHA) Grade II, uncontrolled high blood pressure defined as systolic blood pressure ≥ 150 mmHg and/or diastolic ≥ 100 mmHg within the last 2 months.
4. History of or active autoimmune disease. Persons with vitiligo or thyroid disease taking thyroid replacement are not excluded. Persons with rheumatoid arthritis not requiring immunomodulatory and/or immunosuppressant treatment are not excluded.
5. Known or suspected impairment of immunologic functions including, but not limited to chronic inflammatory bowel disorders, diabetes mellitus type I.
6. History of malignancy other than squamous cell or basal cell skin cancer, unless there has been surgical excision at least 6 months ago that is considered to have achieved cure. Subjects

with history of skin cancer should not be vaccinated at the previous tumor site.

7. Clinically significant mental disorder, not adequately controlled by medical treatment.
8. Active or recent (within the time period of six months before trial participation) history of chronic alcohol abuse and/or intravenous and/or nasal drug abuse.
9. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine, e.g. tris(hydroxymethyl)-amino methane, chicken embryo fibroblast proteins, gentamycin.
10. Known allergy to eggs or aminoglycosides.
11. History of anaphylaxis or severe allergic reaction to any vaccine.
12. Having received any vaccinations or planned vaccinations with a live vaccine within 30 days prior to or after trial vaccination.
13. Having received any vaccinations or planned vaccinations with an inactivated vaccine within 14 days prior to or after trial vaccination.
14. Chronic systemic administration (defined as more than 14 days) of > 5 mg prednisone (or equivalent)/day or any other immune-modifying drugs during a period starting from three months prior to first administration of the trial vaccination and ending at the last visit of the active trial phase. The use of topical, inhaled, ophthalmic and nasal glucocorticoids is permitted.
15. Administration or planned administration of immunoglobulins and/or any blood products during a period starting from three months prior to first administration of the trial vaccination and ending at the last visit of the active trial phase.
16. Use of any investigational or non-registered drug or vaccine other than the trial vaccine within 30 days preceding the first trial vaccination, or planned administration of such a drug between participation in the trial and until 4 weeks after last trial vaccination.
17. Previous or planned vaccination with a RSV vaccine/vaccine candidate.

18. Clinical trial personnel working on the current trial.

Booster Substudy - Subject entry criteria

Inclusion Criteria

1. Prior to performance of any booster substudy specific procedures, the subject has read, signed and dated an informed consent form, having been advised of the risks and benefits of the trial in a language understood by the subject.
2. Subject has completed all vaccinations of the main trial according to protocol.

Exclusion Criteria

1. Any condition that, in the opinion of the investigator, makes it unsafe for the subject to receive a further vaccination.
2. Pregnancy.
3. An anaphylactic reaction following the administration of any vaccine(s).
4. Clinical need for concomitant or ancillary therapy not permitted in the trial as outlined in Section 8.2.2.
5. Having received any vaccinations or planned vaccinations with a live vaccine within 30 days prior to or after booster vaccination.
6. Having received any vaccinations or planned vaccinations with an inactivated vaccine within 14 days prior to or after booster vaccination.
7. Chronic systemic administration (defined as more than 14 days) of > 5 mg prednisone (or equivalent)/day or any other immune-modifying drugs during a period starting from 3 months prior to administration of the booster vaccine and ending at the last visit of the booster active trial phase. The use of topical, inhaled, ophthalmic and nasal glucocorticoids is permitted.
8. Administration or planned administration of immunoglobulins and/or any blood products during a period starting from

3 months prior to administration of the booster vaccine and ending at the last visit of the booster active trial phase.

9. Use of any investigational or non-registered drug or vaccine other than the trial vaccine within 30 days preceding the booster vaccination, or planned administration of such a drug during participation in the booster substudy and until 4 weeks after booster vaccination.

10. Subject's request to discontinue or subject's refusal to receive booster vaccination.

11. Subject unwilling or unable to comply with trial requirements.

12. Any reason that, in the opinion of the investigator contradicts administration of the booster vaccination or otherwise requires early discontinuation of a subject.

1.6 Main Trial Schedule

Visit (V)	SCR	V1	VS [13]	V1b [9]	V2	V3	V3b [9]	V4	EAP	FU1 3m FU	FU2 6m FU
Day/Visit +… Day	**-28 - -1**	**0**	**V1 + 3-4**	**V1 + 7-9**	**V1 + 12-16**	**V1 + 28-35**	**V3 + 7-9**	**V3 + 12-16**	**V3 + 28-35**	**V3 + 84-98**	**V3 + 182-210**
Target week	**-4**	**0**	**0S [13]**	**1**	**2**	**4**	**5**	**6**	**8**	**16**	**30**
Procedures											
Informed consent & HIPAA	■										
Check inclusion / exclusion criteria	■	■									
Check eligibility for second vaccination						■					
Medical History	■										
Complete physical examination incl. auscultation of heart & lungs; measurement of body height & weight	■										
Targeted physical exam incl. auscultation of the heart and lung		■		◆	■	■	◆	■	■	■	■
Vital signs	■	■		◆	■	■	◆	■	■	■	■
ECG [4]	■				□[4]			□[4]		□[4]	□[4]
Recording of prior / concomitant medication	■	■	■	◆	■	■	◆	■	■	■	■
Counseling on avoidance of pregnancy for WOCBP [1]	■	■				■					
AE/SAE recording	■	■	■	◆	■	■	◆	■	■	■[2]	■[2]

Visit (V)	SCR	V1	VS [13]	V1b [9]	V2	V3	V3b [9]	V4	EAP	FU1 3m FU	FU2 6m FU
Day/Visit +… Day	**-28 - -1**	**0**	**V1 + 3-4**	**V1 + 7-9**	**V1 + 12-16**	**V1 + 28-35**	**V3 + 7-9**	**V3 + 12-16**	**V3 + 28-35**	**V3 + 84-98**	**V3 + 182-210**
Target week	**-4**	**0**	**0S [13]**	**1**	**2**	**4**	**5**	**6**	**8**	**16**	**30**
Lab											
Pregnancy test for WOCBP [3]	■	■				■			■		
Obtaining blood for safety lab [4, 5]	■				■			■		□[4]	□[4]
Troponin I testing [4]	■				□[4]			□[4]		□[4]	□[4]
Nasal swab collection for RVP PCR (Polymerase Chain Reaction) [8]			□[8]	□[8]	□[8]	□[8]	□[8]	□[8]	□[8]	□[8]	□[8]
Blood draw for serum collection [5]		■		◆	■	■	◆	■	■	■	■
Nasal swab collection for mucosal immune response [11]		■		◆	■	■	◆	■	■	■	■
Blood draw for PBMC collection [5, 9]		◆		◆	◆		◆	◆		◆	◆

Visit (V)	SCR	V1	VS [13]	V1b [9]	V2	V3	V3b [9]	V4	EAP	FU1 3m FU	FU2 6m FU
Day/Visit +… Day	**-28 - -1**	**0**	**V1 + 3-4**	**V1 + 7-9**	**V1 + 12-16**	**V1 + 28-35**	**V3 + 7-9**	**V3 + 12-16**	**V3 + 28-35**	**V3 + 84-98**	**V3 + 182-210**
Target week	**-4**	**0**	**0S [13]**	**1**	**2**	**4**	**5**	**6**	**8**	**16**	**30**
Vaccination											
Randomization		■									
Vaccine/TBS administration and ≥ 30 minutes subject observation		■				■					
Recording of immediate AEs/ SAEs after vaccination [10]		■				■					
Handout of memory aid [6]		■				■					
Review/ of memory aid [7, 12]			■	◆	■		◆	■			
Collection of memory aid [7]				◆	■		◆	■			
Examination of injection site			■	◆	■		◆	■			

■ = mandatory; □ = in case of medical need or any underlying condition that requires further examinations; ◆ = Subgroup only

[1] Review of acceptable contraceptive methods and recent menstrual history with WOCBP.

[2] New SAEs, new AEs indicating a respiratory tract infection and changes to AEs/SAEs ongoing at the previous visit only.

[3] At Screening Visit, a serum pregnancy test must be performed. At all other visits, a urine pregnancy test is to be performed.

[4] Additional safety measures can be taken at any other trial visit or at unscheduled visits, if clinically indicated.

[5] Approximate amounts of single blood draws: Safety lab: 11 mL (at V2, V4, FU1 and FU2; if applicable), including hematology (3 mL), serum chemistry (including pregnancy test; 8 mL), virology: 5ml (at SCR:)Hepatitits B and C, HIV); Safety lab 17 mL (at SCR), including all above plus HbA1c (3 mL; if

applicable); Troponin I: 3 mL; serum collection (antibody testing): 9 mL; PBMC collection (T cell collection): 64 mL. Maximal total amount of blood taken/subject: up to 176 mL (642 mL for subjects in the subgroup).

[6] The memory aid should be completed daily for an 8-day period (Day 0 to Day 7), starting with the day of vaccination. If symptoms are ongoing after Day 7, temperature/symptom measurements should continue each day until resolved and the last day of the symptom and maximum intensity will be recorded on the memory aid.

[7] The entries on the memory aid card need to be reviewed together with the subject.

[8] Only in the presence of symptoms indicating a respiratory infection at any time point after first vaccination, defined by any case of rhinorrhea, nasal congestion, pharyngitis, cough, wheezing (or increase in baseline wheezing), sputum production (or increase / change in nature of baseline sputum production) or new (or worsening of) shortness of breath. Subjects need to be instructed to return to the site within 3 days after start of symptoms.

[9] Subgroup only.

[10] Refer to Section 8.2.9 for Cardiac Assessment

[11] Nasal swabs will be taken from both nostrils.

[12] During the staggering phase, data from the memory aid need to be transferred to the Electronic Case Report Form (eCRF) immediately for SMT (Safety Monitoring Team) review and the memory aid card will be returned to the subject to complete entries for the remaining days.

[13] Visit VS (Staggering Visit) is only required for the subjects in the staggering phase, i.e. sentinel cohort and safety cohort; the target week is named as 0S.

1.7 Trial Schedule Booster Substudy

Visit (V)	BV0	BV1 [11]	BV1b [8]	BV2	B EAP	BFU1 3m FU	BFU2 6m FU	BFU3[15] 12m FU
Day/Visit +… Day	**-28 - -1**	**0**	**BV1 + 7-9**	**BV1 + 12-16**	**BV1 + 28-35**	**BV1 + 84-98**	**BV1 + 182-210**	**BV1 +364-392**
Target week	**-4**	**0**	**1**	**2**	**4**	**12**	**26**	**52**
Procedures								
Informed consent & HIPAA	■							
Check inclusion / exclusion criteria for booster substudy	■							
Check eligibility for booster vaccination criteria		■						
Recording of SAEs since last FU visit in main trial	■							
Complete physical examination incl. auscultation of heart & lungs; measurement of body weight	■							
Targeted physical exam incl. auscultation of the heart and lung [12]		□[12]	□[12]	□[12]	□[12]	□[12]	□[12]	
Vital signs	■	■	◆	■	■	■	■	
Recording of concomitant medication	■[14]	■	◆	■	■	□[13]	□[13]	

Visit (V)	BV0	BV1 [11]	BV1b [8]	BV2	B EAP	BFU1 3m FU	BFU2 6m FU	BFU3[15] 12m FU
Day/Visit +… Day	**-28 - -1**	**0**	**BV1 + 7-9**	**BV1 + 12-16**	**BV1 + 28-35**	**BV1 + 84-98**	**BV1 + 182-210**	**BV1 +364-392**
Target week	**-4**	**0**	**1**	**2**	**4**	**12**	**26**	**52**
Counseling on avoidance of pregnancy for WOCBP [1]	■	■						
AE/SAE recording		■	◆	■	■	■[2]	■[2]	
Laboratory								
Pregnancy test for WOCBP [3]		■						
Obtaining blood for safety lab [4, 5]	■			■		□[4]	□[4]	
Blood draw for serum collection [5]		■	◆	■	■	■	■	■
Nasal swab collection for mucosal immune response [10]		■	◆	■	■	■	■	
Blood draw for PBMC collection [5, 8]		◆	◆	◆		◆	◆	
Vaccination								
Vaccine administration and ≥ 30 minutes subject observation		■						
Recording of immediate AEs/ SAEs after vaccination [9]		■						
Handout of memory aid [6]		■						
Review/ of memory aid [7]			◆	■				

Visit (V)	BV0	BV1 [11]	BV1b [8]	BV2	B EAP	BFU1 3m FU	BFU2 6m FU	BFU3[15] 12m FU
Day/Visit +… Day	**-28 - -1**	**0**	**BV1 + 7-9**	**BV1 + 12-16**	**BV1 + 28-35**	**BV1 + 84-98**	**BV1 + 182-210**	**BV1 +364-392**
Target week	**-4**	**0**	**1**	**2**	**4**	**12**	**26**	**52**
Collection of memory aid [7]			◆	■				
Examination of injection site			◆	■				

■ = mandatory; □ = in case of medical need or any underlying condition that requires further examinations; ◆ = PBMC Subgroup only

[1] Review of acceptable contraceptive methods and recent menstrual history with WOCBP.

[2] New SAEs and changes to AEs/SAEs ongoing at the previous visit only.

[3] Urine pregnancy test

[4] Additional safety measures can be taken at any other trial visit or at unscheduled visits, if clinically indicated.

[5] Approximate amounts of single blood draws: Safety lab: 11 mL (at BV0 and BV2; BFU1and BFU2 if applicable), including Haematology (3 mL), serum chemistry (including pregnancy test; 8 mL); serum collection (antibody testing): 9 mL; PBMC collection (T cell collection): 64 mL.

[6] The memory aid should be completed daily for an 8-day period (Day 0 to Day 7), starting with the day of vaccination. If symptoms are ongoing after Day 7, temperature/symptom measurements should continue each day until resolved and the last day of the symptom and maximum intensity will be recorded on the memory aid.

[7] The entries on the memory aid card need to be reviewed together with the subject.

[8] PBMC subgroup only.

[9] Refer to Section 8.2.9 for Cardiac Assessment

[10] Nasal swabs will be taken from both nostrils.

[11] BV1 approximately 11-13 months after the first vaccination in the main part of the trial

[12] A targeted physical examination is only needed if guided by any signs or symptoms previously identified or any new symptoms that the subject has experienced since the last visit

[13] Concomitant medication at BFU visits are only to be captured in case the concomitant medication is related to a new SAE and changes to AEs/SAEs ongoing at the previous visit

[14] Concomitant medication between FU2 and BV0 are only to be captured in case the concomitant medication is related to a SAE.

[15] At BFU3 only blood draw for immunogenicity serum collection will be performed (9 mL)

2 Background Information and Scientific Rationale

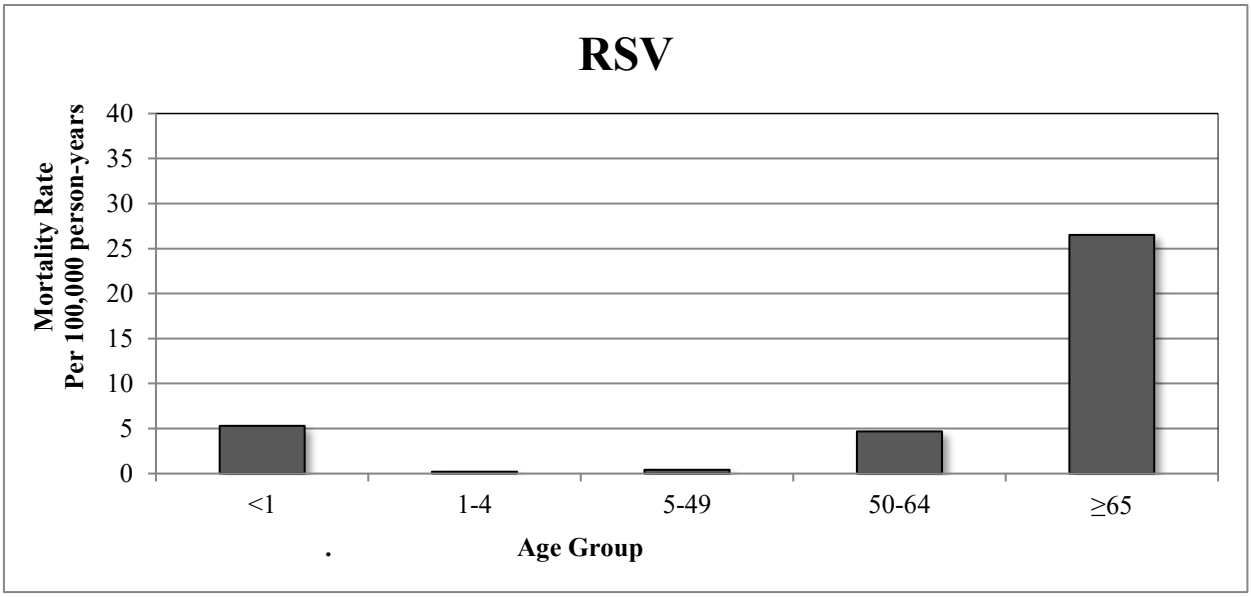
2.1 Introduction to RSV Disease

Respiratory Syncytial Virus (RSV) is a ribonucleic acid (RNA) virus of the Paramyxoviridae family. The RSV genome encodes eleven proteins, two of which play a key role for pathogenesis and are important antigens for generating protective immunity: Glycoprotein G, responsible for viral attachment, and the fusion protein F, which mediates viral penetration and syncytium formation. There are two different strains of RSV circulating concurrently, A and B, which are distinguished mainly by variations within the G protein (Hall, 2001).

RSV is highly infectious and transmitted primarily by contact with infectious respiratory secretions or contaminated objects. Seasonal epidemics overlapping with the influenza season occur yearly in autumn/winter in temperate climates and in the wet season in the tropics. Typically, the primary infection begins with fever, coryza and cough, lasting 10 to 14 days. In more severe infections, the disease spreads from the upper down to the lower respiratory tract and results in bronchiolitis leading to inflammation-induced airway obstruction with associated tachypnea and wheezing, sometimes requiring oxygen support to avoid progression to pneumonia with respiratory failure.

RSV has been recognized as a significant cause of respiratory illness in all age groups. The disease is predominated by febrile upper respiratory tract infections (URTI) in older children and adults and is the leading cause of lower respiratory tract infections (LRTI) in newborns, infants and younger children. While the burden of RSV is highly recognized in the pediatric population, particularly in the very young and those with cardio-respiratory disease, RSV infections are also a serious health concern in the elderly and in immunocompromised adults. Indeed, about 78 % of deaths due to RSV-related underlying respiratory and circulatory disease occur among the population ≥ 65 years of age (Thompson, 2003) (see Figure 1).

Figure 1 Estimated Annual RSV Associated Mortality Rates in Different Age Groups per 100,000 Person-Years for the 1990-1991 Through 1998-1999 Seasons (Thompson, 2003)



RSV infection in the elderly and high-risk adult population in the United States (US) has shown to be a significant health issue. Approximately 170,000 hospitalizations and 10,000 deaths occur annually in people over the age of 65 years (Murata, 2007). Epidemiological surveys performed over several RSV seasons indicate that 3-7 % of healthy elderly and 4-10 % of high-risk adults are diagnosed with RSV per year. Similar to influenza, the burden of RSV disease has been identified as significant in older individuals, causing severe lower respiratory disease such as pneumonia and exacerbation of chronic obstructive pulmonary disease (COPD). COPD patients are even suspected to constitute a reservoir for RSV.

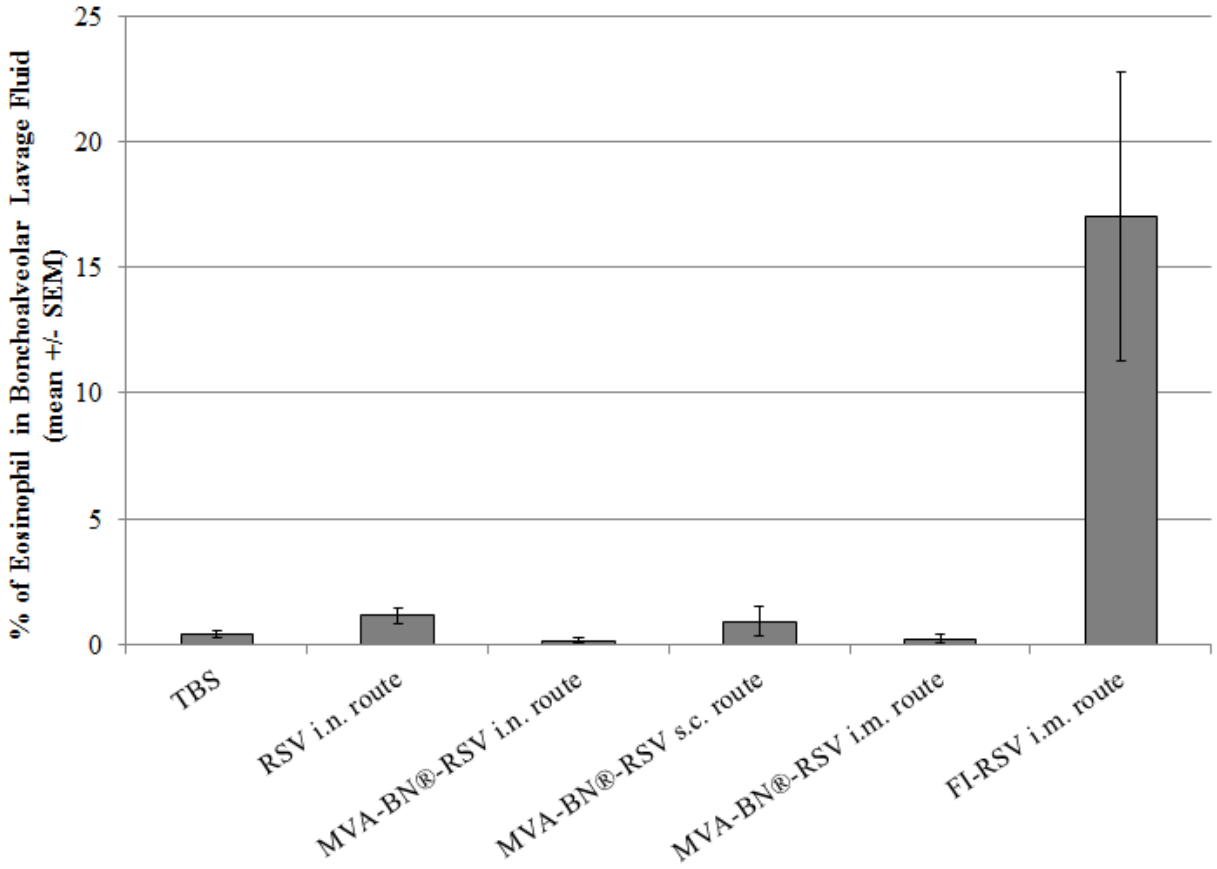
The immunologic factors that are responsible for protection against RSV are not completely understood. RSV infection induces secretory antibodies, serum neutralizing antibodies and T cell immunity, with some protective effect against LRTI provided by high levels of serum neutralizing antibodies (Groothuis, 1993). The F and G proteins are the main targets for induction of neutralizing antibodies. However, naturally acquired immunity is neither complete nor durable (Glezen, 1986; Hall, 2001).

