Statistical Analysis Plan

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

Main Study and Booster Substudy

01-May-2018

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STATISTICAL ANALYSIS PLAN

PROTOCOL 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
PROTOCOL:	RSV-MVA-002
STUDY DRUG:	MVA-BN-RSV Vaccine
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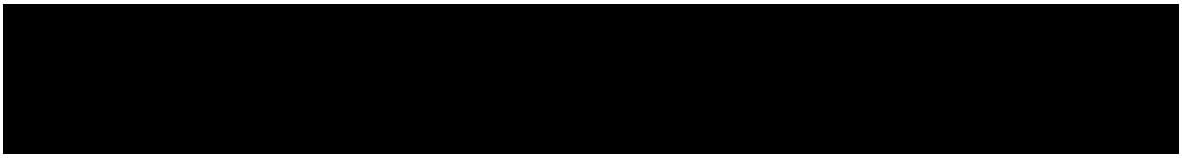
Signature Page

Declaration
The undersigned agree to the statistical methods proposed for the analysis of this clinical trial.

Approved by: Sponsor



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STATISTICAL ANALYSIS PLAN

This Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing trial data and outlines the statistical programming specifications, tables, figures, and listings for clinical trial RSV-MVA-002. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the Clinical Trial Protocol (CTP).

The analyses defined in the SAP will be followed completely. It may be necessary to define some additional explorative analyses, and/or additional analysis populations. If any unforeseen additional analysis is included in the clinical study report (CSR) it will be clearly flagged as an additional unplanned explorative analysis.

The analyses described are based on the final clinical trial protocol RSV-MVA-002 Edition 2.0 dated 27 Jan 2017.

GENERAL DEFINITIONS

Vaccinations

For this trial a vaccination means an intramuscular administration of active MVA-BN-RSV vaccine or Tris-buffered saline (TBS).

Placebo

Tris-buffered saline (TBS)

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 x 10^8 Inf.U per 0.5 mL.

Treatment Group

Subjects are recruited into one of five treatment groups receiving different investigational medicinal product (IMP) doses and schedules.

Age groups: Subjects will be stratified by age into two groups: ≥ 55 to < 70, and ≥ 70 years of age. A minimum of 20 subjects per treatment group in the age stratum ≥ 70 years is required.

Subgroups

The subgroup consists of 20 subjects per treatment group (a total of 100 subjects) 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.

Trial Day
The trial day is based on the day of the first vaccination. The day of first vaccination is defined as Day 0 and the day after first vaccination is Day 1, and so on. Similarly, the day before first vaccination is defined as Day -1, and so on. No reference is made to the time of the vaccination in the calculation of the trial day, i.e. at midnight a new trial day begins regardless of the time of first vaccination. Note that it is possible for Visit 1 (V1) to be performed, for example, on trial Day -1.

Baseline
Baseline refers to the last measurement before first vaccination of trial vaccine. This is either at Visit 1 or at Screening (SCR) Visit (or latest re-screening) as applicable. For example, if there are missing vital sign data at Visit 1, the SCR or latest re-screening data will be used to impute the missing vital sign data as the baseline measurement. Partial rescreen is possible for certain isolated entry criteria. In such case the last measurement before first vaccination of trial drug will be used as the baseline value. This means that a subject's baseline date may differ across screen and rescreen records. This data will be summarized as Baseline data without a direct specification of which visit was used. However, in all other visits no imputation will be used and the actual visit used will be specified in tables or listings.

Staggering visit (VS)
A visit only required by subjects allocated into the sentinel and safety cohort. The staggering process will be performed at one clinical site only.

Vaccination Period
A vaccination period is defined as the period starting at a given vaccination and ending 28 days after this vaccination or until the subject receives another vaccination or discontinues the trial with the following hierarchy:

- If subject receives both vaccinations, the second vaccination represents the end of vaccination period 1.
- The end of vaccination period 2 is 28 days after receiving the second vaccination, unless subject discontinues earlier. In this case, the discontinuation date represents the end of vaccination period 2.
- If subject discontinues before second vaccination, the discontinuation date represents the end of vaccination period 1.