An estimated 90 % of the population experiences their first RSV infection within the first two years of life (Glezen, 1986; Castilow, 2007). However, immune responses after primary infection in young infants are usually weak and short-lived due to immunological immaturity and suppression by maternal antibodies (Karron, 1999; Power, 2008). Re-infections with RSV are common at all ages, although of decreasing severity, since with recurring infections the disease

becomes more limited to the upper respiratory tract (Glezen, 1986). Morbidity and disease severity increases again in people > 50 years.

While the anti-RSV-F monoclonal antibody Palivizumab (Synagis®) is effective for prevention of serious RSV disease in premature and other high-risk infants, options for the healthy pediatric and for the adult population are limited to supportive measures as there is neither an approved RSV vaccine nor any specific treatment available. One of the key set-backs to further development of RSV vaccines in infants and children has been the failed approach with a formalin-inactivated (FI) vaccine in the 1960s, which caused enhanced disease in vaccinated infants after natural exposure to RSV (Fulginiti, 1969). Enhanced disease is believed to be (at least partly) caused by an immoderate Th2 memory response (Castilow, 2007) in a population previously naïve to RSV and is characterized by pulmonary eosinophilia. The clinical testing of several newly developed RSV vaccine candidates during the last decade has not revealed any safety concern and particularly live viral vaccines seem not to be associated with enhanced RSV disease (Wright, 2007). Most importantly, the Modified Vaccinia Ankara Strain (MVA) based RSV vaccine candidate described here induces a balanced Th1/Th2 (T-Helper Cells, Type1/Type2) response combined with a humoral immune response without any signs of enhanced disease in animal models (Figure 2).

Figure 2 Eosinophil Concentration in Bronchoalveolar Lavage in Mice after Administration of MVA-BN-RSV and Formalin Inactivated (FI) RSV Vaccine



Given the severity of disease in elderlies and the lack of treatment options, there is an unmet medical need to prevent RSV-induced respiratory disease which accounts for hospitalizations due to COPD, pneumonia, asthma and congestive heart failure. Thus, the significant impact on public health with a growing elderly community makes the development of a safe and protective RSV vaccine a high priority. Since adults have already experienced several RSV infections, they are no longer naïve to the virus and vaccination is expected to boost a pre-existing, yet not fully protective immune response, i.e. to induce high levels of antibodies combined with a robust T cell response.

2.2 MVA-BN-RSV Vaccine

BN has developed a vaccine candidate against RSV by including RSV surface proteins encoding genes from both circulating RSV strains (A and B), as well as conserved internal antigen encoding genes of the virus into the MVA-BN vector. The vaccine is designed for a broad reactivity to prevent severe RSV LRTI (e.g. RSV bronchiolitis, pneumonia) in both elderlies and

in adults with underlying conditions such as cardiovascular disease and immunosuppression, i.e. populations known to have an increased risk of complications associated with RSV.

The recombinant RSV vaccine candidate MVA-BN-RSV (construct MVA-mBN294B) consists of MVA-BN encoding the following RSV antigens:

- The RSV surface proteins F (Fusion) and G (Glycoprotein) which induce humoral and cell mediated immunity in animal models (mice and cotton rats).
- Two internal proteins N (Nucleoprotein) and M2 (Matrix protein) are expected to enhance immunogenicity, especially in terms of cytotoxic T cell responses, but also cross-protection to infection with other strains, since these two proteins are highly conserved among the different RSV strains.

2.3 Origin and Characteristics of MVA-BN Vector Backbone

Vaccinia Virus (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 Deoxyribonucleic Acid (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 % (31 kbp) 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 susceptible 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).

Bavarian Nordic A/S (BN), an international biopharmaceutical company, is developing a proprietary strain of Modified Vaccinia Ankara (MVA-BN, trade name IMVAMUNE outside the European Union [EU], invented name IMVANEX in the EU) for use as a prophylactic smallpox vaccine.

MVA-BN is a highly attenuated, purified live vaccine produced under serum-free conditions in chicken embryo fibroblasts cells. In contrast to replicating smallpox vaccines MVA-BN can be administered subcutaneously (SC) or IM, and not by scarification. The standard route and schedule of MVA-BN are two subcutaneous injections administered 4 weeks apart. Since MVA-BN is non-replicating in human cells it does not form vesicles (“takes”) (Mayr, 1975).

For IMVANEX a marketing authorization under exceptional circumstances was granted by the European Commission in July 2013. A marketing authorization for IMVAMUNE® was granted by Health Canada in November 2013.

2.4 Summary of Nonclinical Studies with MVA-BN-RSV Vaccine

BN has already performed almost 20 GLP-compliant safety studies for either the vector backbone MVA-BN or MVA-BN based recombinant vaccines. All these studies demonstrated that these investigational products are safe and well tolerated. Similarly, the current MVA-BN-RSV vaccine candidate (MVA-mBN294B) was tested in a GLP-compliant repeat-dose toxicity and local tolerance study in rabbits and found to be safe and well tolerated. There were no MVA-BN-RSV related mortality or clinical observations and no vaccine related findings in the hematology, clinical chemistry, and histopathology.

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

2.5 Clinical Profile of MVA-BN and Recombinant MVA-based Vaccines

To date, 19 clinical trials (13 sponsored by BN and 6 sponsored by the NIH [National Institutes of Health]) evaluating the safety and immunogenicity of MVA-BN have been completed. Currently three clinical trials are ongoing - two sponsored by BN and one sponsored by the NIH. More than 7100 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 atopic dermatitis (AD). Further, MVA-BN has been evaluated in an elderly population, i.e. subjects 56 to 80 years of age. Including the ongoing clinical trials, more than 7700 subjects have been exposed to MVA-BN.

Furthermore, BN has evaluated the safety and immunogenicity of MVA-BN-based recombinant vaccines (including MVA-BN-Filo®) in more than 700 subjects including healthy subjects, HIV infected individuals and populations with cancer and children in completed trials. In trials with recombinant MVA vaccines, doses up to 5×10^8 $TCID_{50}$ (Tissue Culture Infectious Dose 50 %) were administered applying varying schedules of repeat vaccinations, e.g. a 3-dose schedule was used for recombinant HIV vaccines and multiple vaccinations have also been performed in subjects receiving a recombinant therapeutic breast cancer vaccine (MVA-BN-HER2).

Recently the first Phase I clinical trials with an MVA-BN-based recombinant vaccine against filoviruses (MVA-BN Filo®) were completed. Several other Phase I, Phase II and Phase III clinical trials are ongoing. The preliminary safety data are consistent with the experience with MVA-BN, and no related SAEs have been observed so far in these trials.

As of May 2016, more than 1500 subjects have received vaccinations with MVA-BN-Filo, in addition to the 8100 subjects who have received MVA-BN and the MVA-BN based recombinant

products (other than MVA-BN-Filo), which in total sums up to more than 9600 exposed subjects to the MVA-BN platform technology to date.

Details on the first clinical trial with MVA-BN-RSV are provided in Section 2.6.

2.5.1 Safety Overview of MVA-BN and Recombinant MVA-based Vaccines

In all completed and ongoing clinical trials, vaccinations with MVA-BN or MVA-BN based vaccines have shown to be safe and well tolerated in in all populations tested (healthy; elderly; immunocompromised) and at all doses tested (up to 5 x 10^8 $TCID_{50}$). No cases of death, assessed as being even possibly related, have been reported for a subject in a clinical trial using MVA-BN.

Results obtained from completed Phase I and II trials and ongoing trials with several recombinant MVA-BN based vaccines in healthy adults and children, HIV infected and cancer patients demonstrate a similar safety profile as MVA-BN alone.

Additional information on the safety profile of MVA-BN and recombinant MVA-based vaccines is provided in the IB.

Adverse Drug Reactions (ADRs)

Table 3 summarizes the pooled ADR data of all completed MVA-BN trials. The safety profile of each of the trials with recombinant MVA-BN-based vaccines is comparable to the safety profile as displayed in Table 3 as the occurrence of the ADRs is considered to be a reaction to the vector rather than the insert, based on previous experience with recombinant MVA-BN vaccine candidates.

Table 3 Suspected Adverse Drug Reactions Reported by ≥ 1 % of Subjects in Completed MVA-BN Clinical Trials* (N = 7099 subjects)

Preferred Term (PT)	No. of reports by subjects	Frequency (%)
Injection site pain	5798	81.7
Injection site erythema	4577	64.5
Injection site swelling	3341	47.1
Injection site induration	3253	45.8
Injection site induration (solicited)	*3248 out of 7013*	*46.3*
Injection site induration (unsolicited)	*5 out of 86*	*5.8*
Fatigue	2121	29.9
Injection site pruritus	2607	36.7
Injection site pruritus (solicited)	*2396 out of 5904*	*40.6*
Injection site pruritus (unsolicited)	*211 out of 1213*	*17.4*
Fatigue (solicited) +	2121 out of 5904	35.9
Myalgia	2258	31.8
Myalgia (solicited)	*2257 out of 7013*	*32.2*
Myalgia (unsolicited)	*1 out of 86*	*1.2*
Headache	2177	30.7
Headache (solicited)	*2176 out of 7013*	*31.0*
Headache (unsolicited)	*1 out of 86*	*1.2*
Nausea	999	14.1
Nausea (solicited)	*998 out of 7013*	*14.2*
Nausea (unsolicited)	*1 out of 86*	*1.2*
Rigors/chills	604	8.5
Rigors/chills (solicited)	*603 out of 6297*	*9.6*
Rigors/chills (unsolicited)	*1 out of 802*	*0.1*
Body temperature increased	255	3.6
Injection site discoloration	190	2.7
Appetite disorder	150	2.1
Appetite disorder (solicited) ++	*150 out of 1366*	*11.0*
Injection site nodule	149	2.1
Pain in extremity	147	2.1
Pain in extremity (solicited)	*139 out of 1346*	*10.3*
Pain in extremity (unsolicited)	*8 out of 5753*	*0.1*
Arthralgia	129	1.8
Injection site hematoma	107	1.5

* POX-MVA-001, -002, -004, -005, -007, -008, -009, -010, -011, -013, -023, -024, -027, -028, -029, -030, HIV-NEF-004 and HIV-POL-002; 7 subjects in POX-MVA-009 received Dryvax® either on the same day or within 7 days after MVA-BN administration and were therefore not included to avoid a potential bias in the adverse event reporting. + not in POX-MVA-001; ++ only in NIH trials

Looking only at the events that were reported by at least 1 % of subjects, 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 in intensity and resolved completely without intervention within the first 7 days following vaccination. To date, no trends have been identified suggesting the occurrence of any particular unexpected adverse reactions or classes of adverse reactions following vaccinations with MVA-BN.

Cardiac Signs and Symptoms

Based on observations with replicating smallpox vaccines particular attention has been placed on monitoring for cardiac signs and symptoms in all clinical trials using MVA-BN. Despite close cardiac monitoring, no confirmed event indicating a case of myo-/pericarditis has been observed in any completed MVA-BN trial.

Serious Suspected Adverse Drug Reactions

A total of seven (7 out of 7758 vaccinated subjects = 0.09 %) serious suspected ADRs have been reported for MVA-BN smallpox vaccine in completed and ongoing trials (see Table 4). All of them have been thoroughly reviewed by BN and the trial specific Data Safety Monitoring Boards (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.

Table 4 Serious Suspected Adverse Drug Reactions (Assessed by the Investigator to Be At Least Possibly Related to MVA-BN)

Trial Code	Age/ Gender	Days After Vaccination	Event	Outcome	Underlying Diseases/ Circumstances	PI Assessment	BN Opinion
POX-MVA-005	[redacted]	70 days after 2nd vaccination	Sarcoidosis	Stable and asympto-matic	Urinary tract infection with Chlamydia trachomatis at time of first symptoms (arthralgia)	Possibly related	Possibly related
POX-MVA-005	[redacted]	26 months after 2nd vaccination	Crohn's disease	Stable and asympto-matic under therapy	Abnormal lab results (elevated alkaline phosphatase, absolute neutrophils and platelet counts) at screening for 2-year follow-up trial POX-MVA-023 (excluded)	Possibly related	Possibly related
POX-MVA-008	[redacted]	8 days after 2nd vaccination	Transitory ocular muscle paresis	Resolved without sequelae	No relevant medical history	Probably related	Possibly related
POX-MVA-010	[redacted]	133 days after 2nd vaccination	Congestive heart failure due to cardio-myopathy	Stable under cardiac medi-cations	Surgery for ventricular septal defect as child. HIV infection. Concomitant (denied, therefore previously unknown to BN) participation in a Growth-Hormone Releasing Hormone (GH-RH) trial; event also assessed as possibly related to GH-RH	Possibly related	Unlikely related
POX-MVA-011	[redacted]	1 day after 2nd vaccination	Simple pneumonia and pleurisy	Resolved without sequelae	HIV infection (CD4 count 4 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

Trial Code	Age/ Gender	Days After Vaccination	Event	Outcome	Underlying Diseases/ Circumstances	PI Assessment	BN Opinion
POX-MVA-036	[redacted]	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 medical history of shingles. She has received multiple vaccines before but never had previous hives or other problems with vaccines.	Possibly related	Possibly related
POX-MVA-036	[redacted]	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

2.5.2 Safety Profile of MVA-BN-based Recombinant Vaccines in Healthy Compared to Special Populations

BN has evaluated the safety and immunogenicity of MVA-BN-based recombinant vaccines for several indications such as cancer, HIV and measles in more than 700 subjects including healthy and HIV infected populations. In trials with recombinant MVA-BN based vaccines, doses up to 5×10^8 $TCID_{50}$ were administered applying varying schedules of repeated vaccinations, e.g. a 3-dose schedule was used for recombinant HIV vaccines and multiple vaccinations have also been performed in subjects receiving a recombinant therapeutic breast cancer vaccine (MVA-BN-HER2). Results obtained from these Phase I and II trials demonstrate a similar safety profile and vector immunogenicity as compared to MVA-BN alone.

Two of the trials with recombinant vaccines allowed for a direct comparison with MVA-BN as an active control. These trials (HIV-POL-002 and HIV-NEF-004) were performed to evaluate two different recombinant MVA-based HIV vaccine candidates in HIV-infected subjects. In both trials, a total of three vaccinations with either the recombinant HIV vaccine or MVA-BN were performed according to a 0, 8 and 16 week regimen.

Table 5 and Table 6 summarize the safety results of these two trials and demonstrate that there were no significant differences between the recombinant MVA-based vaccine candidates and MVA-BN. For clinical trial HIV-POL-002, singular adverse events are not presented due to the small sample size in this clinical trial (N = 30).

Table 5 Solicited and Common Unsolicited Adverse Events in Clinical Trial HIV-NEF-004

	MVA-NEF 1×10^8 $TCID_{50}$ (N = 25)		MVA-NEF 5×10^8 $TCID_{50}$ (N = 26)		MVA-BN 1×10^8 $TCID_{50}$ (N = 26)	
	n	**%**	**n**	**%**	**n**	**%**
Solicited AE						
Injection Site Pain	23	92	26	100	26	100
Injection Site Erythema	22	88	24	92	20	77
Injection Site Swelling	22	88	23	89	19	73
Injection Site Induration	19	76	23	89	20	77
Fatigue	16	64	21	81	15	58
Headache	17	68	20	77	14	54
Myalgia	14	56	18	69	12	46
Body temp. increased	3	12	8	31	8	31
Nausea	5	20	4	15	6	23
Chills	2	8	10	39	2	8
Unsolicited AE, irrespective of drug-event relationship / time of onset (N total > 5)						
Nasopharyngitis	6	24	5	19	11	42
Lymphadenopathy	6	24	3	12	6	23
Diarrhea	3	12	5	19	4	15
Headache	4	16	4	15	2	8
Injection site pruritus	1	4	5	19	3	12
Cough	4	16	2	8	2	8
Influenza	3	12	3	12	2	8
Night sweats	2	8	4	15	2	8
Arthralgia	3	12	2	8	2	8
Herpes simplex	3	12	2	8	1	4
Paraesthesia	2	8	3	12	1	4
Unsolicited treatment-related AE during vaccination period (N total > 2)						
Injection site pruritus	1	4	5	19	3	12
Lymphadenopathy	2	8	2	8	2	8

N = Number of subjects in the group; n=number of subjects with AE

Percentages are calculated based on the total number of subjects in the respective group

Source: HIV-NEF-004 Clinical Study Report (August 07, 2008), Table 29.

Table 6 Unsolicited and Solicited Adverse Events in Clinical Trial HIV-POL-002

	MVA-BN Polytope 1 x 10^8 $TCID_{50}$ (N = 20)	**MVA-BN 1 x 10^8 $TCID_{50}$ (N = 10)**
	n (%)	**n (%)**
Total no. of patients included	20 (100.0)	10 (100.0)
Number of patients with at least one SAE	0	0
Unsolicited AE		
Number of patients with		
- at least one AE	14 (70.0)	7 (70.0)
- at least one related AE	6 (30.0)	4 (40.0)
Unsolicited AEs: Number of AE		
- reported AE	37	19
- average number of AE per subject	1.85	1.90
Solicited local AE		
Number of patients with		
- at least one AE	17 (85.0)	10 (100.0)
Number of solicited local AE	133	69
- average number of AE per subject	6.65	6.90
Solicited general AE		
Number of patients with		
- at least one AE	11 (55.0)	7 (70.0)
Number of solicited general AE	44	28
- average number of AE per subject	2.20	2.80

N = number of patients per treatment group; n = number of patients with AE; % = (n/N)*100;

Percentages for 'Number of patients with...' were based on the total number of patients included per group.

Solicited local AE: redness, pain, swelling, induration at the injection site; solicited general AEs: body temperature increased, headache, myalgia, rigor/chills, nausea, fatigue

Source: HIV-POL-002 Clinical Study Report (January 12, 2009), Tables 14.3.1.1 and 14.3.5.

2.5.3 Immunogenicity Overview of MVA-BN

MVA-BN was tested for safety and immunogenicity among healthy volunteers in 3 Phase I and II dose finding trials (Vollmar, 2006; Frey, 2007; Von Krempelhuber, 2010). Across these trials a linear dose relationship was observed between the vaccine doses and both vaccinia ELISA and PRNT titers. Maximum ELISA seroconversion rates and peak titers were reached 2 weeks after the second vaccination, with 100 % seroconversion after the second dose for all dose groups receiving at least 2 x 10^7 $TCID_{50}$ per 0.5 mL dose of MVA-BN. Statistical analysis indicated lower doses to be inferior to the standard dose tested throughout all dose ranging trials, whereas the standard dose achieved ELISA seroconversion rates between 81 and 100 % already after the first dose. For the PRNT, the same trend was observed with about 77 % seroconversion rates 2 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 at least 5 x 10^7 $TCID_{50}$ as the most suitable human dose. The final optimal (standard) dose and schedule for the general population was decided to be two doses of at least 5 x 10^7 $TCID_{50}$ MVA-BN (nominal titer of 1 x 10^8 $TCID_{50}$ per dose) administered SC 4 weeks apart. A trial in elderly, i.e. 56-80 years old vaccinia-experienced subjects, indicates that it is sufficient to vaccinate this population only once with MVA-BN.

In the first clinical trial with the MVA-BN-RSV vaccine (RSV-MVA-001 Phase I trial) a low dose with a nominal titer of 1 x 10^7 $TCID_{50}$ per dose was compared against a dose with a nominal titer of 1 x 10^8 $TCID_{50}$ per dose (see Section 2.6).

In this RSV trial (RSV-MVA-002) different doses and schedules will be evaluated: all subjects will receive two vaccinations - either both vaccinations with MVA-BN-RSV vaccine 1 x 10^8 Inf.U per 0.5 mL, 5 x 10^8 Inf.U per 0.5 mL or Placebo or the first vaccination with MVA-BN-RSV vaccine 1 x 10^8 Inf.U or 5 x 10^8 Inf.U per 0.5 mL followed by the second vaccination with Placebo (see Table 1). Please note that the dose was expressed as $TCID_{50}$ for the Phase I clinical trial with 1 x 10^8 $TCID_{50}$ per dose corresponding to 1 x 10^8 Inf.U per dose.

2.6 Clinical Trial Data with MVA-BN-RSV Vaccine

Safety, tolerability and immunogenicity of the recombinant MVA-BN-RSV vaccine were evaluated in the randomized, single-blind, placebo-controlled Phase I trial (RSV-MVA-001). In total 63 healthy adult subjects were vaccinated with either placebo, low or normal dose of MVA-BN-RSV vaccine (Table 7).

Table 7 Treatment Groups in Phase I Clinical Trial RSV-MVA-001

Group	N*	Age (years)	Vaccine: nominal titer per dose ($TCID_{50}$)	Volume per dose [mL]	Schedule (vaccination days)	Route
1	18 + 3	18-49	1 x 10^7	0.5	0; 28	IM
2	18 + 3	18-49	1 x 10^8	0.5	0; 28	IM
3	18 + 3	50-65	1 x 10^8	0.5	0; 28	IM
Total	63					

IM = intramuscular; $TCID_{50}$ = tissue culture infectious dose 50%

*18 subjects in each treatment group receiving MVA-BN-RSV vaccine and 3 subjects in each treatment group receiving placebo

Source: MVA-RSV-001 Clinical Study Report (Ed. 1), Table 1.

63 subjects received two vaccinations 4 weeks apart and completed the active trial phase 4 weeks after the last vaccination. To evaluate long-term safety and immunogenicity of the MVA-BN-RSV vaccine, subjects completed a follow-up (FU) visit 6 months after the second vaccination.

Safety Data

The trial demonstrated that MVA-BN-RSV was well tolerated in adult and elderly subjects receiving either a low dose (1 x 10^7 $TCID_{50}$) or normal dose (1 x 10^8 $TCID_{50}$) of the vaccine. No SAEs occurred and no subject discontinued the trial due to an AE. The incidence of solicited local or solicited general AEs was generally low and comparable between analysis groups. A summary of solicited AEs and unsolicited treatment-emergent Adverse Events (TEAEs) is presented in Table 8.

Table 8 RSV-MVA-001 Trial Summary of Adverse Events per Subject - FAS

	Analysis group							
	Adult low (N=18)		Adult normal (N=18)		Elderly normal (N=18)		Placebo[a] (N=9)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Overall (per subject)								
TEAE	14 (77.8)	29	11 (61.1)	26	9 (50.0)	15	5 (55.6)	5
Non-serious TEAE	14 (77.8)	29	11 (61.1)	26	9 (50.0)	15	5 (55.6)	5
SAE[b]	0	0	0	0	0	0	0	0
Related TEAE[c]	8 (44.4)	11	7 (38.9)	11	3 (16.7)	5	2 (22.2)	2
TEAE Grade ≥3	0	0	1 (5.6)	2	1 (5.6)	1	0	0
Related TEAE Grade ≥3[c]	0	0	0	0	0	0	0	0

E = number of events; FAS = full analysis set; SAE = serious adverse event; TEAE = treatment-emergent adverse event; N = number of subjects per group, n = number of subjects experiencing an AE

[a] Adult and elderly placebo combined.

[b] SAEs are included even if they exceed the 28-day follow-up period after each vaccination.

[c] Unsolicited or general solicited AE the investigator considered to have possible, probable, definite or missing relationship to trial vaccine; although solicited local events are by definition always ADRs they are not included here.

Source: MVA-RSV-001 Clinical Study Report (Ed. 1), Table 15.3.1.1.2.

The most frequently reported unsolicited TEAE was URTI, followed by blood potassium increased. Overall, only few unsolicited TEAEs were considered to be related to trial treatment, all of which were assessed as Grade 1. Furthermore, only 2 subjects were reported as having unsolicited TEAEs assessed as Grade 3 (gastroenteritis and URTI); the majority of subjects had unsolicited TEAEs assessed as Grade 1 and not related to trial treatment.

The most frequent solicited local AEs were injection site pain, injection site erythema, and injection site pruritus; the most frequent solicited general AEs were body temperature increased, fatigue and headache in accordance with the safety profile of the vector backbone MVA-BN (for further details see IB). Solicited local AEs are summarized in Table 9 and related solicited general AEs are summarized in Table 10.

The majority of the solicited local or solicited general AEs were assessed as Grade 1; only few subjects had Grade 2 solicited AEs. Only 1 subject experienced a Grade ≥3 solicited general AE

of nausea, which was reported as not related to trial treatment. All solicited local and general AEs resolved within 8 days (median ≤5 days).

Table 9 Solicited Local Adverse Events (Overall per Subject) – FAS

	Number (%) of subjects			
	Adult low (N=18)	**Adult normal (N=18)**	**Elderly normal (N=18)**	**Placebo[a] (N=9)**
Overall (per subject)				
Injection site erythema	5 (27.8)	4 (22.2)	4 (22.2)	2 (22.2)
Injection site induration	0	1 (5.6)	1 (5.6)	1 (11.1)
Injection site pain	3 (16.7)	9 (50.0)	11 (61.1)	1 (11.1)
Injection site pruritus	2 (11.1)	1 (5.6)	6 (33.3)	0
Injection site swelling	1 (5.6)	1 (5.6)	1 (5.6)	0

FAS = full analysis set

[a] Adult and elderly placebo combined.

Note: no Grade ≥ 3 local Solicited AE was reported

Source: MVA-RSV-001 Clinical Study Report (Ed. 1), Table 15.3.1.2.3.

Table 10 Related Solicited General Adverse Events (Overall per Subject) - FAS

	Number (%) of subjects			
	Adult low (N=18)	**Adult normal (N=18)**	**Elderly normal (N=18)**	**Placebo[a] (N=9)**
Body temperature increased	4 (22.2)	3 (16.7)	0	0
Chills	0	0	0	0
Fatigue	3 (16.7)	2 (11.1)	1 (5.6)	1 (11.1)
Headache	1 (5.6)	2 (11.1)	2 (11.1)	0
Myalgia	1 (5.6)	0	2 (11.1)	0
Nausea	1 (5.6)	1 (5.6)	0	0

FAS = full analysis set

[a] Adult and elderly placebo combined.

Note: Relationship summarized as all symptoms determined by the investigator with reasonable possibility that the vaccine contributed to them (relationship to vaccine documented as 'possible', 'probable', 'definite' or missing).

Source: MVA-RSV-001 Clinical Study Report (Ed. 1), Table 15.3.1.3.5.

Immunogenicity Data

The primary objective of this Phase I trial was the collection of safety data. The trial had a small sample size and was not powered for testing RSV-specific immunogenicity thus the immunogenicity results are descriptive and only of exploratory nature.

Antibody Analyses:

RSV-specific GMTs increased after vaccination in all groups receiving MVA-BN-RSV compared with placebo in the ELISA and PRNT strain A analyses. An at least 2-fold increase was shown for the adult standard dose group for both assays and for the elderly standard dose group for the RSV-specific ELISA. The neutralizing antibody titer measured by PRNT in the elderly standard dose group was lower than in the adult standard dose group; serum RSV-specific baseline and individual peak geometric mean titers by ELISA, PRNT (strain A) and PRNT (strain B) are summarized in Table 11.

Table 11 Serum RSV-Specific Baseline and Individual Peak Geometric Mean Titers – FAS and PPS

	Analysis group							
	Adult low (N=18[b])		Adult standard (N=18)		Elderly standard (N=18)		Placebo[a] (N=9)	
Week (Visit)	GMT	95% CI	GMT	95% CI	GMT	95% CI	GMT	95% CI
Serum RSV-specific IgG ELISA GMT								
Week 0 (V1)	1146	915, 1437	1121	830, 1512	913	726, 1149	1005	710, 1422
Individual Peak GMT	1807	1435, 2276	2238	1622, 3089	2286	1725, 3030	1289	913, 1820
Serum RSV-specific PRNT (strain A) GMT								
Week 0 (V1)	546	380, 783	652	474, 897	625	456, 857	524	374, 734
Individual Peak GMT	926	676, 1268	1394	1087, 1788	944	677, 1315	782	560, 1093
Serum RSV-specific PRNT (strain B) GMT								
Week 0 (V1)	256	173, 379	327	190, 561	242	154, 380	231	116, 456
Individual Peak GMT	379	245, 587	512	322, 814	374	231, 604	347	189, 636

CI = confidence interval; ELISA = enzyme-linked immunosorbent assay; FAS = full analysis set; GMT = geometric mean titers; IgG = immunoglobulin G; PPS = per protocol set; RSV = respiratory syncytial virus

[a] Adult and elderly placebo combined.

[b] Only 17 of 18 subjects had available data in this group at Week 8 (V7).

Source: MVA-RSV-001 Clinical Study Report (Ed. 1), Tables 15.2.2.5, 15.2.4.5 and 15.2.5.5.

The cellular immune response was assessed using an IFN-γ/IL-4 ELISPOT assay using three different RSV peptide pools (F, G and N) as well as RSV for stimulation. IFN-γ secreting T cells specific for the F, G and N protein increased in all active treatment groups, with no substantial differences between vaccine dose and age whereas numbers of IL-4 producing T cells were low or below the detection limit. No dose dependency was seen in terms of Geometric Mean Spot Forming Units (GMSFUs). The T cell response boosted by the normal dose in the adult and elderly group was comparable. The responder rate based on IFN-γ producing PBMCs was highest in the elderly standard dose group, ranging from 66.7% (12/18) to 94.4% (17/18) of subjects for all stimulating agents. Responder rates based on IFN-γ and IL-4 producing PBMCs are summarized in Table 12.

These results showed that the MVA-BN-RSV candidate leads to an increase in the number of IFN-γ producing T cells without inducing IL-4 secreting T cells, thus limiting the risk for emergence of enhanced disease by biasing the immune response strongly towards a Th1 type response.

Table 12 PBMC ELISPOT: IFN-γ/IL-4 Responder Rates – FAS and PPS

	Analysis group							
	Adult low[a] (N=18)		Adult standard (N=18)		Elderly standard (N=18)		Placebo[b] (N=9)	
	IFN-γ	IL-4	IFN-γ	IL-4	IFN-γ	IL-4	IFN-γ	IL-4
	ER (%) 95% CI	ER (%) 95% CI	ER (%) 95% CI	ER (%) 95% CI	ER (%) 95% CI	ER (%) 95% CI	ER (%) 95% CI	ER (%) 95% CI
Pool F	7 (43.8) 19.8, 70.1	1 (6.3) 0.2, 30.2	7 (38.9) 17.3, 64.3	1 (5.6) 0.1, 27.3	14 (77.8) 52.4, 93.6	1 (5.6) 0.1, 27.3	0 0.0, 33.6	0 0.0, 33.6
Pool G	7 (43.8) 19.8, 70.1	2 (12.5) 1.6, 38.3	16 (88.9) 65.3, 98.6	1 (5.6) 0.1, 27.3	17 (94.4) 72.7, 99.9	1 (5.6) 0.1, 27.3	0 0.0, 33.6	0 0.0, 33.6
Pool N	7 (43.8) 19.8, 70.1	1 (6.3) 0.2, 30.2	10 (55.6) 30.8, 78.5	0 0.0, 18.5	12 (66.7) 41.0, 86.7	0 0.0, 18.5	1 (11.1) 0.3, 48.2	0 0.0, 33.6
RSV	8 (50.0) 24.7, 75.3	2 (12.5) 1.6, 38.3	10 (55.6) 30.8, 78.5	5 (27.8) 9.7, 53.5	15 (83.3) 58.6, 96.4	1 (5.6) 0.1, 27.3	0 0.0, 33.6	0 0.0, 33.6

CI = confidence interval; ELISPOT = enzyme-linked immunospot technique; FAS = full analysis set; IFN-γ = interferon gamma; IL-4 = interleukin 4; PPS = per protocol set; ER (%) = Number of subjects with positive ELISPOT responder status (percentage of subjects with positive responder status based on number of subjects with available data); RSV = respiratory syncytial virus

[a] Only 16 of 18 subjects had available data in this group.

[b] Adult and elderly placebo combined.

Note: At least 2 post Week /V1 responses are required for the subject to be defined as a responder.

Source: MVA-RSV-001 Clinical Study Report (Ed. 1), Table 15.2.16.1 and Table 15.2.16.3.

2.7 Rationale

As outlined in Section 2, RSV is an important cause of serious respiratory disease in all age groups. The recently completed Phase I clinical trial RSV-MVA-001 generated first safety and immunogenicity data of the recombinant MVA-BN-RSV vaccine in healthy adult subjects 18-65 years of age. This trial confirmed that the vaccine is safe and well tolerated and was able to increase humoral and cellular immune responses in the population tested.

The main trial is designed to evaluate different doses of the MVA-BN-RSV vaccine in a target population of adult/elderly subjects in terms of immunogenicity and safety.

As RSV is a seasonal disease with peak occurrence in the winter months in the northern hemisphere vaccination for protection against moderate to severe respiratory tract infections caused by RSV would be scheduled shortly before the start of the RSV season. Depending on the durability of the immune responses elicited by a vaccination a yearly booster before the next RSV season might be necessary. Hence a substudy applying a booster vaccination in a subgroup of the main trial will evaluate the durability of the immune response and the ability to booster with the MVA-BN-RSV vaccine.

The objective of the booster substudy is to demonstrate that the immune response of subjects previously vaccinated with MVA-BN-RSV vaccine can be boosted one year later with a single MVA-BN-RSV vaccination. Assessment of individual antibody titers within short time intervals following the booster vaccination and up to 12 months after the vaccination will provide information on how fast and effective measurable antibody titers can be regained. The booster substudy will also evaluate the durability of immune responses 12 months following the primary vaccination (baseline measurement prior to administration of the booster dose) and 12 months following the booster vaccination.

The selection of the treatment groups to be included in the booster substudy is based on the results of the main trial. Selecting subjects of two groups for a booster vaccination will add a one year time point for the two most promising dose regimen treatment groups and will allow to identify further potential differences in durability or boostability of immune responses in the chosen dose regimens. Half of the subjects enrolled for the main part of the trial in the two chosen treatment groups will receive the same vaccine dose (either 1×10^8 or 5×10^8 Inf.U) as in the main part. The two groups to continue into the booster substudy will be selected by the sponsor. The subjects from the remaining groups will be excluded from the booster substudy as the further development of their dose regimen is unlikely at the current time.

2.8 Trial Population

Any ≥ 55 year old women and men of any ethnicity who meet all of the inclusion and none of the exclusion criteria are eligible for participation in this trial.

Groups will be stratified by age: 55 to < 70, ≥ 70 years in the main part of the trial. For the booster substudy 43 evaluable subjects will be chosen randomly from each of the two selected treatment groups. No further age stratification will be done in the booster substudy.

2.9 Risk/Benefit Assessment

2.9.1 Potential Risks

Blood drawing may cause discomfort, bruising, light-headedness or fainting. Rarely, a blood draw may result in infection at the site of venipuncture. Nasal swab collection may cause irritation or dryness at the sampling sites for a short time, usually less than 5 minutes.

Some subjects in the trial will get Placebo instead of the MVA-BN-RSV vaccine. The Placebo consists of the MVA-BN formulation buffer TBS. Placebos are harmless, inactive substances made to look like the real vaccine, used in the clinical trial and contain no active ingredient. The subject may experience discomfort at the injection site, such as pain.

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

There is substantial safety data available for the vector backbone MVA-BN and for other MVA-based recombinant vaccines in healthy and immunocompromised subjects as well as the first safety data for the MVA-BN-RSV vaccine (Phase I clinical trial RSV-MVA-001 in healthy adult subjects; see Section 2.6). Adverse reactions in this trial setting are expected to be comparable to adverse reactions previously reported for MVA-BN or MVA-BN based recombinant vaccines 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 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 and/or dyspnea might occur, appropriate medical treatment and supervision will be readily available.

2.9.2 Benefits

There will be no direct benefit to the trial participants. Trial participants will contribute significantly to the development of a RSV vaccine which is a potential benefit for adults with underlying cardiovascular or pulmonary disease, elderly and children to reduce their risk of severe illness and mortality due to infection with RSV. In addition based on the current immunogenicity and efficacy data collected in non-clinical and clinical studies with MVA-BN, participants in clinical trials are expected to acquire protection against smallpox infection and might potentially also acquire protection against disease symptoms caused by RSV. The immunogenicity results of the first clinical trial with the MVA-BN-RSV vaccine indicate that RSV specific humoral and cellular immune responses are significantly boosted by the vaccine. However, it cannot be said if the vaccine is efficacious against the disease, as data available up to date are limited and do not allow for conclusions on protection against RSV.

Analysis of the samples collected will not directly benefit the subject.

3 Objectives

Refer to trial protocol synopsis Section 1.5.

4 Trial Design

4.1 Experimental Design Forecast

A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine.

In total 400 subjects will be recruited into the main trial. Subjects will receive two administrations 4 weeks apart which will consist of MVA-BN-RSV Dose 1, MVA-BN-RSV Dose 2 or placebo (TBS). To obtain Dose 1 the vaccine will be diluted in TBS according to the vaccination instructions. For details on the treatment groups see Table 13.

Approximately one year after their first vaccination 86 subjects in the selected treatment groups of the main trial will be recruited to participate in the booster substudy and will receive one dose of MVA-BN-RSV vaccine.

Recruitment into the main trial will be performed into a staggered manner as outlined below. Any occurring events as defined in the trial halting rules in Section 4.5 would stop the staggering procedure until further clarification.

Staggering Procedure:

The staggering process will be performed at one clinical trial site. The main trial will start with a sentinel cohort with 2 subjects, of whom one subject will be recruited into Group 2 and the other subject into Group 4 (i.e. 1:1 subjects receiving Dose 1 and Dose 2). Each subject will receive a priming vaccination followed 4 weeks later by a boosting vaccination of the same dose. Safety will be assessed prior to and 3 days post first vaccination. Safety assessments will be based on solicited and unsolicited adverse event data evaluated by the Safety Monitoring Team (SMT) comprising of the national coordinating investigator, investigator and the medical monitors (BN and CRO). Following a positive safety assessment after the first vaccination in both subjects recruited into the sentinel cohort, recruitment in the safety cohort will start.

The safety cohort will include a total of 10 subjects: 5 subjects will be recruited each into Groups 2 and 4 (i.e. 5:5 subjects receiving Dose 1 and Dose 2). Following a positive safety assessment by the SMT based upon solicited and unsolicited adverse event data 3 days post first vaccination recruitment in all groups for the remaining subjects will be opened.

The principal investigator, national coordinating investigator and the medical monitors (BN and CRO) must participate in the SMT meeting and decide on the next staggering step. Project leader BN, Contract Research Organization (CRO), statistician and Clinical Research Associate (CRA) can participate in the meeting, if further information on the trial conduct is required, but will not participate in the decision to go to the next staggering step. In total, two staggering steps and SMT meetings are required until all groups can be recruited in parallel.

Table 13 Treatment Groups Main Trial

Group	N	Age [years]	Volume per dose [mL]	1st vaccination Day 0 [Inf.U]	2nd vaccination Day 28 [Inf.U]	Route
1	80	≥ 55	0.5	1×10^8	Placebo	IM
2	80	≥ 55	0.5	1×10^8	1×10^8	IM
3	80	≥ 55	0.5	5×10^8	Placebo	IM
4	80	≥ 55	0.5	5×10^8	5×10^8	IM
5	80	≥ 55	0.5	Placebo	Placebo	IM
Total	**400**					

Booster Substudy

In total 86 evaluable subjects will receive a booster vaccination approximately one year after their first vaccination in the main trial receiving the same dose they received during the main trial. To obtain 40 evaluable subjects per group up to 43 subjects per selected group will be recruited. Subjects are then followed up for 12 months after their last vaccination.

4.2 Description of Trial Procedures

The trial procedures will be conducted according to the trial procedure schedule (Section 1.5, Section 1.6 and Section 1.7) and as described on the following pages. Visits must be scheduled within the intervals/visit windows given below.

4.2.1 Main Trial

4.2.1.1 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 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 • Obtain medical history

Screening Visit (Days -28 to -1)
• Complete physical examination including auscultation of heart and lungs and measurement of body weight and height • Evaluation of vital signs • Perform Electrocardiogram (ECG) reading • Recording of prior and concomitant medication • Counseling on avoidance of pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP • Recording of AEs/SAEs • Blood draw for safety laboratory 22 mL including o Serum pregnancy test (WOCBP only) o Hematology & serum chemistry o Hepatitis B and C; HIV o Troponin I o **If applicable:** HbA1c (additional blood draw of 3 mL)

If a subject is screened and cannot be vaccinated because of a certain transient condition (e.g. abnormal lab value due to an acute condition or a missing lab evaluation e.g. 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 Day -28 to -1 before first vaccination must not be exceeded. If a subject cannot be vaccinated 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, the complete Screening Visit needs to be repeated and a new Screening number will be assigned. The clock then re-starts at the re-screening visit with Day -28 before the first vaccination.

4.2.1.2 Active Trial Phase

After successfully passing the screening evaluations, the eligible volunteers can enter the active trial phase (Visit 1 to EAP) starting with Visit 1 and ending at either EAP or premature discontinuation.

The first 12 subjects are recruited in a staggered fashion. After completion of the staggering steps all remaining subjects can be vaccinated. The staggering process is described in detail in Section 4.1 and in the Synopsis in Section 1.5.

The procedures performed at Visit 1 and all following visits are listed below. **Collection of immunogenicity samples and all other examinations listed above the vaccination event must always be performed prior to vaccine/TBS administration.**

At Visit 1/Day 0, subjects will receive the first vaccination with 0.5 mL of the recombinant MVA-BN-RSV or TBS given IM preferably in the non-dominant upper arm. Subjects will be blinded to the treatment assignment, i.e. will not be told which group they were assigned until after completion of the main trial.

Following each vaccination subjects will be kept under close observation at the clinical trial site for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the vaccine administration. Any AEs that occur during or after vaccine administration will be recorded.

Solicited local and general AEs will be collected on a memory aid, completed by the subject 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.

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 concomitant medication • Counseling on avoidance of pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP • Recording of AEs/SAEs • Urine pregnancy test (WOCBP only) • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) • **Only for the subgroup: PBMC collection (64 mL)** **If eligible for participation in this trial the subject will be randomized (for the first 12 subjects please refer to Sections 1.5 and 4.1. for details on the staggering procedure). The following tasks will be performed after randomization:** • First MVA-BN-RSV vaccination • Subject observation by CTS staff for at least 30 minutes after vaccination • Recording of immediate AEs/SAEs • Handout of memory aid for first vaccination, ruler and thermometer

Visit 1 (Day 0)
Temporary deferral of vaccination: If an acute illness is present the subject may be vaccinated at a later date within the accepted time window. The vaccine/TBS can be administered to persons with a minor illness such as diarrhea or any other mild condition with or without low-grade febrile illness, i.e. oral temperature < 100.4 °F (< 38.0 °C). In case of minor illness involving the upper respiratory tract, such as mild upper respiratory infection, with or without low-grade febrile illness, the vaccination should be deferred within the accepted time window, until the subject is symptom-free.

Visit VS (V1 + 3-4 days) Sentinel Cohort, Safety Cohort (**first 12 [2 + 10] subjects)** **Groups 2 and 4**
The following tasks will be performed: • Recording of concomitant medication • Recording of AEs/SAEs • Review of the memory aid handed out at Visit 1 ***Note:*** *transfer entries to eCRF for SMT review within 24 hours, keep photocopy of the memory aid and return original to the subject to complete entries for the remaining days.* • Examination of the injection site **Only if clinically indicated:** • Nasal swab collection for Respiratory Viral Panel (RVP) PCR in case of symptoms indicating a respiratory infection

Visit 1b (V1 + 7-9 days) **Subgroup only**
The following tasks will be performed: • Targeted physical exam incl. auscultation of the heart and lung • Evaluation of vital signs • Recording of concomitant medication • Recording of AEs/SAEs • Review of the Memory Aid Card handed out at Visit 1 • Collection of the Memory Aid Card • Blood draw for serum collection (9 mL) and PBMC collection (64 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils)

Visit 1b (V1 + 7-9 days) **Subgroup only**
• Examination of the injection site **Only if clinically indicated:** • Nasal swab collection for RVP PCR in case of symptoms indicating a respiratory infection

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 • Recording of concomitant medication • Recording of AEs/SAEs • Blood draw for safety laboratory (hematology & serum chemistry, 11 mL) • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) • Review of the memory aid handed out at Visit 1 • Collection of the memory aid • Examination of the injection site • **<u>Only for the subgroup:</u> PBMC collection (64 mL)** **Only if clinically indicated:** • Nasal swab collection for RVP PCR in case of symptoms indicating a respiratory infection • ECG • Troponin I (additional blood draw of 3 mL)

Visit 3 (V1 + 28-35 days)
Tasks to be performed prior to vaccination: • Check eligibility for second vaccination (refer to Section 4.2.4) • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medications

Visit 3 (V1 + 28-35 days)
• Counseling on avoidance of pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP • Recording of AEs/SAEs • Urine pregnancy test (WOCBP only) • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) **Only if clinically indicated:** • Nasal swab collection for RVP PCR in case of symptoms indicating a respiratory infection **If the subject is eligible to receive the second vaccination the following tasks will be performed**: • Second MVA-BN-RSV vaccination • Subject observation by CTS staff for at least 30 minutes after vaccination • Recording of immediate AEs/SAEs • Handout of memory aid **If the subject is not eligible to receive the second vaccination, continue with visit EAP.** <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/TBS can be administered to persons with a minor illness such as diarrhea or any other mild condition with or without low-grade febrile illness, i.e. oral temperature < 100.4 °F (< 38.0 °C). In case of minor illness involving the upper respiratory tract, such as mild upper respiratory infection, with or without low-grade febrile illness, the vaccination should be deferred within the accepted time window, until the subject is symptom-free.

Visit 3b (V3 + 7-9 days) Subgroup only
The following tasks will be performed: • Targeted physical exam incl. auscultation of the heart and lung • Evaluation of vital signs • Recording of concomitant medication • Recording of AEs/SAEs • Blood draw for serum collection (9 mL) and PBMC collection (64 mL)

Visit 3b (V3 + 7-9 days) **Subgroup only**
• Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) • Review of the memory aid handed out at Visit 3 • Collection of the memory aid • Examination of the injection site **Only if clinically indicated:** • Nasal swab collection for RVP PCR in case of symptoms indicating a respiratory infection

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 • Blood draw for safety laboratory (hematology & serum chemistry, 11 mL) • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) • Review of the memory aid handed out at Visit 3 • Collection of the memory aid • Examination of the injection site • **<u>Only for the subgroup:</u> PBMC collection (64 mL)** **Only if clinically indicated:** • ECG • Troponin I (additional blood draw of 3 mL) • Nasal swab collection for RVP PCR in case of symptoms indicating a respiratory infection

Visit EAP (V3 + 28-35 days)
The following tasks will be performed: • Targeted physical examination including auscultation of the heart and lungs

Visit EAP (V3 + 28-35 days)
• Evaluation of vital signs • Recording of concomitant medication • Recording of AEs/SAEs • Urine pregnancy test (WOCBP only) • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) **Only if clinically indicated:** • Nasal swab collection for RVP PCR in case of symptoms indicating a respiratory infection

4.2.1.3 Follow-Up (FU) Phase

To monitor long-term safety and antibody persistence, subjects will come to the CTS for follow-up (FU) visits three months (FU1 Visit) and six months (FU2 Visit) after the last vaccination. After all tasks for the trial were performed at FU2 Visit the subject may be unblinded to the assigned dosage group by the investigator.