As the intention is that all subjects will receive two vaccinations, two vaccination periods will be recorded per subject. The overall vaccination period starts from the beginning of period 1 and ends at the end of period 2.

Screening Phase
The Screening Phase is defined from the Screening Visit up to, but not including Visit 1. This includes any Re-screening Visits that are conducted.

Active Trial Phase
The active trial phase is defined as the trial phase starting with and including Visit 1 and ending with and including EAP (End of active trial phase) (V3 + 28-35 days).

End of Active Trial Phase (EAP)
EAP is defined as the last visit of the active trial phase.

Follow-Up Trial Phase
The Follow-Up trial phase is defined as the phase starting after EAP visit and includes the Follow-up visits (FU1 and FU2).

Eligible Subjects
A subject is eligible if the screening question "Is subject eligible and willing to continue?" is answered with "Yes" and there are no subsequent substantial protocol deviations that affect the eligibility of the subject at Visit 1 prior to randomization.

Subjects Receiving Both Vaccinations
A subject is considered as having received both doses of trial vaccination per the randomized group assignment if a date of drug administration is given for the vaccination at Visit 1 and for the vaccination at Visit 3, and no major vaccine preparation or administration deviation is recorded.

Treatment-Emergent Adverse Events (TEAE)
An Adverse Event (AE) with onset either on the day of a vaccination, but after the vaccination or within the 28 days following a vaccination. Note that serious AEs are also considered treatment-emergent after 28 days (see below).

Serious Adverse Events
All Serious Adverse Events (SAEs) from first vaccination to last follow-up visit are considered as treatment-emergent regardless of the day of onset.

AEs related to respiratory tract infections
New AEs related to respiratory tract infections will be assessed and documented at all trial visits, including the FU Visits and are considered as treatment-emergent regardless of the day of onset.

Adverse Drug Reaction
An AE with either a 'possible', 'probable', 'definite' 'unknown' or 'missing' relationship to the vaccine (which means: "causally related").
Nominal Titer
The MVA-BN-RSV (Respiratory Syncytial Virus) vaccine is formulated at a nominal titer of 5×10^8 Inf.U per dose (0.5 mL). The actual titer will be determined in stability testing.

Table 1: Detection Limits (DL)

Test	Detection Limit (DL)	Negative values reported
PBMC RSV-specific IFN-γ ELISPOT (pool F, G(A), G(B), M2, N or RSV virus) PBMC RSV-specific IL-4 ELISPOT (pool F, G(A), G(B), M2, N or RSV virus)	50	25 (half of the DL)
Serum RSV-specific PRNT Strain A Serum RSV-specific PRNT Strain B	20	10 (half of the DL)
Serum RSV-specific IgG ELISA	63	31.5 (half of the DL)
Serum RSV-specific IgA ELISA	100	50 (half of the DL)
Mucosal RSV-specific IgA ELISA (nasal swabs)	2	1 (half of the DL)
Serum RSV (strain A) G protein - specific IgG ELISA Serum RSV (strain B) G protein- specific IgG ELISA	no detection limit applies	negative reported as 50
RSV-specific B cell ELISPOT *IgG and IgA*	no detection limit applies	a measured percentage is considered a positive result

Geometric Mean Titer and Geometric Mean Spot Forming Units
The Geometric Mean Titer (GMT) and Geometric Mean Spot Forming Units (GMSFU) are calculated by taking the antilogarithm of the mean of the $\log_{10}$ transformed titers, and Spot Forming Units, respectively.

(Sero)Negative and (Sero)Positive Results
For each immunogenicity assay a negative result is defined as a titer below the DL, while a positive result is a titer equal to or above the DL.

Response
For each immunogenicity assay, a response to the vaccine (applicable only for post baseline visits) is defined as either the appearance of a positive result for subjects with a negative result at baseline (Visit 1), or an increase by a factor of at least 2 compared to the Visit 1 for subjects with a positive result at Visit 1. Response status is applicable only for V1b, V2, V3, V3b, V4, EAP Visit, and FU1 and FU2 Visits and is not calculated for subjects with missing Visit 1 titer.

The response rate at each post baseline visit is the percentage of subjects who have a positive response status out of the number of subjects with a non-missing response status (positive or negative) at that visit.