For subjects who do not receive the second vaccine/TBS administration for any reason, the FU1 Visit will be performed three months after the first vaccination and the FU2 Visit will be performed 6 months after the first vaccination (see Section 4.2.4).

FU1 Visit (V3 + 84-98 days)
The following tasks will be performed: • Recording of new SAE and new RSV-specific symptoms and changes to AEs /SAEs ongoing at last active trial Visit EAP • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medication • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) • **Only for the subgroup: PBMC collection (64 mL)** **Only if clinically indicated**: • ECG • Troponin I (additional blood draw of 3 mL) • Blood draw for safety laboratory (hematology & serum chemistry, 11 mL) • Nasal swab collection for RSV PCR in case of symptoms indicating a respiratory infection

FU2 Visit (V3 + 182-210 days)
The following tasks will be performed: • Recording of new SAEs, new RSV-specific symptoms and changes to AEs/SAEs ongoing at the FU1 Visit • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medication • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) • **Only for the subgroup: PBMC collection (64 mL)** **Only if clinically indicated**: • ECG • Troponin I (additional blood drawl of 3 mL) • Blood draw for safety laboratory (hematology & serum chemistry, 11 mL) • Nasal swab collection for RVP PCR in case of symptoms indicating a respiratory infection

4.2.2 Booster Substudy

4.2.2.1 Booster Visit 0

All subjects eligible to take part in the booster substudy must be thoroughly informed of all aspects of the booster substudy (e.g. substudy visit schedule, required evaluations and procedures, risks and benefits) as described in the informed consent form (ICF). The ICF and the statement about the 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 baseline period of up to 28 days before the 1 year booster vaccination.

Booster Visit 0 (Days -28 to -1)
The following tasks will be performed: • Subject to read, sign and date ICF and HIPAA • Check Inclusion/Exclusion criteria for booster substudy • Recording of SAEs since last FU visit in main trial

Booster Visit 0 (Days -28 to -1)
• Complete physical examination including auscultation of heart and lungs and measurement of body weight • Evaluation of vital signs • Recording of prior and concomitant medication • Counseling on avoidance of pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP • Recording of AEs/SAEs after ICF signature • Blood draw for safety laboratory 11 mL including o Hematology & serum chemistry

Additional safety measures (which may include troponin testing, ECG, etc.) can be taken at this or at any other trial visit or at unscheduled visits, if clinically indicated.

4.2.2.2 Booster Substudy Active Trial Phase

After successfully passing the baseline evaluations, the eligible volunteers can enter the active phase of the booster substudy (Visit BV1 to BEAP) starting with Visit BV1 and ending at either BEAP or premature discontinuation.

The procedures performed at BV1 and all following visits are listed below. **Collection of immunogenicity samples and all other examinations listed above the vaccination event must always be performed prior to vaccine administration.**

At BV1/Day 0, subjects will receive the booster vaccination with 0.5 mL of the recombinant MVA-BN-RSV given IM preferably in the non-dominant upper arm.

Following the vaccination subjects will be kept under close observation at the clinical trial site for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the vaccine administration. Any AEs that occur during or after vaccine administration will be recorded.

Solicited local and general AEs will be collected on a memory aid, completed by the subject 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.

Booster Visit 1 (Day 0)
Tasks to be performed prior to vaccination: • Check eligibility for booster vaccination (see "Reasons for early discontinuation", Section 4.2.4) • Evaluation of vital signs • Recording of concomitant medication • Counseling on avoidance of pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP • Recording of AEs/SAEs • Urine pregnancy test (WOCBP only) • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) **Only for the subgroup: PBMC collection (64 mL)** **Only if clinically indicated:** Targeted physical examination (see Section 8.2.3) **If eligible for booster vaccination the following tasks will be performed:** • MVA-BN-RSV vaccination • Subject observation by CTS staff for at least 30 minutes after vaccination • Recording of immediate AEs/SAEs • Handout of memory aid for booster vaccination, ruler and thermometer Temporary deferral of 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 or any other mild condition with or without low-grade febrile illness, i.e. oral temperature < 100.4 °F (< 38.0 °C). In case of minor illness involving the upper respiratory tract, such as mild upper respiratory infection, with or without low-grade febrile illness, the vaccination should be deferred within the accepted time window, until the subject is symptom-free.

Booster Visit 1b (BV1 + 7-9 days) Subgroup only
The following tasks will be performed: • Evaluation of vital signs • Recording of concomitant medication

Booster Visit 1b (BV1 + 7-9 days) **Subgroup only**
• Recording of AEs/SAEs • Review of the memory aid handed out at BV1 • Collection of the memory aid • Blood draw for serum collection (9 mL) and PBMC collection (64 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) • Examination of the injection site **Only if clinically indicated:** Targeted physical examination (see Section 8.2.3)

Booster Visit 2 (BV1 + 12-16 days)
The following tasks will be performed: • Evaluation of vital signs • Recording of concomitant medication • Recording of AEs/SAEs • Blood draw for safety laboratory (hematology & serum chemistry, 11 mL) • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) • Review of the memory aid handed out at BV1 • Collection of the memory aid • Examination of the injection site **<u>Only for the subgroup:</u> PBMC collection (64 mL)** **Only if clinically indicated:** Targeted physical examination (see Section 8.2.3)

Booster EAP (BV1 + 28-35 days)
The following tasks will be performed: • Evaluation of vital signs • Recording of concomitant medication • Recording of AEs/SAEs

Booster EAP (BV1 + 28-35 days)
• Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) **Only if clinically indicated:** Targeted physical examination (see Section 8.2.3)

4.2.2.3 Booster Follow-Up (BFU) Phase

To monitor long-term safety and antibody persistence, subjects will come to the CTS for follow-up (FU) visits 3 months (BFU1 Visit), 6 months (BFU2 Visit) and 12 months (BFU3 Visit) after the booster vaccination.

Booster FU1 Visit (BV1 + 84-98 days)
The following tasks will be performed: • Recording of new SAEs and changes to AEs /SAEs ongoing at last active trial Visit BEAP • Evaluation of vital signs • Recording of concomitant medication for ongoing AEs/SAEs since BEAP or new SAEs • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) **Only for the subgroup: PBMC collection (64 mL)** **Only if clinically indicated**: • Blood draw for safety laboratory (hematology & serum chemistry, 11 mL) • Targeted physical examination (see Section 8.2.3)

Booster FU2 Visit (BV1 + 182-210 days)
The following tasks will be performed: • Recording of new SAE and changes to AEs /SAEs ongoing at BFU1 • Evaluation of vital signs • Recording of concomitant medication for ongoing AEs/SAEs since BFU1 or new SAEs • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response (swabs are taken from both nostrils) • **Only for the subgroup: PBMC collection (64 mL)** **Only if clinically indicated**: • Blood draw for safety laboratory (hematology & serum chemistry, 11 mL) • Targeted physical examination (see Section 8.2.3)

Booster FU3 Visit (BV1 + 364-392 days)
The following task will be performed: • Blood draw for serum collection (9 mL)

4.2.3 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.

4.2.4 Early Discontinuation

Reasons for early discontinuations:

A subject may be discontinued from the trial early for different reasons. The decision to discontinue a trial subject early can be made by the investigator or by the subject. Reasons for early discontinuation of a subject may include but are not limited to:

- An AE/SAE that, in the opinion of the investigator, makes it unsafe for the subject to receive a further vaccination
- Pregnancy
- An anaphylactic reaction following the administration of any vaccine(s)

- Clinical need for concomitant or ancillary therapy not permitted in the trial as outlined in Section 8.2.2
- Subject's request to discontinue
- Subject's refusal to receive second / booster vaccination.
- Subject unwilling or unable to comply with trial requirements.
- Any reason that, in the opinion of the investigator contradicts administration of the second / booster vaccination or otherwise requires early discontinuation of a subject.

Handling of early discontinuations main trial

- If a subject discontinues from the trial after first but prior to the second vaccination or does not receive the second vaccination for any reason, the subject should follow the abbreviated visit schedule outlined below:
- Visits 3, 3b (for subgroup) and 4 will not be performed;
- Visit schedule for all following visits will be calculated based on the 1st vaccination, i.e.
  - Visit EAP will be performed 4 weeks post the 1st vaccination
  - The 3 and 6 months FU visits (FU1 and FU2) will be performed 3 and 6 months post the 1st vaccination, respectively.

Handling of early discontinuations booster substudy

- If a subject recruited for the booster substudy (after signature of the ICF for the booster substudy) discontinues from the trial prior to the booster vaccination or does not receive the booster vaccination for any reason, the subject should undergo a concluding safety visit (including pregnancy test for WOCBP).
- If a subject recruited for the booster substudy discontinues from the trial after the booster vaccination, it is highly recommended that the subject undergoes an abbreviated visit schedule (including BEAP, BFU1 and BFU2).

Furthermore, each subject has the right to terminate their trial participation completely at any time for whatever reason and the investigator may terminate a subject's trial participation. Subjects who's trial participation is terminated completely should undergo a concluding safety visit (including pregnancy test for WOCBP), i.e. subjects will be offered to have an optional safety visit performed. The subject has the right to refuse.

4.3 Trial Duration

The total duration of the main trial for each subject including the screening period and follow-up visits will be up to 39 weeks. The total duration of the booster substudy including baseline and

follow up visits will be 56 weeks. The duration of the trial as a whole depends on the recruitment period.

4.4 Safety Review

4.4.1 Safety Monitoring Team

The SMT is a board that oversees the safety of subjects participating in the trial during the staggering phase only. The members of the SMT are the national coordinating investigator, principal investigator (of the staggering site) and the medical monitors (BN and CRO) of the clinical trial. The primary responsibility of the SMT is to review and evaluate the accumulated trial data for safety after each staggering step and make decision to proceed to the next staggering step.

A separate charter describes in detail relevant operational procedures, communication pathways and roles and responsibilities of the SMT .

4.4.2 Safety Monitoring Committee

The Safety Monitoring Committee (SMC) is an independent board that oversees the safety of subjects participating in the trial. The SMC consists of three members who are independent, i.e. not involved as investigators in any BN sponsored trials and have no direct or indirect financial interests in BN or the CRO managing the trial. The primary responsibilities of the SMC 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 Investigator and Principal Investigators (PI) concerning the continuation, modification, or termination of the trial. The SMC 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 and roles and responsibilities of the SMC.

If an event occurs which fulfills the trial halting rules (see Section 4.5 for further details) the SMC will review the event in a timely manner and give a recommendation to BN and the Coordinating Investigator and PIs 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 of the trial as a whole can be decided by the SMT (during the staggering phase) or the SMC in case of an occurrence of

- an SAE
- an unexpected (i.e. not listed in the current IB) Grade 3 or higher systemic reaction or lab toxicity (Appendix 1: Toxicity Scale for Laboratory Values)

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

These parameters are not all-inclusive. Other AEs could occur that would trigger a SMC review.

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

For subjects not fulfilling the eligibility criteria the minimum information documented in the eCRF is confirmation of ICF signature, demographics and reason for screen failure.

5.1 Recruitment Procedure

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

80 subjects will be recruited in each group (400 in total) according to the treatment group schedule, Table 13.

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 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).

From each of the two treatment groups selected for the booster substudy, 43 subjects will be randomly recruited to receive a booster vaccination approximately one year after their first vaccination with the same dose they had received during the main trial. Out of these 86 subjects, in total approximately 26 subjects will be recruited from the PBMC subgroup resulting in approximately 13 subjects for each of the two selected treatment groups.

5.2 Inclusion Criteria

Refer to trial protocol synopsis Section 1.5.

5.3 Exclusion Criteria

Refer to trial protocol synopsis Section 1.5

6 Investigational Medicinal Product and Diluent

MVA-mBN294B (common name MVA-BN-RSV vaccine), highly attenuated, live recombinant virus based on the viral vector MVA-BN, provided as a LF formulation. It is administered as intramuscular application. The packages and vials will be labeled according to the respective Product Specifications.

One vaccine dose has a nominal virus titer of 5 x 10^8 Inf.U (0.5 mL volume) if used undiluted.

To obtain a nominal titer of 1 x 10^8 Inf.U (per 0.5 mL) (Dose 1) the vaccine has to be diluted with MVA-BN formulation buffer, TBS.

The actual titer upon vaccination will be reported in the clinical study report (CSR) based on results from the ongoing stability studies. For further details on MVA-BN-RSV vaccine see current version of the IB.

6.1 Production, Packaging and Labeling

The MVA-BN-RSV bulk drug substance and the TBS are manufactured by Bavarian Nordic A/S, DK.

Address:

Bavarian Nordic A/S
[redacted]

6.2 Shipment, Storage and Handling

TBS and MVA-BN-RSV vaccine are packed separately and will be shipped temperature controlled and monitored to the CTS (if applicable via a warehouse). At the CTS, the package is handed over to the personnel in charge of vaccine preparation, e.g. the pharmacist. After receipt the CTS personnel are responsible for proper storage of vaccine and diluent.

MVA-BN-RSV vaccine is shipped and stored frozen at -4°F ± 9°F (-20°C ± 5°C) avoiding direct light. A vial must not be re-frozen once it has been thawed. Details on shipment, storage and handling of the LF formulation of MVA-BN-RSV vaccine are provided in BN Standard Operating Procedure (SOP) [redacted]

[redacted] (see also Section 6.3).

TBS has to be shipped and stored refrigerated at 36°F to 46°F (+2°C to +8°C).

6.3 Preparation, Administration and Dosage

Details on vaccine storage, preparation and administration of MVA-BN-RSV vaccine are provided in [redacted]

Study specific vaccination instructions detailing the preparation/dilution and application procedure and handling of TBS will be provided to the CTS.

6.4 Accountability and Disposal

After receipt of the 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 must 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 the 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/ancillary supply should be autoclaved or incinerated and discarded at the CTS according to local regulations.

7 Assessment of Immunogenicity

The immunogenicity of the vaccine will be assessed by measuring humoral, cellular and mucosal immune responses on collected serum, nasal swab and PBMC samples.

- RSV-specific, G protein A strain-specific, G protein B strain-specific systemic antibody levels will be determined from serum samples using IgG/IgA ELISAs. Further, two

separate PRNTs will be performed to measure neutralizing antibody levels to RSV strains A and B.

- RSV-specific mucosal antibody levels will be determined from nasal swab samples using an RSV-specific IgA ELISA.
- IFN-γ and IL-4 secreting, RSV-specific T cells will be quantified using an ELISPOT assay on PBMC samples.
- RSV-specific Memory B cells will be measured on PBMC samples obtained at the (B)FU visits and compared between treatment groups

All immunogenicity testing will be performed at Bavarian Nordic GmbH, [redacted] Testing SOPs, effective at the time of testing will be filed in the electronic Trial Master File.

The procedures for collection, preparation, storage and shipment of specimens for immunogenicity testing (i.e. serum, nasal swabs and PBMC) are specified in separate Study Specific Instructions, which will be provided to the investigators / clinical trial site personnel as well as to the processing laboratories before recruitment commences. Additionally, the procedures will be trained during the investigator meeting / site initiation visit.

7.1 Systemic Humoral Immune Responses

Serum samples will be collected as outlined in the trials procedure schedule in Section 1.6.

All samples for immunogenicity testing obtained on vaccination visits will be collected prior to vaccination.

The procedures for the immunogenicity tests performed are outlined in Sections 7.1.1 and 7.1.2 below.

7.1.1 RSV-specific ELISA

RSV-specific IgG/IgA antibody responses will be determined using several ELISAs. Details of the procedure are defined in the SOP [redacted] "ELISA to determine RSV-Specific Antibody Titers (IgG) in Human Serum Samples", SOP [redacted] "ELISA to determine RSV-Specific IgA Titers in Human Serum Samples", SOP [redacted] "ELISA to determine RSV G Protein (A-strain) Specific Antibody Titers (IgG) in Human Serum Samples" and SOP [redacted] "ELISA to determine RSV G Protein (B1-strain) Specific Antibody Titers (IgG) in Human Serum Samples".

The individual peak titer is calculated as the maximum of all post baseline titer measurements for that individual. The individual peak titer is only missing if all post baseline titers are missing, otherwise the maximum of the available post baseline titers is used.

The GMT is calculated per visit as well as based on individual peak titers by taking the antilogarithm of the mean of the $\log_{10}$ titer transformations. The Geometric Mean Fold Increase (GMFI) is calculated analogously per post-baseline visit as the geometric mean of the individual fold increases, i.e. the subjects' post-baseline titers at Visit X, divided by their corresponding baseline titer.

The RSV-specific antibody response rate (applicable only to post-baseline visits) is calculated per visit as well as based on individual peak titers and is defined as the percentage of subjects with antibody response based on the total number of subjects with test results available. The response status is assessed with regard to the corresponding baseline (Visit 1) test result.

7.1.2 RSV-specific PRNT

Two PRNTs will be performed to determine RSV-specific neutralizing antibody titers against RSV strain A and B, respectively. Details on the procedures can be found in SOP [redacted] (for strain A) "PRNT to determine RSV A Strain Specific Neutralizing Antibody Titers in Human Serum Samples" and [redacted] (for strain B) "PRNT to determine RSV B Strain Specific Neutralizing Antibody Titers in Human Serum Samples".

The individual peak titer is calculated as the maximum of all post baseline titer measurements for that individual. The individual peak titer is only missing if all post baseline titers are missing, otherwise the maximum of the available post baseline titers is used.

The GMT is calculated per visit as well as based on individual peak titers by taking the antilogarithm of the mean of the $\log_{10}$ titer transformations. The GMFI is calculated analogously per post-baseline visit as the geometric mean of the individual fold increases, i.e. the subjects' post-baseline titers at Visit X, divided by their corresponding baseline titer.

The RSV-specific antibody response rate (applicable only to post-baseline visits) is calculated per visit as well as based on individual peak titers and is defined as the percentage of subjects with antibody response based on the total number of subjects with test results available. The response status is assessed with regard to the corresponding baseline (Visit 1) test result.

7.2 Mucosal Immune Responses

Nasal swab samples will be collected as outlined in Section 1.6 and Section 1.7. Nasal samples will be collected from both nostrils using nylon flocked swabs ([redacted]). Samples obtained on vaccination visits will be taken prior to vaccination. RSV-specific IgA antibody responses will be determined using an ELISA. Details of the procedure are defined in SOP [redacted] "ELISA to determine RSV-specific Antibody Titers (IgA) in Human Nasal Swab Samples".

The individual peak titer is calculated as the maximum of all post baseline titer measurements for that individual. The individual peak titer is only missing if all post baseline titers are missing, otherwise the maximum of the available post baseline titers is used.

The GMT is calculated per visit as well as based on individual peak titers by taking the antilogarithm of the mean of the $\log_{10}$ titer transformations. The GMFI is calculated analogously per post-baseline visit as the geometric mean of the individual fold increases, i.e. the subjects' post-baseline titers at Visit X, divided by their corresponding baseline titer.

The RSV-specific antibody response rate (applicable only to post-baseline visits) is calculated per visit as well as based on individual peak titers and is defined as the percentage of subjects with antibody response based on the total number of subjects with test results available. The response status is assessed with regard to the corresponding baseline (Visit 1) test result.

7.3 Systemic Cellular Immune Responses

PBMC samples will be collected as outlined in Section 1.6 and Section 1.7.

Blood samples obtained on vaccination visits will be drawn prior to vaccination.

SFU per 1 x 10^6 PBMC will be determined using an IFN-γ / IL-4 ELISPOT assay using five different RSV peptide pools as well as RSV as stimulating agent. Details of the ELISPOT procedure are defined in SOP [redacted] "Dual Color (IFN-γ/IL-4) RSV ELISPOT using Human PBMC".

The geometric mean SFU/1 x 10^6 PBMC are calculated per visit.

The response rate is calculated per visit and is defined as the percentage of subjects with a response based on the total number of subjects with test results on the respective visit. The response status is assessed with regard to the corresponding baseline (Visit 1) test result.

The number of ELISPOT pools where there is a response is also calculated on a per subject basis per visit.

A subject is an ELISPOT responder to the vaccine in a particular test agent (e.g. RSV virus) if the subject has a response for at least two post baseline visits within the same test agent.

The responder rate for each test agent is the percentage of subjects who are responders to the relevant test agent out of the number of subjects with a non-missing responder status.

Furthermore, PBMC collected at the (B)FU visits will be used to determine memory B cells secreting IgG and/or IgA in an ELISPOT. Details of the procedure are defined in SOP [redacted] "Fluorospot to measure RSV-specific IgG/IgA secreting cells in human PBMCs".

7.4 Future Use of Lab Specimen

Serum, PBMC and nasal swab samples remaining after completion of all immunogenicity testing for the trial will be stored for future testing supporting the licensure path of recombinant MVA-BN vaccines. Future testing will facilitate the bridging of trial results to animal immunogenicity results and/or to immune response data collected from subjects vaccinated with competitor vaccines. Further, remaining samples might be used for assay development and controls. 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, pseudonymized 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.

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

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 medicinal product (MP) which does not necessarily have a causal relationship with this IMP/MP. Any new signs, symptoms or changes in health starting after ICF signature are documented in the subjects' records and the AE section of the eCRF (data collection requirements for screen failures see Section 12.1). 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 AEs observed by the subject/investigator or which are not pre-listed on the memory aid card. 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.

After the first vaccination, abnormal laboratory values assessed as being clinically significant by the investigator are to be documented as AEs. In addition, after first vaccination, abnormal laboratory values fulfilling the Grade 3 or Grade 4 criteria according to the toxicity scale (Appendix 1: 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 Grade 4 criteria, 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 subjects 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.

Any adverse events starting during the screening phase, i.e. after informed consent is given but before the first vaccination, are considered as pre-treatment adverse events.

8.1.2.2 Solicited AEs

In this clinical trial protocol solicited AEs are defined as all symptoms specifically listed in the memory aid provided to the subjects following each vaccination. After 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 7 days (Days 0-7, 8 day period).

8.1.2.3 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
- 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 screening 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.

8.2.2 Prior and Concomitant Medication

Exclusionary medication or medication where washouts periods need to be adhered to are defined in the eligibility criteria in Section 1.5.

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 3 months prior to screening or BV0, will also be recorded in the eCRF and the subjects medical record: vaccines (e.g. Influenza/Pneumococcal), 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 screening.

If given after the first but prior to the second or the booster vaccination, the following will result in subject's ineligibility to receive the second or booster vaccination and the subject should follow the abbreviated visit schedule (see Section 4.2.4)

- Vaccination with any licensed live vaccine within 30 days prior to or after trial vaccination or any licensed inactivated vaccine within 14 days prior to or after trial vaccination.
- 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.

8.2.3 Physical Examination

Complete physical examination

A complete physical examination will be performed at screening and BV0. The examination includes a review of major organ systems as well as body 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 Appendix 3: Grading Scale for Lymphadenopathy). In addition, auscultation of the heart and lungs will be performed to check specifically for signs of any heart condition.

Targeted physical examination

In the main trial, 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 except VS.

In the booster substudy, a targeted physical examination will only be performed if clinically indicated, by the presence of signs/symptoms since last visit at BV1 to BFU2. If performed, auscultation of the heart and lungs will be included.

8.2.4 Vital Signs

At all visits except the Staggering Visit and BFU3, blood pressure and pulse rate will be taken after the subject has been sitting upright 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 and all required details (e.g. start and stop date, intensity) will be assessed. Unsolicited AEs will be reported in the respective section of the eCRF and the subject's medical record (requirements for screen failures see Section 12.1).

Unsolicited AEs will be assessed and documented as indicated in the trial schedule (see Section 1.6 and Section 1.7).

SAEs will be assessed and documented at all trial visits, excluding the BFU3 Visit. SAEs will be followed up until resolution or achievement of stable clinical conditions.

In the main trial, new AEs related to respiratory tract infections will be assessed and documented at all trial visits, including the FU Visits.

Assessment of Intensity

For all unsolicited AEs not represented in the toxicity scale for Laboratory Values (Appendix 1: 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 corrective therapy.

Grade 4 Life-threatening or disabling

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 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 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) 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 7 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 subjects.

To standardize procedures, uniform rulers will be handed out to subjects for measurements of erythema, swelling and induration diameters.

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 subjects. To standardize procedures, digital thermometers for oral measurements of body temperature will be handed out to subjects.

Assessment of Intensity

Subjects are asked to document the solicited general AEs in the memory aid as described in Table 14 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 14 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 Respiratory Viral Panel (Main Trial)

In case of any symptoms indicating a respiratory tract infection at any time point after the first vaccination a nasal swab will be obtained at scheduled or unscheduled visits to assess if a current RSV infection is underlying. This determination will be done in the central laboratory by measuring the standard respiratory viral panel (RVP) utilizing Nanosphere Verigene RP Flex technology. Subjects need to be instructed to return to the site within 3 days after start of symptoms as specified in Section 8.2.8.

8.2.8 RSV-specific symptoms

RSV-specific symptoms are defined by any case of rhinorrhea, nasal congestion, pharyngitis, cough, wheezing (or increase in baseline wheezing), sputum production (or increase or change in nature of baseline sputum production) or new (or worsening of) shortness of breath plus RSV infection confirmed by the RVP (see Section 8.2.7) within 3 days of symptom(s) (main trial only). RSV-specific symptoms are documented as Adverse Event from Visit 1 until the last FU Visit.

8.2.9 Cardiac Assessment

Electrocardiogram

A standard 12-lead ECG will be taken in the main trial at the Screening Visit. At Visit 2, Visit 4 and FU Visits an ECG is only done if clinically indicated. A central ECG reading center will assess if ECGs are normal, normal variant or abnormal.

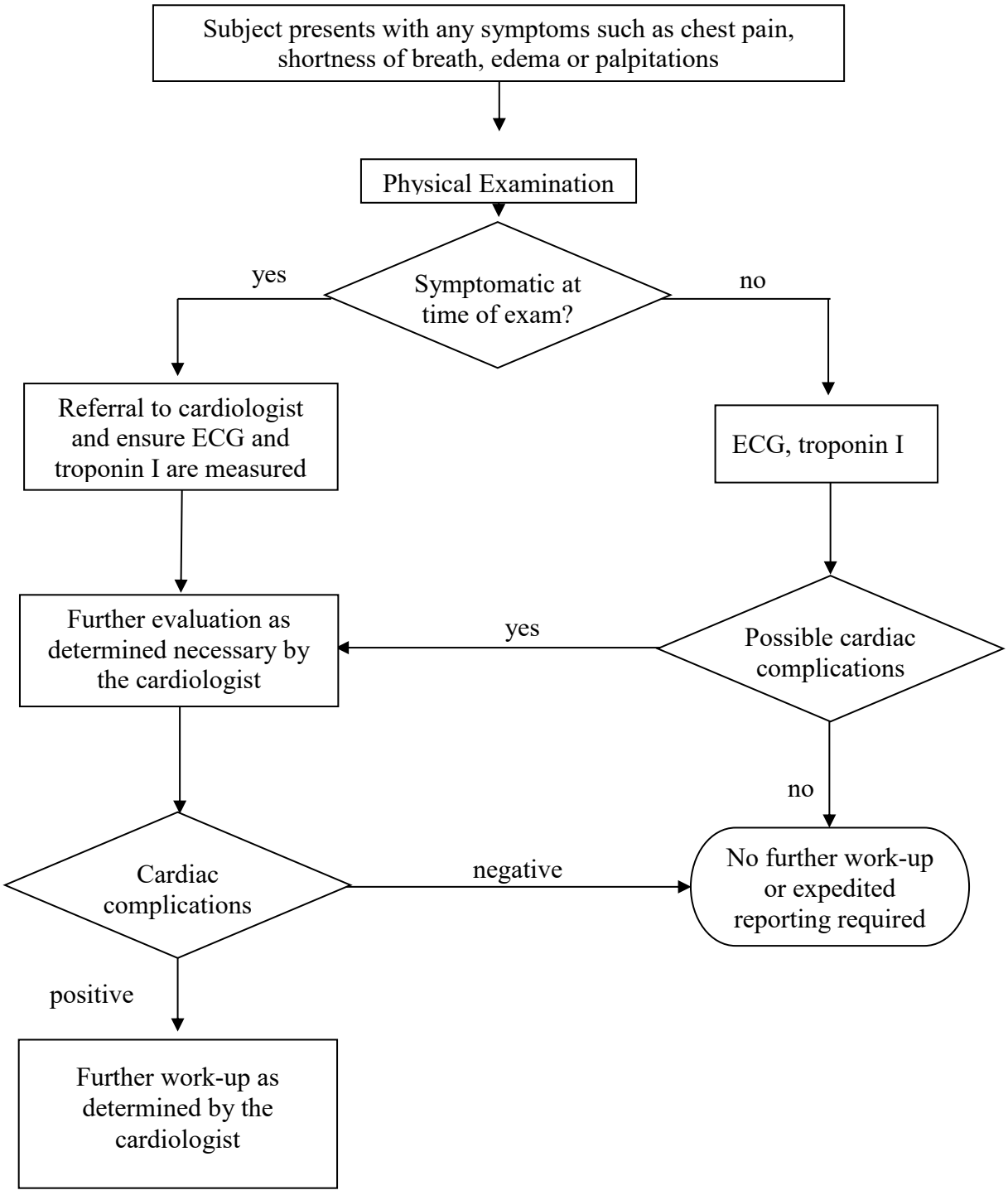
The clinical investigator will assess the clinical significance for abnormal ECGs. Interpretation support for screening ECGs is provided in Appendix 2: Interpretation Support for Assessment of Screening ECGs.

Troponin I

Troponin I will be measured in the main trial at screening and if clinically indicated on the following visits: Visit 2, Visit 4, FU1 and FU2 Visits or at unscheduled visits.

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 will be documented as adverse events and will require cardiac follow-up at a local cardiologist as outlined in Figure 3. The cardiologic examination should include at a minimum an ECG and troponin I determination.
The cardiologist should further evaluate the case as deemed necessary (e.g. by application of long-term or treadmill ECG, measurement of further cardiac enzymes and/or echocardiogram). Depending on the results of these evaluations, further diagnostic tests may be done as recommended by the cardiologist.

Figure 3 Algorithm for Cardiac Follow-up



8.2.10 Safety Laboratory Measurements

The intensity of laboratory / systemic toxicities measured quantitatively will be graded according to the toxicity scale in Appendix 1: 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 Appendix 1: Toxicity Scale for Laboratory Values, the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Biologics Evaluation and Research, September 2007) will be used for grading of laboratory toxicities.

Safety laboratory is determined at screening, Visit 2 and Visit 4 in the main trial and at BV0 and BV2 during the booster substudy 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.

Serum chemistry:

Total bilirubin, Alkaline Phosphatase (AP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), serum creatinine, sodium, potassium, calcium, troponin I (troponin mandatory only at SCR Visit).

For subjects with type II diabetes mellitus HbA1c is assessed at the SCR visit only in case documented HbA1c result within three months prior to SCR is not available.

Pregnancy test:

In the main trial, a β-human choriogonadotropin (HCG) pregnancy test will be conducted for all WOCBP at SCR Visit, prior to each vaccination and at the individual last active trial phase visit (Visits 1, 3 and EAP). At SCR Visit a serum β-HCG pregnancy test will be performed; all other pregnancy tests will be conducted as urine β-HCG tests.

In the booster substudy, a β-human choriogonadotropin (HCG) pregnancy test will be conducted for all WOCBP at BV1, prior to the booster vaccination.

Virology:
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:

HIV antibody test (anti HIV)

HBsAG

Hepatitis C antibody test

8.2.11 Pregnancy

As per inclusion criteria, women of childbearing potential must have a negative serum pregnancy test at SCR Visit and a negative urine pregnancy test 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 4.2.4). 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.

A woman is considered of childbearing potential unless post-menopausal (defined as ≥ 12 months without a menstrual period) or who is permanently sterile (i.e. is at least 6 months post-surgical sterilization via hysterectomy or bilateral oophorectomy). Acceptable contraception methods are restricted to abstinence, barrier contraceptives, intrauterine devices (IUD), intrauterine systems (IUS), licensed hormonal products or tubal ligation.

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 AE.

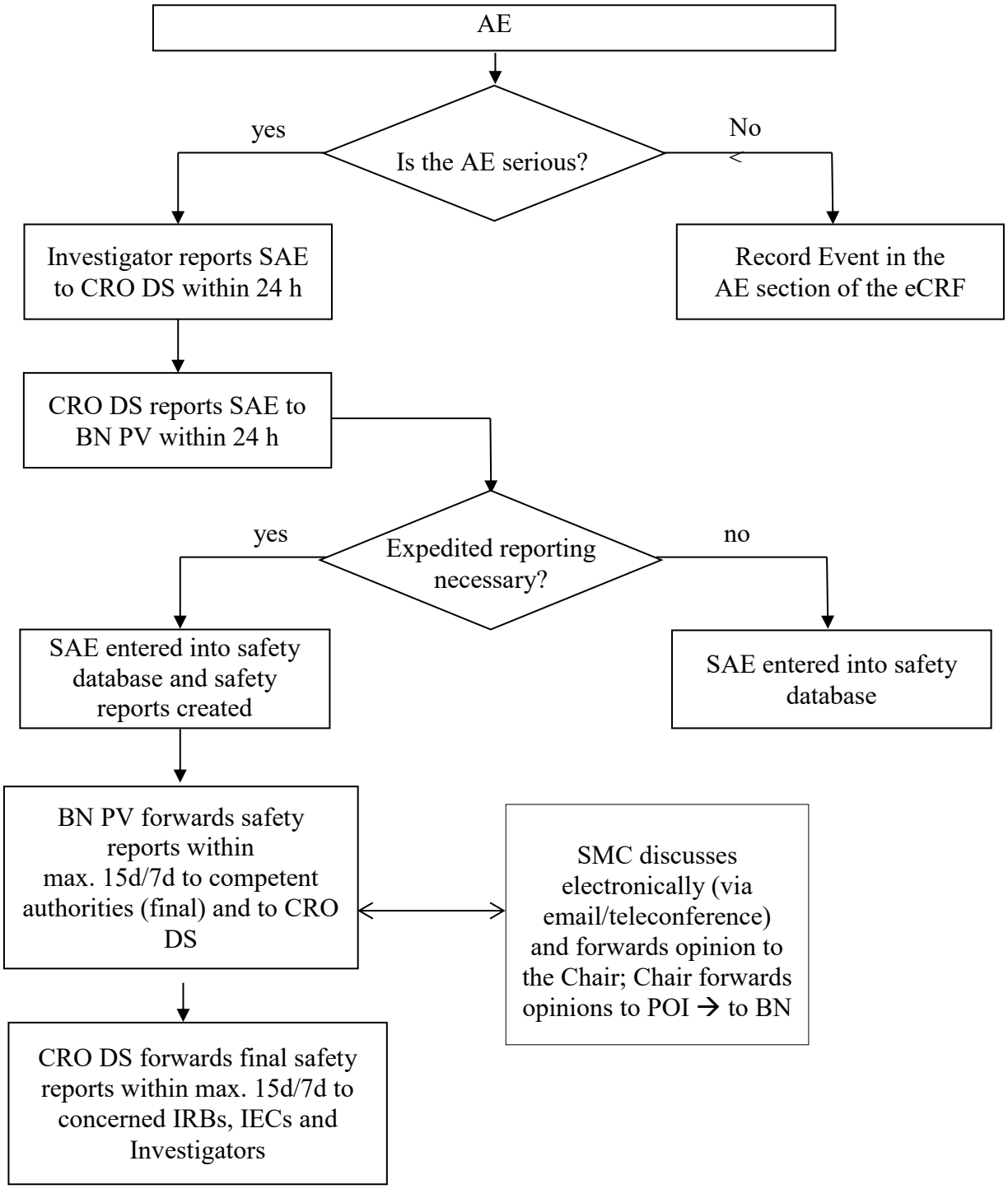
SAE should be sent to:

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
- date of onset

The CRO DS Department alerts BN PV of all SAEs and provides the available information within 24 hours to BN PV. BN is responsible for expedited as well as periodic reporting to the involved regulatory authorities (e.g. Food and Drug Administration, European Medicines Agency (EMA), Paul Ehrlich Institut [PEI]) according to applicable laws and guidelines. Regulatory authorities will be notified as soon as possible but no later than 7 days after first knowledge of a fatal or life-threatening unexpected SAE with an at least possible relationship to the IMP (SUSAR) and no later than 15 days after knowledge of any other unexpected SADR. The investigator or the CRO is responsible for reporting to the Ethics Committees or IRBs. Figure 4 outlines the reporting process and timelines for SAEs.

Figure 4 Algorithm for Reporting of SAEs



8.3.2 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 (via eCRF) 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 PV/CRO DS (see Section 8.3.1). However, hospitalization for delivery is a prospectively planned hospitalization and is not considered a SAE per se.

9 Statistical Considerations

The primary endpoint of this trial is to determine the GMTs after one or two MVA-BN-RSV vaccinations or placebo measured by PRNT (against strain A) 2 weeks post last vaccination.

9.1 Randomization Procedure and Blinding

The main part of the trial is randomized using an automated randomization system, integrated in the eCRF: Details on the randomization will be outlined in a separate randomization specification.

Assignment to the groups is done in a randomized manner. The main trial is single-blinded, i.e. subjects will be blinded to the group assignment.

In total 86 subjects from two selected treatment groups will be chosen randomly for the booster substudy outlined in a separate randomization specification.

For details on staggering and randomization refer to trial protocol synopsis (see Sections 1.5 and 4.1).

9.2 Sample Size Calculation

The primary analysis will be performed on the PRNT (A strain) titers 2 weeks after the last vaccination in the main trial. Testing of the primary objective will be performed by assuming that the $\log_{10}$ of the titers are normally distributed. Testing will be conducted in a descriptive manner and no adjustment for multiple testing will be performed.

The upper 95% confidence limit of the standard deviation (SD) of the $\log_{10}$ titers from the Phase I trial RSV-MVA-001 at Visit 6 (2 weeks post second vaccination) was calculated as 0.46 (the SD was very similar in all groups).

The GMTs, GMFIs from baseline, and the response rates and associated 95 % confidence limits will be presented for each group at each sampling point.

The following descriptive comparison of the ratios of the GMTs between groups will be calculated along with the corresponding 95% Confidence Interval by assuming that the $\log_{10}$ PRNT (A strain) titers are normally distributed:

1. Group 2 / Group 1 – Two vaccinations compared to one vaccination using Dose 1
2. Group 4 / Group 3 – Two vaccinations compared to one vaccination using Dose 2
3. Group 3 / Group 1 – Dose 2 compared to Dose 1 using one vaccination
4. Group 4 / Group 2 – Dose 2 compared to Dose 1 using two vaccinations
5. Group 2 / Group 5 – Two vaccinations using Dose 1 compared to Placebo
6. Group 4 / Group 5 – Two vaccinations using Dose 2 compared to Placebo

With a group sample size of 70 per group (recruiting 80 per group to account for 12 % dropouts), and an assumed SD of 0.46 for the $\log_{10}$ PRNT titers (A strain), this will give 80 % power to detect a relative change in titers from the Group 1 of a 66 % increase. The SD is similar to what was seen in the RSV Phase I trial (RSV-MVA-001).

A secondary descriptive quadratic orthogonal regression of the $\log_{10}$ titers for the three doses using Group 2, Group 4 and Group 5 will also be performed. If the linear contrast (i.e. slope) of the regression fit is significant at the standard significance level of 0.05 then a dose response relationship will have been demonstrated. If the quadratic contrast is significantly different from zero then this will indicate that the dose response is not linear within the dose range used in this trial. Assuming the quadratic effect is negative over the higher dose ranges, this will be seen as confirmation of a plateau effect in terms of responses for higher dose.

In addition, an explorative two way ANOVA will be conducted on the $\log_{10}$ titers using dose (2 levels) and number of vaccinations (2 levels) fitting both main effects and the interaction term.

All other immunogenicity results (PRNT strain B, ELISPOT, ELISA IgG/IgA) will be considered as secondary descriptive analyzes and will be analyzed similarly to the primary endpoint analysis.

The actual variability observed for the $\log_{10}$ titers for PRNT (A strain) 2 weeks after the second vaccination in RSV-MVA-002 turned out to be lower than anticipated from the Phase I trial results. Thus, based on an adapted assumption for the SD of 0.335 for the $\log_{10}$ titers to be measured 2 weeks after the booster vaccination, a number of 40 evaluable subjects per group will provide 80% power to detect a difference of 0.213 (log10-scale) at a significance level of 5% (two-sided), which corresponds to a ratio of GMTs between groups of 1.63. Accounting for a drop-out rate of 5% 43 subjects per group are to receive a booster vaccination. However, only a descriptive comparison is planned between the two dose groups in the sub-study.

9.2.1 Treatment Groups/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” will be applied, since this could introduce an optimistic bias into the analysis.

Full Analysis Set (FAS):

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

The main analysis of safety as well as humoral and mucosal immunogenicity endpoints of the main trial 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 in the main trial, completed all visits of the active trial phase (Visit 1 to EAP) 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 datasets will be made on a case-by-case basis in a data review meeting (DRM) prior to database lock.

The statistical procedures applied to the FAS for humoral and mucosal immunogenicity endpoints will also be applied to the PPS.

Immunogenicity Analysis Set (IAS):

This is the subset of subjects in the FAS which were assigned to the PBMC subgroup.

The main analysis of the cellular immunogenicity endpoints of the main trial will be performed on the IAS.

Booster Full Analysis Set (BFAS):

This is the subset of subjects who received a booster vaccination and for whom any post-booster data are available.

The analysis of safety as well as humoral and mucosal immunogenicity endpoints of the booster trial will be performed on this analysis set.

Booster Immunogenicity Analysis Set (BIAS):

This is the subset of subjects in the BFAS which were assigned to the PBMC subgroup.

The analysis of the cellular immunogenicity endpoints of the booster trial will be performed on the BIAS.

Additional analysis sets may need to be defined during the data review meeting and would be described in the clinical study report.

9.3 Biometrical Evaluation

9.3.1 Analysis

As soon as the last subject has completed Visit FU1 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 data sets defined for the main trial (FAS, PPS, IAS, see Section 9.2.1). After the data review meeting and necessary settlement of queries that may arise during the data review meeting, the database will be locked. The safety analysis will then be performed based on this assignment and will include all safety data up to Visit FU1. Results will be reported in the clinical study report.

As soon as the last subject has completed FU2 Visit and after any necessary settlement of queries etc. in the eCRFs a data review meeting will be held. The assignment of the subjects to the datasets as described in Section 9.2.1 will be the same as in the CSR. 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 of the main trial will then be performed and will include all immunogenicity results as well as the follow-up safety data. Results of this analysis will be reported in an addendum to the clinical study report.

For the booster substudy, there will be a topline readout when the last subject included in the booster substudy has completed the BFU1 visit, the immunogenicity data up to BFU1 are available, and the data in EDC have been properly cleaned. The set of topline tables and figures will be specified in the statistical analysis plan.

As soon as the last subject included in the booster substudy has completed BFU3 Visit and after any necessary settlement of queries etc. in the eCRFs a data review meeting will be held. Protocol deviations will be reviewed to determine whether an additional analysis set compared to those described in Section 9.2.1 will be needed. After the data review meeting and necessary settlement of queries that may arise during the data review meeting, the database will be locked. The booster substudy analysis will then be performed and will include all immunogenicity results as well as the follow-up safety data. Results of this final analysis will be reported in an addendum to the clinical study report.

9.3.2 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 analyses as defined in the SAP will be followed.

If any unforeseen additional analysis is included in the clinical study report it will be clearly flagged as an additional unplanned explorative analysis. The CRO will be responsible for data management and statistical evaluation. Data will be analyzed using SAS®.

GMTs, GMFIs and antibody response rates for RSV-specific humoral immune responses determined from serum and nasal swab samples will be determined as described in Section 7.1 and Section 1.5.

Median and geometric mean SFU/1 x 10^6 PBMC, GMFIs as well as response and responder rates for RSV-specific cellular immune responses will be determined as described in Section 1.5

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.

Details for all ECGs will be listed. In addition the central ECG assessment of either normal, normal variant and abnormal as well as the investigator's interpretation as to whether ECGs, assessed as abnormal by the central ECG assessor, are clinically significant or not clinically significant will be summarized.

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 Medical Dictionary for Regulatory Activities (MedDRA) coding terminology. The intensity of AEs will be graded according to Section 8.2.

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

10 Ethical Aspects

10.1 Ethical and Legal Regulations

The PI is 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 and IBC

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.

The MVA-BN-RSV vaccine meets the exemption criteria set forth in Appendix M-VI-A of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules and is therefore exempt from the requirements of submission of the protocol to NIH OBA (Office of Biotechnology Activities), RAC (Recombinant DNA Advisory Committee) review and subsequent reporting but is expected to follow all other requirements of the NIH Guidelines. This includes having the protocol reviewed and approved by the responsible Institutional Biosafety Committee (IBC) for each site before research participants are recruited.

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-RSV 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 recruitment 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 persons authorized by the Sponsor or the PI or to 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 (see Section 7.4) 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.

Subjects eligible for the booster substudy have to sign a new ICF at BV0.

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

12 eCRF, Retention of Records and Monitoring

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 in the eCRF (including discontinuations or changes in trial vaccine or other medications) 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.

For subjects not fulfilling the eligibility criteria the minimum information documented in the eCRF is the ICF information, demographics and reason for screen failure.

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 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 into the subject’s record. If a subject refuses to consent to this procedure, he/she may not participate 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

Site audits and inspections may be carried out by the BN quality assurance department, 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 aspects (see Section 10 of this protocol).