Responder
A subject is an ELISPOT Responder to the vaccine in a particular test agent (F pool, G(A) pool, G(B) pool, N pool, M2 pool, RSV Virus) if the subject has a response for at least two post baseline visits (V1b to V 4) within the same test agent. The responder evaluation applies only to subjects with at least two post baseline results available.

The responder rate for each test agent F pool, G(A) pool, G(B) pool, N pool, M2 pool, RSV Virus) 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).

Individual peak titer
The individual peak titer is the maximum of titers recorded on V1b, V2, V3, V3b, V4, EAP Visit.

Fold Increase
The fold increase is defined as a subject's post-Baseline titer at Visit X, divided by the baseline titer.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ATC	Anatomical-Therapeutic-Chemical
ATP	Active Trial Phase
BMI	Body Mass Index
BN	Bavarian Nordic
CI	Confidence Interval
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
DL	Detection Limit
DRM	Data Review Meeting
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked Immuno Spot Technique
FAS	Full Analysis Set
FU	Follow-up
FU1	Follow-up Visit 1
FU2	Follow-up Visit 2
GMFI	Geometric Mean Fold Increase
GMSFU	Geometric Mean Spot Forming Units
GMT	Geometric Mean Titer
HCG	Human Choriogonadotropin
HIV	Human Immunodeficiency Virus
IAS	Immunogenicity Analysis Set
IFN-γ	Interferon-gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL-4	Interleukin 4
Inf.U	Infectious Unit
Log_{10}	Logarithm base 10
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MVA-BN®	Modified Vaccinia Ankara – Bavarian Nordic
n	Number of Observations
PBMC	Peripheral Blood Mononuclear Cells
PI	Principal Investigator

PPS	Per Protocol Set
PRNT	Plaque Reduction Neutralization Test
PT	Preferred Term
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCR	Screening
SD	Standard Deviation
SFU	Spot Forming Units
SMT	Safety Monitoring Team
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of child bearing potential

1. Trial Overview

1.1 Trial Description

This trial is 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. A total of 400 subjects will be recruited into five treatment groups in this trial (see Table 2).

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

In general, subjects are stratified by age into two groups: ≥ 55 to < 70 and ≥ 70 years. However, during the staggering phase performed by the staggering site (sentinel cohort and safety cohort) only the younger age group is recruited. In order to have the best power to detect differences between the strata the aim is to achieve equally distributed recruitment across the age strata but at least 20 subjects per treatment group are required in the age stratum ≥ 70 years.

The PBMC subgroup consists of 20 subjects per group recruited after the staggering phase. A total of three sites recruit all PBMC subjects.

Recruitment into the trial is performed in a staggered manner. The staggering process is performed at one clinical trial site. The trial starts with a sentinel cohort with a total of 2 subjects, 1 subject recruited into Group 2 and one subject into Group 4 (i.e. 1:1 subjects receiving Dose 1 and Dose 2). Following a positive safety assessment for the subjects in the sentinel cohort, recruitment in the safety cohort starts. The safety cohort includes a total of 10 subjects, 5 subjects each into Groups 2 and 4 (i.e. 5:5 subjects receiving Dose 1 and Dose 2). Following a positive safety assessment for the subjects in the safety cohort, recruitment in all groups for the remaining subjects is opened. The open recruitment phase includes all treatment groups. The open recruitment phase randomization is stratified by age and site.

PBMC collection is performed in a subgroup of 20 subjects in each treatment group (total of 100 subjects). This subgroup also has 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.

1.2 Objectives

1.2.1 Primary Objective

The primary objective of the study is to assess the optimal dose and schedule of the MVA-BN-RSV vaccine in ≥ 55 year old subjects in terms of immunogenicity.

1.2.2 Secondary Objectives

The secondary objectives are:

- 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.

1.3 Trial Population

A total of 400 subjects ≥ 55 years old will be recruited into five treatment groups (80 subjects per treatment group).

1.4 Endpoints

1.4.1 Primary Endpoint

The primary endpoint is 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.

1.4.2 Secondary Endpoints

The secondary endpoints are classified as safety and immunogenicity.