Changes to the protocol require written "Amendments to the protocol" and written approval by the IEC/IRB and IBC, 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 is 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 partially 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 and regulatory and institutional requirements for the protection of confidentiality of subjects. He/she will permit authorized representatives of the Sponsor and regulatory authorities 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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Appendix 1: Toxicity Scale for Laboratory Values

Grade 1 or Grade 2 toxicity is only graded according to Table 15, Table 16 and Table 17 if the value is outside of the institutional normal range applicable for this trial. Any laboratory value that is between either the Lower Limit of Normal (LLN) or Upper Limit of Normal (ULN) and Grade 1 should not be graded. The values provided in Table 15, Table 16 and Table 17 are based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, (Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, September 2007).

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, hospitalization 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 15 Toxicity Scale for Serum Chemistry

Lab Value, Serum*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mmoL/L	132 < 136	130-131	125-129	< 125
Sodium – Hypernatremia mmoL/L	146	147	148-150	> 150
Potassium – Hyperkalemia mmoL/L	5.1-5.2	5.3-5.4	5.5-5.6	> 5.6
Potassium – Hypokalemia mmoL/L	3.4	3.3	3.1-3.2	< 3.1
Calcium – Hypercalcaemia mg/dL	> 10.2-11.0	11.1-11.5	11.6-12.0	> 12.0
Calcium- Hypocalcaemia mg/dL	8.0 < 8.6	7.5-7.9	7.0-7.4	< 7.0
Creatinine mg/dL	1.5-1.7	1.8-2.0	2.1-2.5	> 2.5 or requires dialysis
Alkaline Phosphatase increase by factor	1.1-2.0 x ULN	2.1-3.0 x ULN	3.1-10.0 x ULN	> 10.0 x ULN
ALT (SGPT) and AST (SGOT) increase by factor	1.1-2.5 x ULN	2.6-5.0 x ULN	5.1-10.0 x ULN	> 10.0 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test; increase by factor	1.10- 1.25 x ULN	1.26- 1.50 x ULN	1.51- 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1-1.5 x ULN	1.6-2.0 x ULN	2.1-3.0 x ULN	> 3.0 x ULN

* The laboratory values provided in the table serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mmoL/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

"ULN" is the upper limit of the normal range.

Table 16 Toxicity Scale for Hematology

Lab Value, Haematology*	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) – gm/dL	11.0-12.0	9.5-10.9	8.0-9.4	< 8.0
Hemoglobin (Male) – gm/dL	12.5-13.5	10.5-12.4	8.5-10.4	< 8.5
WBC Increase cell/mm3	> 11,000-15,000	15,001-20,000	20,001-25,000	> 25,000
WBC Decrease cell/mm3	2500 - < 4500	1500-2499	1000-1499	< 1000
Lymphocytes Decrease cell/mm3	750 - < 1000	500-749	250-499	< 250
Neutrophils Decrease cell/mm3	1200 - < 1800	1000-1199	500-999	< 500
Platelets Decrease cell/mm3	125,000- < 130,000	100,000-124,999	25,000-99,999	< 25,000

* The laboratory values provided in the table serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Table 17 Grading for Troponin I

Lab Value	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Cardiac troponin I	> ULN-< 2 x ULN	≥ 2-< 5 x ULN	≥ 5 x ULN	N/A

"ULN" is the upper limit of the normal range.

Appendix 2: Interpretation Support for Assessment of Screening ECGs

For a clearer and mutual understanding of inclusion criterion #9 of the main trial (see Section 1.5), the following provides clarifying explanations and examples pertaining to eligibility for trial participation.

Examples of subjects eligible for participation in the trial:

- Non-specific ST and T wave changes are not considered clinically significant and subject can participate
- Sinus bradycardia which does not require clinical intervention is not considered clinically significant and subject can participate.
- Subjects who present with atrial disease which does not require clinical intervention, e.g. a pacemaker or drug treatment, are allowed to be enrolled, as this can be considered not clinically significant. Examples are premature atrial contractions or ectopic atrial beats.
- Occasional Premature Ventricular Contractions (PVCs) which do not require clinical intervention are not considered clinically significant and subject can participate.
- 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 participate.
- 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 participation.

Examples of subjects NOT eligible for participation in the trial:

- Second or third degree atrioventricular block could represent significant heart disease and subject should not participate.
- Incomplete left bundle branch blocks could represent significant heart disease and subject should not participate.
- 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 participate.
- ST elevation consistent with ischemia, subject should not participate.
- Two PVCs in a row, subject should not participate.

Appendix 3: 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 1 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

Appendix 4: Amendment#1 to the Clinical Trial Protocol Edition 1.0 dated 07-Jul-2016

A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine

Amendment#1 to the Clinical Trial Protocol Edition 1.0 dated 07-Jul-2016

Date of Amendment#1: 27-Jan-2017

Rationale

The protocol Edition 1.0 is set up to measure cellular immune responses at Baseline (Visit 1) and one and two weeks following each vaccination in a subset of each treatment group. To measure the memory B cell responses to the trial vaccinations the protocol Edition 2.0 is generated and includes increased blood volume due to two additional blood draws to be taken for PBMC collection in these subgroups at the 3 month FU1 and 6 month FU2 visit . The respective protocol sections were amended accordingly.

These changes and additional minor changes are outlined in section 2 below.

The reason for the protocol amendment#1 is the implementation of two additional blood draw time points for PBMC collection: Additonal blood draw at the FU1 and FU2 visit. Consequently, an additional secondary endpoint is included.

Changes

General changes:

- Update of Section 1.3 (Sponsor Signature Page) and 1.4 (Responsibilities) to reflect the change of the BN Biostatistician. [redacted] left the company and is replaced by [redacted]
- Update of Section 1.4 (Responsibilities) to reflect the change of the ACM (safety) Laboratory contact person: [redacted] is replaced by [redacted]
- Update of Section 1.4 (Responsibilities) to add the contact person, [redacted], for the [redacted] PBMC Laboratory
- Update of section 4.2.2 (Active Trial Phase; Task sections): order of tasks was harmonized, ‘swabs are taken from both nostrils’ was added to harmonize the task sections
- Spelling and formatting was corrected

Major changes are as follows:

Changes/ added terms are highlighted in **bold** letters in the text (table below), removed terms are marked using ~~strikethrough~~.

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
Page 17, 1.5 Protocol Synopsis	**Page 18, 1.5 Protocol Synopsis**
Secondary Objective To assess the RSV-specific humoral and cellular immune responses against the MVA-BN-RSV vaccine in adult/elderly subjects in a subgroup population of each group.	**Secondary Objective** To assess the RSV-specific humoral **immune responses (in all subjects)** and cellular immune responses (**in a subgroup population of each group**) against the MVA-BN-RSV vaccine in adult/elderly subjects . **Reason for change:** *Clarification of analysis group for humoral immune responses against the MVA-BN-RSV vaccine.*
Page 19, 1.5 Protocol Synopsis	**Page 20, 1.5 Protocol Synopsis**
Secondary Endpoints Immunogenicity RSV-specific median and geometric mean Spot Forming Units (SFU) measured by IFN-ɣ / IL-4 ELISPOT at all PBMC sampling time points.	**Secondary Endpoints Immunogenicity** RSV-specific median and geometric mean Spot Forming Units (SFU) measured by IFN-ɣ / IL-4 ELISPOT at all PBMC sampling time points **until EAP.** **Reason for change:** *Specification of PBMC sampling time points for measurement by the* IFN-ɣ / IL-4 ELISPOT assay.

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
Page 19, 1.5 Protocol Synopsis	**Page 20, 1.5 Protocol Synopsis**
Secondary Endpoints Immunogenicity	**Secondary Endpoints Immunogenicity** **Additional endpoint added:** RSV-specific memory B cells measured at FU1 and FU2. **Reason for change:** *Evaluation of memory B cell response to measure durability of immune response after administration of MVA-BN-RSV vaccine.*
Page 25/26, 1.6 Trial Schedule and footnote	**Page 26/27, 1.6 Trial Schedule and footnote**
Blood draw for PMBC collection checked at visits: V1, V1b, V2, V3b, V4 Maximal total amount of blood taken/subject: up to 176 mL (514 mL for subjects in the subgroup).	Blood draw for PMBC collection checked at visits: V1, V1b, V2, V3b, V4, **FU1, FU2** Maximal total amount of blood taken/subject: up to 176 mL (~~514~~ **642** mL for subjects in the subgroup). **Reason for change:** *Additional blood draw for PBMC collection at the follow–up visits FU1 and FU2 added to get two further time points 3 and 6 month after EAP for immune response analysis*

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
Page 44, 2.6 Clinical Trial Data with MVA-BN-RSV Vaccine, Table 7	**Page 45, 2.6 Clinical Trial Data with MVA-BN-RSV Vaccine, Table 7**
Footnote b missing	Footnote b added **[b] SAEs are included even if they exceed the 28-day follow-up period after each vaccination.** **Reason for change:** *Missing information (footnote) added.*
Page 58/59, 4.2.2 Active Trial Phase	**Page 60, 4.2.2 Active Trial Phase**
FU1 Visit (V3 + 84-98 days) **The following tasks will be performed**: • Recording of new SAE and new RSV-specific symptoms and changes to AEs /SAEs ongoing at last active trial Visit EAP • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medication • Nasal swab collection for mucosal immune response, swabs taken from both nostrils) • Blood draw for serum collection (9 mL)	FU1 Visit (V3 + 84-98 days) **The following tasks will be performed**: • Recording of new SAE and new RSV-specific symptoms and changes to AEs /SAEs ongoing at last active trial Visit EAP • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medication • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response, swabs are taken from both nostrils) • **Only for the subgroup: PBMC collection (64 mL)**

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
	Reason for change: *Additional blood draw for PBMC collection at the follow–up visit FU1 for immune response analysis*
FU2 Visit (V3 + 182-210 days) **The following tasks will be performed**: • Recording of new SAEs, new RSV-specific symptoms and changes to AEs/SAEs ongoing at the FU1 Visit • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medication • Nasal swab collection for mucosal immune response (antibody testing; swabs taken from both nostrils) • Blood draw for serum collection (9 mL)	FU2 Visit (V3 + 182-210 days) **The following tasks will be performed**: • Recording of new SAEs, new RSV-specific symptoms and changes to AEs/SAEs ongoing at the FU1 Visit • Targeted physical examination including auscultation of the heart and lungs • Evaluation of vital signs • Recording of concomitant medication • Blood draw for serum collection (9 mL) • Nasal swab collection for mucosal immune response ~~(antibody testing~~; swabs are taken from both nostrils) **<u>Only for the subgroup:</u> PBMC collection (64 mL)** **Reason for change:** *Additional blood draw for PBMC collection at the follow–up visit FU2 for immune response analysis*
Page 63, 6.2 Shipment, Storage and Handling	**Page 64/65, 6.2 Shipment, Storage and Handling**

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
Details on shipment, storage and handling of the LF formulation of MVA-BN-RSV vaccine are provided in BN Standard Operating Procedure (SOP) [redacted] "Storage, Handling and Vaccination Procedures of Liquid Frozen MVA-BN (IMVAMUNE) and Recombinant MVA-Based Vaccines in Clinical Trials" (see also Section 6.3).	Details on shipment, storage and handling of the LF formulation of MVA-BN-RSV vaccine are provided in BN Standard Operating Procedure (SOP) [redacted] "Storage, Handling and Vaccination Procedures of Liquid Frozen MVA-BN (IMVAMUNE), Recombinant MVA-Based **and FPV-Based** Vaccines in Clinical Trials" (see also Section 6.3). **Reason for change:** *Correction of SOP title*
Page 64, 6.3 Preparation, Administration and Dosage	**Page 65, 6.3 Preparation, Administration and Dosage**
Details on vaccine storage, preparation and administration of MVA-BN-RSV vaccine are provided in SOP [redacted], entitled "Storage, Handling and Vaccination Procedures of Liquid Frozen MVA-BN (IMVAMUNE), Recombinant MVA-Based Vaccines in Clinical Trials".	Details on vaccine storage, preparation and administration of MVA-BN-RSV vaccine are provided in SOP [redacted], entitled "Storage, Handling and Vaccination Procedures of Liquid Frozen MVA-BN (IMVAMUNE), Recombinant MVA-Based **and FPV-Based** Vaccines in Clinical Trials". **Reason for change:** *Correction of SOP title*
Page 65, 7.0 Assessment of Immunogenicity	**Page 66, 7.0 Assessment of Immunogenicity**
The immunogenicity of the vaccine will be assessed by measuring humoral, cellular and mucosal immune responses on collected serum, nasal swab and PBMC samples. • RSV-specific systemic antibody levels will be determined from serum samples using a RSV-specific IgG/IgA ELISA. Further, two separate PRNTs	The immunogenicity of the vaccine will be assessed by measuring humoral, cellular and mucosal immune responses on collected serum, nasal swab and PBMC samples. • RSV-specific systemic antibody levels will be determined from serum samples using a RSV-specific IgG/IgA ELISA. Further, two separate PRNTs

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
will be performed to measure neutralizing antibody levels to RSV strains A and B. • RSV-specific mucosal antibody levels will be determined from nasal swab samples using an RSV-specific IgA ELISA. • IFN-γ and IL-4 secreting, RSV-specific T cells will be quantified using an ELISPOT assay on PBMC samples.	will be performed to measure neutralizing antibody levels to RSV strains A and B. • RSV-specific mucosal antibody levels will be determined from nasal swab samples using an RSV-specific IgA ELISA. • IFN-γ and IL-4 secreting, RSV-specific T cells will be quantified using an ELISPOT assay on PBMC samples. • **RSV-specific Memory B cells will be measured on PBMC samples obtained at the FU visits and compared between treatment groups** **Reason for change:** *Immunogenicity assessment for Memory B cells added*
Page 66, 7.2 Mucosal Immune Responses	**Page 67,7.2 Mucosal Immune Responses**
Nasal swab samples will be collected from subjects of all four treatment groups as outlined in Section 1.6. Nasal samples will be collected from both nostrils using regular nylon flocked swabs ([redacted]) prior to vaccination. RSV-specific IgA antibody responses will be determined using a direct ELISA. Details of the procedure are defined in SOP [redacted] "ELISA to determine RSV-specific Antibody Titers (IgA) in Human Nasal Swab Samples".	Nasal swab samples will be collected from subjects of all four treatment groups as outlined in Section 1.6. Nasal samples will be collected from both nostrils using ~~regular~~ nylon flocked swabs ([redacted]s). **Samples obtained on vaccination visits will be taken prior to vaccination**. RSV-specific IgA antibody responses will be determined using a direct ELISA. Details of the procedure are defined in SOP [redacted] "ELISA to determine RSV-specific Antibody Titers (IgA) in Human Nasal Swab Samples". **Reason for change:**

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
	Explanation specified
Page 67: 7.3 Systemic Cellular Immune Responses	**Page 68: 7.3 Systemic Cellular Immune Responses**
PBMC samples will be collected from subjects as outlined in Section 1.6. Blood samples obtained on vaccination visits will be drawn prior to vaccination. SFU per 1 x 10^6 PBMC will be determined using an IFN-γ / IL-4 ELISPOT assay using three different RSV peptide pools as well as RSV virus as stimulating agent. Details of the ELISPOT procedure are defined in the SOP [redacted] "Dual Color (IFN-γ/IL-4) RSV ELISPOT using Human PBMC". The geometric mean SFU/1 x 10^6 PBMC are calculated per visit. Any SFU value below the assay detection limit is assigned the arbitrary value of 1 (negative result). Results equal or above the detection limit are considered positive test results. The response rate is calculated per visit and is defined as the percentage of subjects with a response based on the total number of subjects with test results on the respective visit. The response status is assessed with regard to the corresponding baseline (Visit 1) test result.	PBMC samples will be collected from subjects as outlined in Section 1.6. Blood samples obtained on vaccination visits will be drawn prior to vaccination. SFU per 1 x 10^6 PBMC will be determined using an IFN-γ / IL-4 ELISPOT assay using **five** different RSV peptide pools as well as RSV virus as stimulating agent. Details of the ELISPOT procedure are defined in SOP [redacted] "Dual Color (IFN-γ/IL-4) RSV ELISPOT using Human PBMC". The geometric mean SFU/1 x 10^6 PBMC are calculated per visit. ~~Any SFU value below the assay detection limit is assigned the arbitrary value of 1 (negative result). Results equal or above the detection limit are considered positive test results.~~ The response rate is calculated per visit and is defined as the percentage of subjects with a response based on the total number of subjects with test results on the respective visit. The response status is assessed with regard to the corresponding baseline (Visit 1) test result.

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
The number of ELISPOT pools where there is a response at each visit is also calculated on a per subject basis. A subject is an ELISPOT Responder to the vaccine in a particular test agent (e.g. RSV virus) if the subject has a response for at least two post baseline visits within the same test agent. The responder rate for each test agent is the percentage of subjects who are responders to the relevant test agent out of the number of subjects with a non-missing responder status (positive or negative) within the relevant analysis population.	The number of ELISPOT pools where there is a response at each visit is also calculated on a per subject basis. A subject is an ELISPOT responder to the vaccine in a particular test agent (e.g. RSV virus) if the subject has a response for at least two post baseline visits within the same test agent. The responder rate for each test agent is the percentage of subjects who are responders to the relevant test agent out of the number of subjects with a non-missing responder status (positive or negative) within the relevant analysis population. **Furthermore, PBMC collected at the FU visits will be used to determine memory B cells secreting IgG and/or IgA in an ELISPOT. Details of the procedure are defined in SOP [redacted] "B Cell ELISpot to quantify RSV-specific IgG and IgA Secreting Cells in Human CD19 Positive Cells".** **Reason for change:** *Details for Memory B cell assay added and immune response analysis definitions corrected.*
Page 75, 8.2.9 Cardiac Assessment	**Page 77, 8.2.9 Cardiac Assessment**
<u>Troponin I</u> Troponin I will be measured at screening and if clinically indicated on the following	<u>Troponin I</u> Troponin I will be measured at screening and if clinically indicated on the following

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
visits: Visit 2, Visit 4 and FU1 Visit or at unscheduled visits.	visits: Visit 2, Visit 4, FU1 **and FU2** Visit**s** or at unscheduled visits. **Reason for change:** *Troponin I will be analyzed optionally also at FU2*
Page 82, 9 Statistical Considerations	**Page 83, 9 Statistical Considerations**
The primary endpoint of this trial is to determine the GMTs after one or two MVA-BN-RSV vaccinations measured by PRNT (against strain A) 2 weeks post last vaccination.	The primary endpoint of this trial is to determine the GMTs after one or two MVA-BN-RSV vaccinations **or placebo** measured by PRNT (against strain A) 2 weeks post last vaccination. **Reason for change:** *'Placebo' was added for correctness.*
Page 83, 9.2 Sample Size Calculation	**Page 84, 9.2 Sample Size Calculation**
The following descriptive comparison of the ratios of the GMTs between groups will be calculated along with the corresponding 95% Confidence Interval by assuming that the $\log_{10}$ PRNT (A strain) titers are normally distributed: 1. Group 2 / Group 1 – Two vaccinations compared to one vaccination using Dose 1 2. Group 4 / Group 3 – Two vaccinations compared to one vaccination using Dose 2	The following descriptive comparison of the ratios of the GMTs between groups will be calculated along with the corresponding 95% Confidence Interval by assuming that the $\log_{10}$ PRNT (A strain) titers are normally distributed: 1. Group 2 / Group 1 – Two vaccinations compared to one vaccination using Dose 1 2. Group 4 / Group 3 – Two vaccinations compared to one vaccination using Dose 2

Clinical Trial Protocol Edition 1.0, dated 07-Jul-2016 **Previously written:**	**Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017** **Changed to:**
3. Group 3 / Group 1 – Dose 2 compared to Dose 1 using one vaccination 4. Group 4 / Group 2 – Dose 2 compared to Dose 1 using two vaccinations 5. Group 2 / Group 5 – Two vaccinations compared using Dose 1 compared to Placebo 6. Group 4 / Group 5 – Two vaccinations compared using Dose 2 compared to Placebo	3. Group 3 / Group 1 – Dose 2 compared to Dose 1 using one vaccination 4. Group 4 / Group 2 – Dose 2 compared to Dose 1 using two vaccinations 5. Group 2 / Group 5 – Two vaccinations ~~compared~~ using Dose 1 compared to Placebo 6. Group 4 / Group 5 – Two vaccinations ~~compared~~ using Dose 2 compared to Placebo **Reason for change:** *Correction of wording*
Page 83, 9.2 Sample Size Calculation	**Page 84, 9.2 Sample Size Calculation**
With a group sample size of 70 per group (recruiting 80 per group to account for 12 % dropouts), and an assumed SD of 0.46 for the $\log_{10}$ PRNT titers (A strain), this will give 80 % power to detect a relative change in titers from the Group 1 of a 40 % increase. This is a similar range to what is expected given what was seen in the RSV Phase I trial (RSV-MVA-001).	With a group sample size of 70 per group (recruiting 80 per group to account for 12 % dropouts), and an assumed SD of 0.46 for the $\log_{10}$ PRNT titers (A strain), this will give 80 % power to detect a relative change in titers from the Group 1 of a **66 %** increase. **The SD is similar to what was seen in the RSV Phase I trial (RSV-MVA-001).** **Reason for change:** *Correction of the percentage of the relative change as the sample size was corrected*

All changes are considered not to have any negative influence on the trial procedures in general, on the safety of the trial participants or on the validity of the main trial result.

Appendix 5: Amendment#2 to the Clinical Trial Protocol

A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine

Amendment#2 to the Clinical Trial Protocol

Date of Amendment#2: 20-Jul-2017

Rationale

The protocol Edition 3.0 is set up to add a booster substudy after the main part of the trial. Subjects from the two treatment groups with the best safety/immunogenicity profile will receive a MVA-BN-RSV vaccination to boost their immune response approximately one year after having received the first vaccination in the main part of the trial. Assessment of individual antibody titers within short time intervals following the booster vaccination will provide information on how fast and effective measurable antibody titers can be reactivated. After ICF has been collected, subjects will enter a baseline period of up to 28 days before the 1 year booster vaccination. All subjects vaccinated in the booster subgroup will be followed up for 6 months after vaccination. Hence, the substudy will also evaluate the durability of immune responses 12 months following the primary vaccination (i.e. baseline measurement prior to administration of the booster dose) and 6 months following the booster vaccination.

Edition 3.0 was generated to measure safety and immunogenicity after a booster vaccination approximately one year after the first vaccination. These changes and additional minor changes are outlined below.

The reason for the protocol amendment#2 is the implementation of the booster substudy which includes up to seven additional visits for the participating subjects :

Changes

General changes:

- Update of Section 1.3 (Sponsor Signature Page) and 1.4 (Responsibilities) to reflect the change of the BN Biostatistician: [redacted] is replaced by [redacted]
- Update of Section 1.4 (Responsibilities) to reflect the change of the ABL (PBMC) Laboratory contact person: [redacted] is replaced by [redacted]
- Update of Section 1.5 (Synopsis) regarding eligibility criteria of booster substudy
- Addition of Section 1.7 (Trial Schedule Booster Substudy)
- Update of Section 2.7 (Rationale) to include rationale for booster substudy
- Addition of Section 4.2.2 (Description of Trial Procedures – Booster Substudy)
- Spelling, formatting and wording was corrected and adaptions to BN writing conventions were made

Major changes are as follows:

Changes/ added terms are highlighted in **bold** letters in the text (table below), removed terms are marked using ~~strikethrough~~.

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Page 14, List of Abbreviations	**Page 16, List of Abbreviations**
	BFU: Booster Follow Up BV: Booster Visit
~~GMR: Geometric Mean Ration~~	GMFI: Geometric Mean Fold Increase
Page 16, Definitions	**Page 19, Definitions**
Active trial phase: The trial phase starting with and including Visit 1 and ending with and including Visit EAP (End of active trial phase) (V3 + 28-35 days; for details see Section 1.6).	Active trial phase: The trial phase starting with and including **(Booster)** Visit 1 and ending with and including **(B)**EAP (End of active trial phase) (V3/**BV1** + 28-35 days; for details see Section 1.6 **and Section 1.7**). **Booster Baseline: Immune responses measured at BV0** **Booster Substudy: Administration of a signle (booster) dose of MVA-BN-RSV vaccine approximately one year after the first MVA-BN-RSV vaccination in subjects previously vaccinated with MVA-BN-RSV in the main trial.**
End of active trial phase (EAP): The last visit of the active trial phase (for details see Section 1.6).	End of active trial phase (**[B]**EAP): The last visit of the active trial phase (for details see Section 1.6 **and Section 1.7**).

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
	Fold increase: The fold increase is defined as a subject's post-baseline titer at Visit X, divided by the baseline titer **Main Trial: In the main trial subjects will receive two administrations 4 weeks apart consisting of MVA-BN-RSV Dose 1 (1×10^8 Inf.U), MVA-BN-RSV Dose 2 (5×10^8 Inf.U) or Placebo (TBS).**
Staggering visit (VS): A visit only required by subjects enrolled into the sentinel and safety cohort.	Staggering visit (VS): A visit only required by subjects enrolled into the sentinel and safety cohort **in the main trial**.
Subgroup: The subgroup consists of 20 subjects per treatment group who ~~will~~ have peripheral blood mononuclear cells (PBMC) collection as well as an additional serum and nasal swab sample collection time point one week post each vaccination.	Subgroup: The subgroup consists of 20 subjects per treatment group **in the main trial** who have peripheral blood mononuclear cells (PBMC) collection as well as an additional serum and nasal swab sample collection time point one week post each vaccination. **Out of this subgroup, approximately 13 subjects per treatment group will be recruited into the booster substudy.**
Page 17ff, 1.5 Synopsis	**Page 20ff, 1.5 Synopsis**
Vaccination Dose and Schedule: […] In total 400 subjects will be recruited into this trial. Subjects will receive two administrations 4 weeks apart which will consist of MVA-BN-RSV Dose 1	Vaccination Dose and Schedule: […] In total 400 subjects will be recruited into this trial. Subjects will receive two administrations 4 weeks apart which will consist of MVA-BN-RSV Dose 1

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
(1 x 10^8 Inf.U), MVA-BN-RSV Dose 2 (5 x 10^8 Inf.U) or Placebo (TBS). To obtain Dose 1 the MVA-BN- RSV vaccine will be diluted in MVA-BN formulation buffer (TBS) according to the study specific administration instructions. For details on the treatment groups see Table 1. ~~Subjects in all groups are blinded and will not be told to which group they were assigned.~~	(1 x 10^8 Inf.U), MVA-BN-RSV Dose 2 (5 x 10^8 Inf.U) or Placebo (TBS). To obtain Dose 1 the MVA-BN- RSV vaccine will be diluted in MVA-BN formulation buffer (TBS) according to the study specific administration instructions. **Following the main trial, two subgroups will be identified, which will continue in the booster substudy. The selection is based on safety and immunogenicity data obtained in the main trial.** **86 subjects from 2 treatment groups (43 per treatment group) are supposed to receive one (booster) dose of MVA-BN-RSV vaccine approximately one year after their first vaccination. In this booster substudy, eligible subjects will receive the same dose they received during the main trial.** For details on the treatment groups see Table 1.

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Trial duration: Up to 39 weeks per subject Sample size: […]	Trial duration: Up to 39 weeks per subject **in the main trial and up to additional 34 weeks per subject enrolled in the booster substudy**. Sample size **main trial**: […] **Sample size booster substudy: From two treatment groups selected based on immunogenicity/safety parameters following primary vaccination (as determined by the sponsor) 43 subjects will be recruited into the booster substudy (86 subjects in total). Out of these, in total 26 subjects will be recruited from the PBMC subgroup, approximately 13 subjects for each of the two selected treatment groups. Subjects will receive a single booster vaccination approximately 1 year after the first vaccine administration with the same dose they received during the main trial.**

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Secondary objectives: […]	Secondary objectives: […] **To assess the RSV-specific immune responses (in subjects of the selected treatment groups) one year after the last vaccination in the main trial in adult/elderly subjects.** **To assess the RSV-specific humoral immune responses (in subjects of the selected treatment groups) and cellular immune responses (in the respective subgroup population of the selected treatment groups) following a one year booster MVA-BN-RSV vaccination in adult/elderly subjects.**
[…] **Secondary Endpoints:** **Immunogenicity** RSV-specific antibody response rate measured by Immunoglobulin G (IgG) Enzyme-linked Immunosorbent Assay at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers.	[…] **Secondary Endpoints:** **Immunogenicity** RSV-specific antibody response rate measured by Immunoglobulin G (IgG) Enzyme-linked Immunosorbent Assay **(ELISA) (total RSV, G protein A strain, G protein B strain)** at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers **(separately for main trial and booster substudy of the clinical trial).** RSV-specific GMT measured by IgG ELISA at all immunogenicity serum sampling time

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
RSV-specific GMT measured by IgG ELISA at all immunogenicity serum sampling time points and based on the individual peak titers. RSV-specific antibody response rate measured by Immunoglobulin A (IgA) ELISA at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers. RSV-specific GMT measured by IgA ELISA at all immunogenicity serum sampling time points and based on the individual peak titers. RSV-specific antibody response rate measured by PRNT (RSV strain A) at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers. RSV-specific GMT measured by PRNT (RSV strain A) at all immunogenicity serum sampling time points and based on the individual peak titers. RSV-specific antibody response rate measured by PRNT (RSV strain B) at all post vaccination immunogenicity serum sampling	points and based on the individual peak titers **(separately for main trial and booster substudy of the clinical trial).** RSV-specific antibody response rate measured by Immunoglobulin A (IgA) ELISA at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers **(separately for main trial and booster substudy of the clinical trial).** RSV-specific GMT measured by IgA ELISA at all immunogenicity serum sampling time points and based on the individual peak titers **(separately for main trial and booster substudy of the clinical trial).** RSV-specific antibody response rate measured by PRNT (RSV strain A) at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers **(separately for main trial and booster substudy of the clinical trial).** RSV-specific GMT measured by PRNT (RSV strain A) at all immunogenicity serum sampling time points and based on the individual peak titers **(separately for main trial and booster substudy of the clinical trial).** RSV-specific antibody response rate measured by PRNT (RSV strain B) at all post vaccination immunogenicity serum sampling time points and based on the individual peak

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
time points and based on the individual peak titers.	titers **(separately for main trial and booster substudy of the clinical trial).**
RSV-specific GMT measured by PRNT (RSV strain B) at all immunogenicity serum sampling time points and based on the individual peak titers.	RSV-specific GMT measured by PRNT (RSV strain B) at all immunogenicity serum sampling time points and based on the individual peak titers **(separately for main trial and booster substudy of the clinical trial).**
RSV-specific antibody response rate measured by IgA ELISA at all post vaccination nasal swab sampling time points (mucosal IgA) and based on the individual peak titers.	RSV-specific antibody response rate measured by IgA ELISA at all post vaccination nasal swab sampling time points (mucosal IgA) and based on the individual peak titers **(separately for main trial and booster substudy of the clinical trial).**
RSV-specific GMT measured by IgA ELISA at all nasal swab sampling time points (mucosal IgA) and based on the individual peak titers.	RSV-specific GMT measured by IgA ELISA at all nasal swab sampling time points (mucosal IgA) and based on the individual peak titers **(separately for main trial and booster substudy of the clinical trial).**
RSV-specific response and responder rates measured by Interferon gamma (IFN-ɣ) and Interleukin 4 (IL-4) Enzyme-linked Immuno Spot Technique (ELISPOT) at all PBMC post vaccination sampling time points until EAP.	RSV-specific response and responder rates measured by Interferon gamma (IFN-ɣ) and Interleukin 4 (IL-4) Enzyme-linked Immuno Spot Technique (ELISPOT) at all PBMC post vaccination sampling time points until EAP **and until BEAP.**
RSV-specific median and geometric mean Spot Forming Units (SFU) measured by IFN-ɣ / IL-4 ELISPOT at all PBMC sampling time points until EAP.	RSV-specific median and geometric mean Spot Forming Units (SFU) measured by IFN-ɣ / IL-4 ELISPOT at all PBMC sampling time points until EAP **and until BEAP.**
	RSV-specific memory B cells measured at FU1 and FU2 **as well as Booster Follow Up**

<table>
<tr><td>Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017

Previously written:</td><td>Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017

Changed to:</td></tr>
<tr><td>RSV-specific memory B cells measured at FU1 and FU2.

[…]</td><td>Visit 1 (BFU1) and Booster Follow Up Visit 2 (BFU2).

[…]</td></tr>
<tr><td>Trial design

[…]</td><td>Trial design

main trial

[…]

Trial design booster substudy

From each of the two treatment groups chosen for the booster substudy, 43 subjects will be recruited to receive a booster vaccination approximately one year after their first vaccination in the main trial. Subjects will receive the same dose as in the main trial. All 86 subjects will be followed up for 6 months after their last vaccination.

Table 2 Treatment Groups Booster Substudy
<table>
<tr><th>Group</th><th>N</th><th>Age [years]</th><th>Volume per dose [mL]</th><th>Booster vaccination Day 0</th><th>Route</th></tr>
<tr><td>1</td><td>43</td><td>≥ 55</td><td>0.5</td><td>Same dose as defined in main trial</td><td>IM</td></tr>
<tr><td>2</td><td>43</td><td>≥ 55</td><td>0.5</td><td>Same dose as defined in main trial</td><td>IM</td></tr>
<tr><td>Total</td><td>86*</td><td></td><td colspan="3"></td></tr>
</table>
*at least 40 evaluable subjects from the two chosen treatment groups</td></tr>
<tr><td>Reports:</td><td>Reports</td></tr>
</table>

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Final ~~Safety Report after EAP (4 weeks after last vaccination)~~ ~~Addendum~~ Report (including immunogenicity data ~~and~~ 3 and 6 months follow-up data for safety and immunogenicity)	Final **Clinical Study** Report (including **safety and** immunogenicity data **until** 3 **months follow-up visit)** **Clinical Study** Report **Addendum 1 (including additional immunogenicity data not yet included in the Final Clinical Study Report** and 6 months follow-up data for safety and immunogenicity) **Clinical Study Report Addendum 2 (including safety and immunogenicity data of the 3-month and 6-month follow-up visits of the booster substudy**
Page 34, 2.5 Clinical Profile of MVA-BN and Recombinant MVA-based Vaccines	**Page 44, 2.5 Clinical Profile of MVA-BN and Recombinant MVA-based Vaccines**
To date, 1~~8~~ clinical trials (13 sponsored by BN and ~~5~~ sponsored by the NIH [National Institutes of Health]) evaluating the safety and immunogenicity of MVA-BN have been completed. Currently three clinical trials are ongoing - two sponsored by BN and one sponsored by the NIH. A total of 7,106 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 atopic dermatitis (AD). Further MVA-BN has been evaluated in an elderly population, i.e. subjects 56 to 80 years of age. Including the ongoing clinical trials, more than 7,~~600~~ subjects have been exposed to MVA-BN.	To date, 1**9** clinical trials (13 sponsored by BN and **6** sponsored by the NIH [National Institutes of Health]) evaluating the safety and immunogenicity of MVA-BN have been completed. Currently three clinical trials are ongoing - two sponsored by BN and one sponsored by the NIH. **More than 7100** 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 atopic dermatitis (AD). Further MVA-BN has been evaluated in an elderly population, i.e. subjects 56 to 80 years of age. Including the ongoing clinical trials, more than 7**700** subjects have been exposed to MVA-BN. **Reason for change:**

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
	Update of Investigators Brochure
Page 35, 2.5.1 Safety Overview of MVA-BN and Recombinant MVA-based Vaccines	**Page 46, 2.5.1 Safety Overview of MVA-BN and Recombinant MVA-based Vaccines**
Serious Suspected Adverse Drug Reactions ~~As of 31 August 2015~~ a total of seven (7 out ~~of 7,675~~ vaccinated subjects = 0.09 %) serious suspected ADRs have been reported for MVA-BN smallpox vaccine in completed and ongoing trials (see Table 3).	Serious Suspected Adverse Drug Reactions **A** total of seven (7 out of **7758** vaccinated subjects = 0.09 %) serious suspected ADRs have been reported for MVA-BN smallpox vaccine in completed and ongoing trials (see Table 3). **Reason for change:** *Update of number of vaccinated subjects*
Page 41, 2.5.2 Safety Profile of MVA-BN-based Recombinant Vaccines in Healthy Compared to Special Populations	**Page 50, 2.5.2 Safety Profile of MVA-BN-based Recombinant Vaccines in Healthy Compared to Special Populations**
BN has evaluated the safety and immunogenicity of MVA-BN-based recombinant vaccines for several indications such as cancer, HIV and measles in more than ~~400~~ subjects including healthy and HIV infected populations. […]	BN has evaluated the safety and immunogenicity of MVA-BN-based recombinant vaccines for several indications such as cancer, HIV and measles in more than **700** subjects including healthy and HIV infected populations. […] **Reason for change:** *Update of number of vaccinated subjects*
Page 50, 2.8 Trial Population	**Page 59, 2.8 Trial Population**
[…]	[…]

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Groups will be stratified by age: 55 to < 70, ≥ 70 years.	Groups will be stratified by age: 55 to < 70, ≥ 70 years **in the main part of the trial. For the booster substudy 43 evaluable subjects will be chosen randomly from each of the two selected treatment groups. No further age stratification will be done in the booster substudy.**
Page 51f, 4.1 Experimental Design Forecast	**Page 60f, 4.1 Experimental Design Forecast**
[…] In total 400 subjects will be recruited into ~~this~~ trial. Subject will receive two administrations 4 weeks apart which will consist of MVA-BN-RSV Dose 1, MVA-BN-RSV Dose 2 or placebo (TBS). To obtain Dose 1 the vaccine will be diluted in TBS according to the vaccination instructions. For details on the treatment groups see Table 12. Recruitment into the trial will be performed into a staggered manner as outlined below. Any occurring events as defined in the trial halting rules in Section 4.5 would stop the staggering procedure until further clarification.	[…] In total 400 subjects will be recruited into **the main** trial. Subjects will receive two administrations 4 weeks apart which will consist of MVA-BN-RSV Dose 1, MVA-BN-RSV Dose 2 or placebo (TBS). To obtain Dose 1 the vaccine will be diluted in TBS according to the vaccination instructions. For details on the treatment groups see Table 1**3**. **Approximately one year after their first vaccination 86 subjects in the selected treatment groups of the main trial will be recruited to participate in the booster substudy and will receive one dose of MVA-BN-RSV vaccine.** Recruitment into the **main** trial will be performed into a staggered manner as outlined below. Any occurring events as defined in the trial halting rules in Section 4.5 would stop the staggering procedure until further clarification.

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Staggering Procedure: The staggering process will be performed at one clinical trial site. The trial will start with a sentinel cohort with 2 subjects, of whom one subject will be recruited into Group 2 and the other subject into Group 4 (i.e. 1:1 subjects receiving Dose 1 and Dose 2). […]	**Staggering Procedure:** The staggering process will be performed at one clinical trial site. The **main** trial will start with a sentinel cohort with 2 subjects, of whom one subject will be recruited into Group 2 and the other subject into Group 4 (i.e. 1:1 subjects receiving Dose 1 and Dose 2). […] **Booster Substudy** **In total 86 evaluable subjects will receive a booster vaccination approximately one year after their first vaccination in the main trial receiving the same dose they received during the main trial. To obtain 40 evaluable subjects per group up to 43 subjects per selected group will be recruited. Subjects are then followed up for 6 months after their last vaccination.**
Page 61, 4.2.4 Early Discontinuation	**Page 75, 4.2.4 Early Discontinuation**
<u>Reasons for early discontinuations:</u> […] • Subject's refusal to receive second vaccination. • Subject unwilling or unable to comply with trial requirements. • Any reason that, in the opinion of the investigator contradicts administration of the second vaccination or otherwise	<u>Reasons for early discontinuations:</u> […] • Subject's refusal to receive second / **booster** vaccination. • Subject unwilling or unable to comply with trial requirements. • Any reason that, in the opinion of the investigator contradicts administration of the second / **booster** vaccination or

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
requires early discontinuation of a subject. Handling of early discontinuations trial […]	otherwise requires early discontinuation of a subject. Handling of early discontinuations **main** trial […] **Handling of early discontinuations booster substudy** • **If a subject recruited for the booster substudy (after signature of the ICF for the booster substudy) discontinues from the trial prior to the booster vaccination or does not receive the booster vaccination for any reason, the subject should undergo a concluding safety visit (including pregnancy test for WOCBP).** • **If a subject recruited for the booster substudy discontinues from the trial after the booster vaccination, is is highly recommended that the subject undergoes an abbreviated visit schedule (including BEAP, BFU1 and BFU2).**
Page 62, 4.3 Trial Duration	**Page 76, 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 39 weeks. The duration of the trial as a whole depends on the recruitment period.	The total duration of the **main** trial for each subject including the screening period and follow-up visits will be up to 39 weeks. **The total duration of the booster substudy including baseline and follow up visits will be 34 weeks.** The duration of the trial as a whole depends on the recruitment period.

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Page 63, 4.5 Trial Halting Rules	**Page 77, 4.5 Trial Halting Rules**
A temporary halting or termination of the trial as a whole can be decided by the SMT (during the staggering phase) or the SMC in case of an occurrence of • an SAE • an unexpected (i.e. not listed in the current IB) Grade 3 or higher systemic reaction or lab toxicity (Appendix 1: Toxicity Scale for Laboratory Values)	A temporary halting or termination of the trial as a whole can be decided by the SMT (during the staggering phase) or the SMC in case of an occurrence of • an SAE • an unexpected (i.e. not listed in the current IB) Grade 3 or higher systemic reaction or lab toxicity (Appendix 1: Toxicity Scale for Laboratory Values) **with an at least reasonable possibility of a causal relationship to the administration of MVA-BN-RSV vaccine, i.e. the relationship cannot be ruled out.** **Reason for change:** *Update of halting rules*
Page 63, 5.1 Recruitment Procedure	**Page 78, 5.1 Recruitment Procedure**
[…]	**[...]** **From each of the two treatment groups selected for the booster substudy, 43 subjects will be randomly recruited to receive a booster vaccination approximately one year after their first vaccination with the same dose they had received during the main trial. Out of these 86 subjects, in total approximately 26 subjects will be recruited from the PBMC subgroup resulting in**

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
	approximately 13 subjects for each of the two selected treatment groups.
Page 65, 7. Assessment of Immunogenicity	**Page 80, 7. Assessment of Immunogenicity**
The immunogenicity of the vaccine will be assessed by measuring humoral, cellular and mucosal immune responses on collected serum, nasal swab and PBMC samples. • RSV-specific systemic antibody levels will be determined from serum samples using a RSV-specific IgG/IgA ELISA. Further, two separate PRNTs will be performed to measure neutralizing antibody levels to RSV strains A and B.	The immunogenicity of the vaccine will be assessed by measuring humoral, cellular and mucosal immune responses on collected serum, nasal swab and PBMC samples. • RSV-specific, **G protein A strain-specific, G protein B strain-specific** systemic antibody levels will be determined from serum samples using a RSV-specific IgG/IgA ELISA. Further, two separate PRNTs will be performed to measure neutralizing antibody levels to RSV strains A and B. **Reason for change:** *Update of immunogenicity definitions*
Page 66, 7.1.1 RSV-specific ELISA	**Page 81, 7.1.1 RSV-specific ELISA**
RSV-specific IgG/IgA antibody responses will be determined using ~~a direct~~ ELISA ~~utilizing a standard curve for titer calculation~~. Details of the procedure are defined in the SOP [redacted] "ELISA to determine RSV-Specific Antibody Titers (IgG) in Human Serum Samples" and SOP [redacted] "ELISA to determine RSV-Specific IgA Titers in Human Serum Samples". […]	RSV-specific IgG/IgA antibody responses will be determined using **several** ELISA**s**. Details of the procedure are defined in the SOP [redacted] "ELISA to determine RSV-Specific Antibody Titers (IgG) in Human Serum Samples" and SOP [redacted] "ELISA to determine RSV-Specific IgA Titers in Human Serum Samples". […]

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
The GMT is calculated per visit as well as based on individual peak titers by taking the antilogarithm of the mean of the log_{10} titer transformations. The Geometric Mean ~~Ratio (GMR) is calculated as (GMT at Visit X / GMT at Visit 1).~~	The GMT is calculated per visit as well as based on individual peak titers by taking the antilogarithm of the mean of the log_{10} titer transformations. The **Geometric Mean Fold Increase (GMFI)** is calculated **analogously per post-baseline visit** as **the geometric mean of the individual fold increases, i.e. the subjects' post-baseline titers at Visit X, divided by their corresponding baseline titer**. **Reason for change:** *Update of immunogenicity definitions*
Page 67, 7.1.2 RSV-specific PRNT	**Page 82, 7.1.2 RSV-specific PRNT**
Two ~~parallel~~ PRNTs will be performed to determine RSV-specific neutralizing antibody titers against RSV strain A and B, respectively. […] The GMT is calculated per visit as well as based on individual peak titers by taking the antilogarithm of the mean of the log_{10} titer transformations. The ~~GMR~~ is calculated ~~as (GMT at Visit X / GMT at Visit 1).~~	Two PRNTs will be performed to determine RSV-specific neutralizing antibody titers against RSV strain A and B, respectively. […] The GMT is calculated per visit as well as based on individual peak titers by taking the antilogarithm of the mean of the log_{10} titer transformations. The **GMFI** is calculated **analogously per post-baseline visit as the geometric mean of the individual fold increases, i.e. the subjects' post-baseline titers at Visit X, divided by their corresponding baseline titer.** **Reason for change:**

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
	Update of immunogenicity definitions
Page 67, 7.2 Mucosal Immune Response	**Page 82, 7.2 Mucosal Immune Response**
[…] The GMT is calculated per visit as well as based on individual peak titers by taking the antilogarithm of the mean of the log_{10} titer transformations. The ~~GMR~~ is calculated ~~as (GMT at Visit X / GMT at Visit 1).~~	[…] The GMT is calculated per visit as well as based on individual peak titers by taking the antilogarithm of the mean of the log_{10} titer transformations. The **GMFI** is calculated **analogously per post-baseline visit as the geometric mean of the individual fold increases, i.e. the subjects' post-baseline titers at Visit X, divided by their corresponding baseline titer.** **Reason for change:** *Update of immunogenicity definitions*
Page 68, 7.4 Future Use of Lab Specimen	**Page 83, 7.4 Future Use of Lab Specimen**
[…] 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.	[…] Specimens will be stored in BN's secured laboratory area or at an external storage facility in a coded, **pseudonymized** manner to ensure data protection. Genetic testing will not be performed. **Reason for change:** *Update to reflect correct wording*

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Page 71, 8.2.2 Prior and Concomitant Medication	**Page 86, 8.2.2 Prior and Concomitant Medication**
[…] The following medication, taken within 3 months prior to screening, will also be recorded in the eCRF and the subjects medical record: vaccines (e.g. Influenza/Pneumococcal), 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 screening. If given after the first but prior to the second vaccination, the following will result in subject's ineligibility to receive the second vaccination and the subject should follow the abbreviated visit schedule (see Section 4.2.4)	[…] The following medication, taken within 3 months prior to screening **or BV0**, will also be recorded in the eCRF and the subjects medical record: vaccines (e.g. Influenza/Pneumococcal), 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 screening. If given after the first but prior to the second **or the booster** vaccination, the following will result in subject's ineligibility to receive the second **or booster** vaccination and the subject should follow the abbreviated visit schedule (see Section 4.2.4)
Page 71, 8.2.3 Physical Examination	**Page 87, 8.2.3 Physical Examination**
[…] 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 except VS. ~~In~~	**[…]** Targeted physical examination **In the main trial**, 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 except VS.