The safety endpoints are:

- 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.

The immunogenicity endpoints are:

- RSV-specific antibody response rate measured by Immunoglobulin G (IgG) Enzyme-linked Immunosorbent Assay (ELISA) at all post vaccination immunogenicity serum sampling time points and based on the individual peak titers.
- 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 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.
- 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 GMT measured by IgA ELISA at all nasal swab sampling time points (mucosal IgA) and based on the individual peak titers.
- 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.
- 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 memory B cells measured at FU1 and FU2.

- Incidence of RSV-specific disease and correlation with immunogenicity readouts.

1.5 Interim Analysis

No interim analysis is planned for this trial.

1.6 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 to make the decision to proceed to the next staggering step.

1.7 Safety Monitoring Committee

The Safety Monitoring Committee (SMC) is an independent board that oversees the safety of subjects participating in 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. 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, the SMC will review the event in a timely manner and will 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.

2. Trial Design

Visit (V)	SCR	V1	VS [13]	V1b [9]	V2	V3	V3b [9]	V4	EAP	FU1	FU2
										3m FU	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 incl. / excl. 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	FU2
										3m FU	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	FU2
										3m FU	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: 19 mL (at V2, V4, FU1 and FU2; if applicable), including Haematology (3 mL), serum chemistry (including pregnancy test; 8 mL), virology (Hepatitis B and C, HIV; 5 mL); Safety lab 22 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 timepoint 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 Protocol 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.

3. Statistical Methods

3.1. Planned Sample Size

A group sample size of 70 per group (recruiting 80 per group to account for a 12% dropout rate), and an assumed SD of 0.46 for the $\log_{10}$ PRNT titers (A strain) will give 80% power to detect a relative change in titers from the Group 1 of a 66% increase.

Assumptions used to determine the sample size of the trial are below.

- Testing of the primary objective will be performed by assuming that the $\log_{10}$ of the titers are normally distributed.
- No adjustment for multiple comparison is considered.
- 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 SD is assumed to be similar to that observed in the RSV Phase I trial (RSV-MVA-001).

3.2. Analysis Populations

3.2.1 Full Analysis Set (FAS)

This is the subset of subjects who will have received at least one vaccination and for whom any post-baseline data are available. The primary analysis of safety and efficacy will be performed on this analysis set.

In the case where a subject might receive the wrong randomized treatment, safety summaries for this subject will be based on actual treatment received. However, for a subject randomized to Group 2 or Group 4, and who received only one vaccination instead of two, safety summaries for this subject will be based on their randomized treatment group.

3.2.2 Per-Protocol Set (PPS)

This is the subset of subjects in the FAS who have received all vaccinations, completed all visits of the active trial phase (Visit 1 to EAP) and adhered to all protocol conditions. Subjects with major protocol violations will not be included in this dataset. However, 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 at the data review meeting (DRM) prior to database lock.

Potential major protocol violations are (but are not restricted to):

1. Premature discontinuation of the trial during the active trial phase (the question "did the subject prematurely discontinue the trial?" is answered with "yes" even where no other reason exists to exclude the subject from further participation in accordance with the protocol).
2. Subject did not meet all of the inclusion criteria.
3. Subject met one or more of the exclusion criteria.
4. Withdrawal from the second vaccination.
5. Major vaccine preparation and administration deviation from specification as given in the protocol including cases where the subject fulfils at least one of the criteria specified in the protocol for withdrawal from vaccination.
6. Major deviations of the visit window as determined during the DRM(s).
7. Prohibited Prior or Concomitant Medication use.
8. Missing immunogenicity data at any critical visits (the decision on what is a critical visit will be made at the DRM).
9. Respiratory Viral Panel result positive for RSV A or RSV B.

The main analysis of humoral and mucosal immunogenicity endpoints will be performed on the FAS. The same statistical procedures will also be applied to the PPS. If there is no substantial difference in FAS and PPS then only the FAS will be presented in the main part of the CSR.

3.2.3 Immunogenicity Analysis Set (IAS)

This is the subset of subjects in the FAS which was assigned to the PBMC subgroup. The main analysis of the cellular immunogenicity endpoints will be performed on the IAS. Additional subgroups may need to be defined during the DRM before database lock and would be described in the CSR.