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
~~addition, auscultation of the heart and lungs will be performed.~~	**In the booster substudy, a targeted physical examination will only be performed if clinically indicated, by the presence of signs/symptoms since last visit. If performed, auscultation of the heart and lungs will be included.**
Page 72, 8.2.5 Unsolicited AEs	**Page 87, 8.2.5 Unsolicited AEs**
[…] Unsolicited AEs will be assessed and documented at all visits except FU1 Visit and FU2 Visit (i.e. Screening to EAP) and if ongoing at EAP, followed until resolution or until the FU2 Visit at the latest. ~~SAEs and new AEs related to respiratory tract infections will be assessed and documented at all trial visits, including the FU Visits. SAEs will be followed up until resolution or achievement of stable clinical conditions.~~ Assessment of Intensity […] **Grade 4** Life-threatening, ~~hospitalization~~ or disabling.	[…] Unsolicited AEs will be assessed and documented at all visits except **(B)**FU1 Visit and **(B)**FU2 Visit (i.e. Screening/**BV0** to EAP/**BEAP**) and if ongoing at EAP/**BEAP**, followed until resolution or until the **(B)**FU2 Visit at the latest. **SAEs will be assessed and documented at all trial visits, including the (B)FU Visits. SAEs will be followed up until resolution or achievement of stable clinical conditions.** **In the main trial, new AEs related to respiratory tract infections will be assessed and documented at all trial visits, including the FU Visits.** Assessment of Intensity […] **Grade 4** Life-threatening or disabling

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Page 76, 8.2.7 Respiratory Viral Panel	**Page 91, 8.2.7 Respiratory Viral Panel**
Respiratory Viral Panel	Respiratory Viral Panel **(Main Trial)**
Page 76, 8.2.9 Cardiac Assessment	**Page 92, 8.2.9 Cardiac Assessment**
Electrocardiogram A standard 12-lead ECG will be taken at the Screening Visit. At Visit 2, Visit 4 and FU Visits an ECG is only done if clinically indicated. A central ECG reading center will assess if ECGs are normal, normal variant or abnormal. […] Troponin I Troponin I will be measured at screening and if clinically indicated on the following visits: Visit 2, Visit 4, FU1 and FU2 Visits or at unscheduled visits.	Electrocardiogram A standard 12-lead ECG will be taken **in the main trial** at the Screening Visit. At Visit 2, Visit 4 and FU Visits an ECG is only done if clinically indicated. A central ECG reading center will assess if ECGs are normal, normal variant or abnormal. […] Troponin I Troponin I will be measured **in the main trial** at screening and if clinically indicated on the following visits: Visit 2, Visit 4, FU1 and FU2 Visits or at unscheduled visits.
Page 79, 8.2.10 Safety Laboratory Measurement	**Page 94, 8.2.10 Safety Laboratory Measurement**
[…] Safety laboratory is determined at screening, Visit 2 and Visit 4 or 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	**[…]** Safety laboratory is determined at screening, Visit 2 and Visit 4 **in the main trial and at BV0 and BV2 during the booster substudy** or at any other visit(s) if clinically indicated. The safety laboratory measurements are performed at a central laboratory. Laboratory

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
in the Investigator File. Safety laboratory parameters to be evaluated are: **[…]** Pregnancy test: A β-human choriogonadotropin (HCG) pregnancy test will be conducted for all WOCBP at SCR Visit, prior to each vaccination and at the individual last active trial phase visit (Visits 1, 3 and EAP). At SCR Visit a serum β-HCG pregnancy test will be performed; all other pregnancy tests will be conducted as urine β-HCG tests.	normal ranges are provided by the central laboratory and filed in the Investigator File. Safety laboratory parameters to be evaluated are: **[…]** Pregnancy test: **In the main trial**, a β-human choriogonadotropin (HCG) pregnancy test will be conducted for all WOCBP at SCR Visit, prior to each vaccination and at the individual last active trial phase visit (Visits 1, 3 and EAP). At SCR Visit a serum β-HCG pregnancy test will be performed; all other pregnancy tests will be conducted as urine β-HCG tests. **In the booster substudy, a β-human choriogonadotropin (HCG) pregnancy test will be conducted for all WOCBP at BV1, prior to the booster vaccination.**
Page 82, Figure 4 Algorithm for Reporting of SAEs	**Page 97 , Figure 4 Algorithm for Reporting of SAEs**
	Box added in figure after "BN PV forwards safety reports within max. 15d/7d to competent authorities (final) and to CRO DS": **SMC discusses electronically (via email/teleconference) and forwards opinion to the Chair; Chair forwards opinions to POI –> to BN**

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
	Reason for change: *Update of Algorithm*
Page 83, 9.1 Randomization Procedure and Blinding	**Page 98, 9.1 Randomization Procedure and Blinding**
~~This~~ trial is randomized using an automated randomization system, integrated in the eCRF: Details on the randomization will be outlined in a separate randomization specification. Assignment to the groups is done in a randomized manner. The trial is single-blinded, i.e. subjects will be blinded to the group assignment.	**The main part of the** trial is randomized using an automated randomization system, integrated in the eCRF: Details on the randomization will be outlined in a separate randomization specification. Assignment to the groups is done in a randomized manner. The **main** trial is single-blinded, i.e. subjects will be blinded to the group assignment. **In total 86 subjects from two selected treatment groups will be chosen randomly for the booster substudy outlined in a separate randomization specification.**
Page 83, 9.2 Sample Size Calculation	**Page 98, 9.2 Sample Size Calculation**
The primary analysis will be performed on the PRNT (A strain) titers 2 weeks after the last vaccination. […] The GMTs, ~~GMR~~ from baseline, and the response rates and associated 95 % confidence limits will be presented for each group at each sampling point.	The primary analysis will be performed on the PRNT (A strain) titers 2 weeks after the last vaccination **in the main trial**. […] The GMTs, **GMFIs** from baseline, and the response rates and associated 95 % confidence limits will be presented for each group at each sampling point.

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
	[…] **The actual variability observed for the log_{10} titers for PRNT (A strain) 2 weeks after the second vaccination in RSV-MVA-002 turned out to be lower than anticipated from the Phase I trial results. Thus, based on an adapted assumption for the SD of 0.335 for the log_{10} titers to be measured 2 weeks after the booster vaccination, a number of 40 evaluable subjects per group will provide 80% power to detect a difference of 0.213 (log10-scale) at a significance level of 5% (two-sided), which corresponds to a ratio of GMTs between groups of 1.63. Accounting for a drop-out rate of 5% 43 subjects per group are to receive a booster vaccination.**
Page 84,9.2.1 Treatment Groups/Datasets to be Evaluated	**Page 100,9.2.1 Treatment Groups/Datasets to be Evaluated**
[…] 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 EAP) and adhered to all protocol conditions. Subjects with only minor (not relevant) protocol deviations are included into this dataset. […]	**[…]** Per Protocol Set (PPS): This is the subset of subjects in the FAS who have received all vaccinations **in the main trial**, completed all visits of the active trial phase (Visit 1 to EAP) and adhered to all protocol conditions. Subjects with only minor (not relevant) protocol deviations are included into this dataset. […]

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Immunogenicity Analysis Set (IAS): This is the subset of subjects in the FAS which were assigned to the subgroup. The main analysis of the cellular immunogenicity endpoints will be performed on the IAS. Additional ~~subgroups~~ may need to be defined during the data review meeting and would be described in the clinical study report.	Immunogenicity Analysis Set (IAS): This is the subset of subjects in the FAS which were assigned to the **PBMC** subgroup. The main analysis of the cellular immunogenicity endpoints will be performed on the IAS. **Booster Full Analysis Set (BFAS):** **This is the subset of subjects who received a booster dose of MVA-BN-RSV vaccine and for whom any post-booster data are available.** **Booster Immunogenicity Analysis Set (BIAS):** **This is the subset of subjects in the BFAS which were assigned to the PBMC subgroup.** Additional **analysis sets** may need to be defined during the data review meeting and would be described in the clinical study report.
Page 85, 9.3.1 Analysis	**Page 101, 9.3.1 Analysis**
As soon as the last subject has completed Visit ~~EAP~~ and after any necessary settlement of queries etc. in the eCRFs a data review meeting will be held and the subjects will be	As soon as the last subject has completed Visit **FU1** 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 **data sets defined for the**

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
assigned to the ~~datasets as described in Section 9.2.1~~. […] 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 results as well as the follow-up safety data. Results of this analysis will be reported in an addendum to the clinical study report.	**main trial (FAS, PPS, IAS, see Section 9.2.1**). […] 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 **of the main trial** will then be performed and will include all immunogenicity results as well as the follow-up safety data. Results of this analysis will be reported in an addendum to the clinical study report. **As soon as the last subject recruited into the booster substudy has completed BFU2 Visit and after any necessary settlement of queries etc. in the eCRFs a data review meeting will be held. The assignment of the subjects to the analysis sets as described in Section 9.2.1 will be the same as for the 2nd addendum to the CSR. After the data review meeting and necessary settlement of queries that may arise during the data review meeting, the database will be locked. The booster substudy analysis will then be performed and will include all immunogenicity results as well as the follow-up safety data. Results of this analysis will be reported in an addendum to the clinical study report.**
Page 86, 9.3.2 Presentation of Data	**Page 101, 9.3.2 Presentation of Data**
[…]	[…]

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
GMTs and antibody response rates for RSV-specific humoral immune responses determined from serum and nasal swab samples will be determined as described in Section 7.1 and Section 1.5. Median and geometric mean SFU/1 x 10^6 PBMC as well as response and responder rates for RSV-specific cellular immune responses will be determined as described in Section 1.5.	GMTs**, GMFIs** and antibody response rates for RSV-specific humoral immune responses determined from serum and nasal swab samples will be determined as described in Section 7.1 and Section 1.5. Median and geometric mean SFU/1 x 10^6 PBMC**, GMFIs** as well as response and responder rates for RSV-specific cellular immune responses will be determined as described in Section 1.5. **Reason for change:** *Update of immunogenicity definitions*
Page 88, 11. Informed Consent	**Page 103, 11. Informed Consent**
[…] The Informed Consent will be prepared in accordance with ICH GCP guidelines and must be approved by the appropriate IEC/IRB	**[…]** **Subjects eligible for the booster substudy have to sign a new ICF at BV0.** The Informed Consent will be prepared in accordance with ICH GCP guidelines and must be approved by the appropriate IEC/IRB
Page 94, Table 14 Toxicity Scale for Serum Chemistry	**Page 111, Table 14 Toxicity Scale for Serum Chemistry**
[…] Sodium – Hypernatremia mmoL/L	[…] Sodium – Hypernatremia mmoL/L

Clinical Trial Protocol Edition 2.0, dated 27-Jan-2017 **Previously written:**	**Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017** **Changed to:**
Mild (Grade 1) ~~≥ 145 -~~146 Moderate (Grade 2) 147~~–148~~ Severe (Grade 3) 148-150 Potentially Life Threatening (Grade 4) > 150 […] Potassium – Hypokalemia mmoL/L Mild (Grade 1) 3.4 ~~< 3.5~~ Moderate (Grade 2) 3.3~~–3.4~~ Severe (Grade 3) 3.1-3.2 Potentially Life Threatening (Grade 4) < 3.1	Mild (Grade 1) **146** Moderate (Grade 2) **147** Severe (Grade 3) 148-150 Potentially Life Threatening (Grade 4) > 150 […] Potassium – Hypokalemia mmoL/L Mild (Grade 1) **3.4** Moderate (Grade 2) **3.3** Severe (Grade 3) 3.1-3.2 Potentially Life Threatening (Grade 4) < 3.1 **Reason for change:** *Correction of former typos, previously clarified via file note.*

Appendix 6: Amendment#3 to the Clinical Trial Protocol

A randomized, single-blind, placebo controlled, dose-ranging Phase II trial in ≥ 55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine

Amendment#3 to the Clinical Trial Protocol

Date of Amendment#3: 26-Apr-2018

Rationale:

The protocol Edition 4.0 is set up to add a 12 month FU visit to the booster substudy. All subjects vaccinated in the booster subgroup will be invited for an additional FU visit approximately 1 year after the booster vaccination. Assessment of individual RSV-specific antibody titres will provide data on the durability of immune responses 12 months after a booster vaccination with either of the two MVA-BN-RSV vaccine doses 1 x 10^8 or 5 x 10^8 Inf.U.

Changes:

General changes:

- Update of Section 1.3 (Sponsor Signature Page) and 1.4 (Responsibilities) to reflect changes in BN personnel.
- Correction of blood volume for safety lab due to typo in previuos edition in Section 1.6 (Main Trial Schedule; footnote 5) and section 4.2.1.2 (Active Trial Phase) where applicable.
- Update of Section 1.7 (Trial Schedule Booster Substudy) to account for additional BFU3 visit.
- Update of Section 4.2.2 (Description of Trial Procedures – Booster Substudy): Added procedure for BFU3 visit
- Update of section 9.2.1 for further clarification of the data sets used for analysis.
- Throughout the protocol, rewording of some sections for ease of understanding.
- Spelling, formatting and wording was corrected where applicable

Major changes are as follows:

Changes/ added terms are highlighted in **bold** letters in the text (table below), removed terms are marked using ~~strikethrough~~.

Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017 **Previously written:**	**Clinical Trial Protocol Edition 4.0, dated 26-Apr-2018** **Changed to:**
Page 24 ff, 1.5 Protocol Synopsis	**Page 20 ff, 1.5 Protocol Synopsis**
Trial Duration: Up to 39 weeks per subject in the main trial and up to additional 34 weeks per subject enrolled in the booster substudy. **Secondary Objectives:** […]	**Trial Duration:** Up to 39 weeks per subject in the main trial and up to additional **56 weeks** per subject enrolled in the booster substudy. **Secondary Objectives:** […] **To identify further potential differences in durability and/or boostability of immune responses in the two chosen MVA-BN-RSV dose regimens.** **To assess safety and reactogenicity of the MVA-BN-RSV vaccine following the booster vaccination in adult/elderly subjects.** **Reason for changes:** *Additional secondary objectives added due to additional BFU3 visit.*
Trial Design Booster Substudy: […] All 86 subjects will be followed up for 6 months after their last vaccination. **Reports:**	**Trial Design Booster Substudy:** […] All 86 subjects will be followed up for **12 months** after their last vaccination. **Reports:**

Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017 **Previously written:**	**Clinical Trial Protocol Edition 4.0, dated 26-Apr-2018** **Changed to:**
[…] Clinical Study Report Addendum 2 (including safety and immunogenicity data of the 3-month and 6-month follow-up visits of the booster substudy)	[…] Clinical Study Report Addendum 2 (including safety and immunogenicity data ~~of the 3-month and 6-month follow-up visits of the booster substudy~~ **of the booster substudy and additional immunogenicity data not yet included in the Final Clinical Study Report or Addendum 1**) **Reason for changes:** *All data from booster substudy will be added in the Addendum 2 to the clinical study report.*
Page 32-34, 1.7 Trial Schedule Booster Substudy and Footnotes	**Page 36-38, 1.7 Trial Schedule Booster Substudy and Footnotes**
No BFU3 visit	Additional column added for BFU3 Visit, Trial procedure contains serum collection for antibody analysis. **Reason for changes:** *Addition of BFU3 Visit.*
Page 58, 2.7 Rationale	**Page 59, 2.7 Rationale**
[…] Assessment of individual antibody titers within short time intervals following the booster vaccination and up to 6 months after the vaccination will provide information on	[…] Assessment of individual antibody titers within short time intervals following the booster vaccination and **up to 12 months** after the vaccination will provide

Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017 **Previously written:**	**Clinical Trial Protocol Edition 4.0, dated 26-Apr-2018** **Changed to:**
how fast and effective measurable antibody titers can be regained. The booster substudy will also evaluate the durability of immune responses 12 months following the primary vaccination (baseline measurement prior to administration of the booster dose) and 6 months following the booster vaccination.	information on how fast and effective measurable antibody titers can be regained. The booster substudy will also evaluate the durability of immune responses 12 months following the primary vaccination (baseline measurement prior to administration of the booster dose) and **12 months** following the booster vaccination.
Page 62, 4. Trial Design	**Page 62, 4. Trial Design**
Booster Substudy: […] To obtain 40 evaluable subjects per group up to 43 subjects per selected group will be recruited. Subjects are then followed up for 6 months after their last vaccination.	Booster Substudy: […] To obtain 40 evaluable subjects per group up to 43 subjects per selected group will be recruited. Subjects are then followed up **for 12 months** after their last vaccination.
Page 74, 4.2.2.3 Booster Follow-Up (BFU) Phase	**Page 74, 4.2.2.3 Booster Follow-Up (BFU) Phase**
To monitor long-term safety and antibody persistence, subjects will come to the CTS for follow-up (FU) visits 3 months (BFU1 Visit) and 6 months (BFU2 Visit) after the booster vaccination. No additional BFU3 Visit	To monitor long-term safety and antibody persistence, subjects will come to the CTS for follow-up (FU) visits 3 months (BFU1 Visit), 6 months (BFU2 Visit) **and 12 months (BFU3 Visit)** after the booster vaccination. Addition of tasks performed at BFU3 Visit
Page 77, 4.3 Trial duration	**Page 76-77, 4.3 Trial duration**
[…]	[…]

Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017 **Previously written:**	**Clinical Trial Protocol Edition 4.0, dated 26-Apr-2018** **Changed to:**
The total duration of the booster substudy including baseline and follow up visits will be 34 weeks.	The total duration of the booster substudy including baseline and follow up visits will be **56 weeks**.
Page 83, 7.3 Systemic Cellular Immune Responses	**Page 83, 7.3 Systemic Cellular Immune Responses**
[…] The responder rate for each test agent is the percentage of subjects who are responders to the relevant test agent out of the number of subjects with a non-missing responder status within the relevant analysis population. Furthermore, PBMC collected at the FU visits will be used to determine memory B cells secreting IgG and/or IgA in an ELISPOT. Details of the procedure are defined in SOP BN0004344 "B Cell ELISpot to quantify RSV-specific IgG and IgA Secreting Cells in Human CD19 Positive Cells".	[…] The responder rate for each test agent is the percentage of subjects who are responders to the relevant test agent out of the number of subjects with a non-missing responder status ~~within the relevant analysis population~~. Furthermore, PBMC collected at the **(B)**FU visits will be used to determine memory B cells secreting IgG and/or IgA in an ELISPOT. Details of the procedure are defined in ~~SOP BN0004344 "B Cell ELISpot to quantify RSV-specific IgG and IgA Secreting Cells in Human CD19 Positive Cells"~~ **SOP BN0005663 "Fluorospot to measure RSV-specific IgG/IgA secreting cells in human PBMCs"**. **Reason for changes:** *A different assay will be used to measure memory B cells.*
Page 87, 8.2.3 Targeted Physical Examinations	**Page 87, 8.2.3 Targeted Physical Examinations**
[…]	[…]

Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017 **Previously written:**	**Clinical Trial Protocol Edition 4.0, dated 26-Apr-2018** **Changed to:**
In the booster substudy, a targeted physical examination will only be performed if clinically indicated, by the presence of signs/symptoms since last visit. If performed, auscultation of the heart and lungs will be included.	In the booster substudy, a targeted physical examination will only be performed if clinically indicated, by the presence of signs/symptoms since last visit **at BV1 to BFU2.** If performed, auscultation of the heart and lungs will be included.
Page 87, 8.2.4 Vital Signs	**Page 87, 8.2.4 Vital Signs**
At all visits except the Staggering Visit, blood pressure and pulse rate will be taken after the subject has been sitting upright for approximately two minutes. Body temperature will be measured orally.	At all visits except the Staggering Visit **and BFU3**, blood pressure and pulse rate will be taken after the subject has been sitting upright for approximately two minutes. Body temperature will be measured orally.
Page 87, 8.2.5 Unsolicited AEs	**Page 87, 8.2.5 Unsolicited AEs**
[…] Unsolicited AEs will be assessed and documented ~~at all visits except (B)FU1 Visit and (B)FU2 Visit (i.e. Screening/BV0 to EAP/BEAP) and if ongoing at EAP/BEAP, followed until resolution or until the (B)FU2 Visit at the latest.~~ SAEs will be assessed and documented at all trial visits, ~~including the (B)FU Visits~~. SAEs will be followed up until resolution or achievement of stable clinical conditions.	[…] Unsolicited AEs will be assessed and documented **as indicated in the trial schedule (see Section 1.6 and Section 1.7)**. SAEs will be assessed and documented at all trial visits, **excluding the BFU3 Visit**. SAEs will be followed up until resolution or achievement of stable clinical conditions. **Reason for changes:** *Adjustments and clarification due to additional BFU3 Visit.*

Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017 **Previously written:**	**Clinical Trial Protocol Edition 4.0, dated 26-Apr-2018** **Changed to:**
Page 99, Sample Size Calculation	**Page 99, Sample Size Calculation**
[…] Accounting for a drop-out rate of 5% 43 subjects per group are to receive a booster vaccination.	[…] Accounting for a drop-out rate of 5% 43 subjects per group are to receive a booster vaccination. **However, only a descriptive comparison is planned between the two dose groups in the sub-study**.
Page 101, 9.3.1 Analysis	**Page 101, 9.3.1 Analysis**
[…] As soon as the last subject included in the booster substudy has completed BFU2 Visit and after any necessary settlement of queries etc. in the eCRFs a data review meeting will be held. ~~The assignment of the subjects to the analysis sets as described in Section 9.2.1 will be the same as for the 2nd addendum to the CSR.~~ After the data review meeting and necessary settlement of queries that may arise during	[…] **For the booster substudy, there will be a topline readout when the last subject included in the booster substudy has completed the BFU1 visit, the immunogenicity data up to BFU1 are available, and the data in EDC have been properly cleaned. The set of topline tables and figures will be specified in the statistical analysis plan.** As soon as the last subject included in the booster substudy has completed **BFU3** Visit and after any necessary settlement of queries etc. in the eCRFs a data review meeting will be held. **Protocol deviations will be reviewed to determine whether an additional analysis set compared to those described in Section 9.2.1 will be needed.** After the data review meeting and necessary settlement of queries that may arise during

Clinical Trial Protocol Edition 3.0, dated 20-Jul-2017 **Previously written:**	**Clinical Trial Protocol Edition 4.0, dated 26-Apr-2018** **Changed to:**
the data review meeting, the database will be locked. […]	the data review meeting, the database will be locked. […]