3.3. Data Definitions, Data Conventions and Handling of Missing Data

3.3.1 Missing Immunogenicity Data

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.

For assay results that are below the detection limit, refer to Table 1: Detection Limits (DL) in the general definition section.

3.3.2 Missing Adverse Event and Concomitant Medication Data

In the case of incomplete AE and/or medication start and end dates, the following rules will be used to assign AEs to the correct vaccination period, and medications as prior/concomitant:

For analysis purposes of any Prior and Concomitant Medication or any AE, imputation of partial start and end dates will be performed based on the following rules:

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

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

Partial/Missing Start Date

- If day is missing, then impute the 1st of the month as in the table above, but if the month is the same as the month of the first vaccination date then assign the imputed start date as the first vaccination date.
- If month and day are missing, then impute as above to January 1 unless the year is the same as the first vaccination date then assign imputed start date as the first vaccination date.
- If the date is completely missing, then impute the first vaccination date unless the end date indicates that the AE/medication could have started/been taken prior to this in which case the date is imputed to 1st January of the same year as the start date.

Partial/Missing End Date

- If day is missing, then impute the last day of the month as in the table above unless the month is the same as the month of the first vaccination date then impute the end date as the last vaccination date.
- If month and day are missing, then impute as above to December 31 unless the year is the same as the first vaccination date then assign imputed end date as the last vaccination date.
- If the date is completely missing, check if AE/medication is ongoing before imputing a date and when the AE/medication started in relation to vaccination date. If the ongoing flag is missing, then assume that the AE/medication is still ongoing/medication is still being taken. In this case, do not impute the date. If the AE/medication stopped and the start date is prior to the first vaccination date, then impute the first vaccination date. If the AE/medication started on or after first vaccination date, then impute an end date which is one day after the last vaccination date.

These imputation methods will be used for the table summaries. However, all listings will display the original dates as captured in the eCRF.

3.3.3 Assignment of AEs to Vaccination Period

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

- All AEs starting at or after the first vaccination but before vaccination 2 (Visit 3) will be assigned to vaccination period 1.
- All AEs starting on or after the second vaccination but before or at EAP will be assigned to vaccination period 2. If the subject missed the second vaccination for any reason, the AEs will be assigned to the overall vaccination period.
- Any AEs starting after EAP up to the FU2 Visit belong to the FU period.

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

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

Worst-case principle:
To avoid a potential misclassification of an AE to a vaccination period or to the overall vaccination period, if an imputed start date corresponds to the first of the month or to the first of the year, and matches the month and year of the first or second vaccination date, then the AE will be assigned to the vaccination period with matching month and year. If the AE cannot be assigned to a vaccination period because of a (partially) missing start date then it will be only assigned to the overall vaccination period.

3.3.4 General Considerations for AEs

Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 will be used for coding of AEs.

Duration of an AE will be calculated as follows:

For Unsolicited AEs: expressed in [days]

- End date – start date of AE + 1 day. Note that duration can be calculated even if time of day is missing for either start or end dates, or if time is missing for both.
- In case of partially missing start date (month and/or day missing) or partially missing end date (month and/or day missing), duration will not be calculated.
- In case of an ongoing AE, the duration will not be calculated.

For Solicited AEs: expressed in [days]

- End date of AE – start date of AE + 1, where end date is the last day the symptom is defined as an AE and start date is the first day symptom is defined as an AE (no matter if the AE occurred at every day between first day and last day). In case of an ongoing AE, the duration will not be calculated.

Relative day of onset between vaccination and start of AE will be calculated as follows:

For Unsolicited AEs: expressed in [days]

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

For Solicited AEs: expressed in [days]

- The relative day is calculated as the day of first symptom intensity recording > 0.
- Start date of AE – corresponding vaccination date, where start date is the first day a symptom is defined as an AE; vaccination day corresponds to Day 0.

3.4. Analysis Variables

3.4.1 Demographic and other Baseline Characteristics

Demographics

- Age (years)
- Age Group (≥ 55 to < 70 ≥ 70)
- Gender (male, female)
- Race (White/Caucasian, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Other, Missing)
- Ethnicity (Hispanic or Latino, or Not Hispanic or Latino, Missing)
- Height [cm]
- Body weight [kg]
- Body Mass Index (BMI)

Other baseline characteristics

- Medical history
- Prior and concomitant medications
- Pre-vaccination AEs pre-existing to vaccination

Demographics tables will be presented by treatment group for the FAS, PPS, and IAS populations. Other baseline characteristics will be summarized by treatment group for the FAS only. Demographics and other baseline characteristics will be presented in separate subject listings.

3.4.2 Safety Variables

Physical examination (complete examination at Screening Visit and targeted physical examination at V1, V2, V3, V4, EAP, FU1 and FU2 Visits)
(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.)

A subgroup of subjects who will provide additional PBMC samples also will have physical examination reported at V1b and V3b.

Only abnormal physical examinations will be listed.

Vital signs (at Screening, V1, V2, V3, V4, EAP, FU1 and FU2 Visits)

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

The PBMC subgroup also has vital signs reported at V1b and V3b.

Baseline, actual and change from baseline vital sign parameters will be summarized and individual subject listings will be presented.

12-lead electrocardiogram (ECG) (at Screening and if clinically indicated at V2, V4, FU1 and FU2 Visits)
(Additional ECGs will be performed and reported if clinically indicated, or in case any clinically significant cardiac events are present).

- Assessment of ECG (categorized as normal, normal variant, abnormal)
- Interpretation of ECGs assessed as abnormal (categorized as abnormal not clinically significant or abnormal clinically significant)

Screening ECG parameters and overall interpretation will be summarized. Individual subject listings will also be presented.

Safety laboratory data (at Screening Visit, V2 and V4 and if clinically indicated at FU1 or FU2 Visits)
The safety laboratory measurements are performed at a central laboratory. Laboratory normal ranges are provided by the central laboratory.

Serum chemistry:

- Total Bilirubin (mg/dL)
- Alkaline Phosphatase (AP) (U/L)

- Aspartate Aminotransferase (AST) (U/L)
- Alanine Aminotransferase (ALT) (U/L)
- Creatinine (mg/dL)
- Sodium (mmol/L)
- Potassium (mmol/L)
- Calcium (mg/dL)
- Troponin I (ng/mL) (at Screening Visit and if clinically indicated at V2, V4, FU1 or FU2 Visits).

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.

Hematology:

- Red blood cell count (x $10^6/\mu L$)
- Hemoglobin (g/dL)
- Total and differential White Blood Cell count (WBC) (x $10^3/\mu L$)
- Platelet count (x $10^3/\mu L$)
- Hematocrit (%)
- Mean corpuscular/cell volume (MCV) (fL)
- Mean corpuscular/cellular hemoglobin (MCH) (pg)
- Mean corpuscular hemoglobin concentration (MCHC) (g/dL)
- Red blood cell distribution width (RDW) (%)

Baseline, actual values at each visit, and change from baseline safety laboratory parameters (serum chemistry and hematology) will be summarized and individual subject listings will be presented.

Shift tables will also be presented for serum chemistry and hematology using the categories of Missing, Below Lower Limit of Normal, Normal, and Above Upper Limit of Normal.

Pregnancy Test (Screening, V1, V3 and EAP)

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.

Pregnancy test results will be presented as individual subject listings for all WOCBP in the study.

Virology (Screening)

The following viruses are only evaluated during the screening period for assessment of inclusion/ exclusion criteria and at subsequent visits only if clinically indicated:

- HIV antibody test (anti HIV)
- HBsAG
- Hepatitis C antibody test

If appropriate, virology results will be presented as individual subject listings.

Respiratory Viral Panel

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. Subjects are instructed to return to the site within 3 days after start of symptoms.

Respiratory viral panel results will be presented as individual subject listings.

Solicited local AEs reported in the subject memory aid (at each vaccination, on day of vaccination and during the following 7 days)

- Injection Site Erythema (0 = 0, 1 denotes < 30 mm, 2 denotes ≥ 30 - < 100 mm, 3 denotes ≥ 100 mm)
- Injection Site Swelling (0 = 0, 1 denotes < 30 mm, 2 denotes ≥ 30 - < 100 mm, 3 denotes ≥ 100 mm)
- Injection Site Induration (0 = 0, 1 denotes < 30 mm, 2 denotes ≥ 30 - < 100 mm, 3 denotes ≥ 100 mm)
- Injection Site Pruritus (0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe)
- Injection Site Pain (0 = Absent, 1 = Painful to Touch, 2 = Painful when limb is moved, 3 = Spontaneously painful / prevents normal activity)

Solicited local AEs will be summarized by maximum intensity and vaccination period (and overall). Individual subject listings for solicited local AEs will also be presented.

Solicited general AEs reported in the subject memory aid (at each vaccination, on day of vaccination and during the following 7 days)

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).

Solicited general AEs will be summarized by maximum intensity and vaccination period (and overall). Individual subject listings for solicited general AEs will also be presented.

Other safety variables include:

- SAEs

3.4.3 Immunogenicity Variables

Antibody titers (at V1, V1b, V2, V3, V3b, V4, EAP, FU1, FU2)

- Serum RSV-specific antibodies (IgG ELISA)
- Serum RSV-specific antibodies (IgA ELISA)
- Serum RSV-strain A – G protein specific antibodies (IgG ELISA)
- Serum RSV-strain B – G protein specific antibodies (IgG ELISA)
- Serum RSV-strain A specific neutralizing antibodies (PRNT)
- Serum RSV-strain B specific neutralizing antibodies (PRNT)
- Mucosal RSV-specific antibodies ELISA (IgA ELISA)

ELISPOT SFU/1x10^6 PBMC (at V1, V1b, V2, V3b, V4 for PBMC subgroup only)

- IFN-γ RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)
- IL-4 RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)

(Sero)positivity ELISA and PRNT (yes/no) (at V1, V1b, V2, V3, V3b, V4, EAP, FU1, FU2)

- Serum RSV-specific antibodies (IgG ELISA)
- Serum RSV-specific antibodies (IgA ELISA)
- Serum RSV- strain A – G protein specific antibodies (IgG ELISA)
- Serum RSV-strain B – G protein specific antibodies (IgG ELISA)
- Serum RSV-strain A specific neutralizing antibodies (PRNT)

- Serum RSV-strain B specific neutralizing antibodies (PRNT)
- Mucosal RSV-specific antibodies ELISA (IgA ELISA)

Positivity ELISPOT (yes/no) (at V1, V1b, V2, V3b, V4 for PBMC subgroup only)

- IFN-γ RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)
- IL-4 RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)

Response ELISA and PRNT (yes/no) (at V1b, V2, V3, V3b, V4, EAP, FU1, FU2)

- Serum RSV-specific antibodies (IgG ELISA)
- Serum RSV-specific antibodies (IgA ELISA)
- Serum RSV-strain A – G protein specific ELISA (IgG ELISA)
- Serum RSV-strain B – G protein specific ELISA (IgG ELISA)
- Serum RSV-strain A specific neutralizing antibodies (PRNT)
- Serum RSV-strain B specific neutralizing antibodies (PRNT)
- Mucosal RSV-specific antibodies ELISA (IgA ELISA)

Response ELISPOT (yes/no) (at V1b, V2, V3b, V4 for PBMC subgroup only)

- IFN-γ RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)
- IL-4 RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)

ELISPOT RSV-specific Responder Status (yes/no) (per subject V1b through V4 for PBMC subgroup only)

- IFN-γ RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)
- IL-4 RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)

Refer to Section 3.5.7 for details of immunogenicity analyses.

3.4.4 Pharmacokinetic Variables

Not applicable.

3.4.5 Pharmacodynamic Variables

Not applicable.

3.5. Analysis and Presentation of Methods

3.5.1 Listings and Descriptive Statistics

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

For all ELISA and PRNT titers descriptive statistics will be based on number of observations (n), Geometric Means, confidence intervals (CI), minimum (Min), median, maximum (Max). Other continuous measurements will be summarized using descriptive statistics (i.e., number of observations (n), arithmetic mean, standard deviation (SD), Min, median, Max and categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise. Unless otherwise stated, the Min and Max will be reported with the same number of decimal places as the individual values are recorded. CIs, Means, Medians, and SD will be reported to one additional decimal place.

Descriptive statistics for the SFU values will be based on both the GMSFU and the median (with associated CI) and Min and Max.

A non-parametric percentile based CI (Hahn G and Meeker W (1991) Statistical Intervals: A Guide for Practitioners, New York: John, 1991) will be placed around the median for each group, using the SAS UNIVARIATE Procedure, i.e.:

PROC UNIVARIATE DATA=<dataset_name> CIPCTLDF; VAR SFU; BY GROUP; RUN;

Repeated assessments/measurements and unscheduled assessments/measurements will be included in the Individual Subject Data Listing. All tables and listings will be sorted by scheduled visit with unscheduled visits listed in-between scheduled visits (and by subject, if appropriate).

All tables will be presented by treatment groups. Solicited AEs will be presented by treatment and age group (≥55 to <70 and ≥70 years). For immunogenicity analysis, only PRNT strain A and ELISA IgA will be presented by treatment and age group (≥55 to <70 and ≥70 years). The remaining ELISA immunogenicity analyses will be presented by treatment group only.

Summary by subject refers to summary of the overall period, e.g., the overall vaccination period, or the ATP. An event will only be counted once during the period.

3.5.2 Software

All statistical summaries and analyses of safety and immunogenicity data will be performed using SAS® 9.4 or higher (Statistical Analysis System, SAS-Institute, Cary, NC, USA) on a Windows 2016 server.

3.5.3 Disposition of Subjects

All subjects screened will be accounted for.

A summary table will be presented specifying:

- The number of subjects screened (i.e., signed informed consent)
- The number of subjects randomized
- The number of subjects vaccinated (i.e., receiving at least 1 of 2 vaccinations)
- The number and percentage of subjects eligible for the full analysis set (FAS)
- The number and percentage of subjects eligible for the per-protocol analysis set (PPS)
- The number and percentage of subjects eligible for the immunogenicity analysis set (IAS)

An additional summary table will be presented specifying:

- The number of subjects vaccinated (i.e., receiving at least 1 of 2 vaccinations)
- The number of subjects who never received any vaccination
- The number of subjects who received only the first vaccination
- The number and percentage of subjects who received both vaccinations.
- The number and percentage of subjects who completed the active trial phase (i.e., have a disposition event in the database designated as "ACTIVE COMPLETED")
- The number and percentage of subjects withdrawn from the second vaccination before Visit 3 as well as the frequency and percentage of the reason for withdrawal from second vaccination
- The number and percentage of subjects prematurely discontinuing from the trial before EAP as well as the frequency and percentage of the reason for withdrawal from the trial
- The number and percentage of subjects attending FU1
- The number and percentage of subjects attending FU2
- The number and percentage of subjects who discontinued from the Follow Up Phase as well as the frequency and percentage of the reason for withdrawal from the Follow Up Phase

The percentages will be based on the number of subjects who received at least one vaccination.

A listing will present for all subjects in FAS the following:

- Completion Status for the Active Trial Phase (Yes/No)
- If completion status is No, then the listing will present the Trial Premature Discontinuation Date, Day and Reason
- Receipt (Yes/No) and date of first and second vaccination
- If the second vaccination was not received, then the listing will present the reason
- Completion of FU1 and FU2 (Yes/No)

A listing will present all violations of the inclusion criteria for the FAS. Similarly, a listing will present all exclusion criteria fulfilled for the FAS.

3.5.4 Demographic and Other Baseline Data

Demographics

Descriptive statistics for the demographics will be produced for the FAS, PPS, and IAS. Continuous variables include: age at screening (years), height at screening (cm), weight at screening (kg) and BMI at screening (kg/m^2). If there is a full rescreening then the information from the rescreening visit will be used.

Age is presented as captured in the SDTM Subject Characteristics (SC) domain. Age is auto-calculated from the eCRF where age is calculated as the difference between informed consent date and date of birth converted to years using the Joda-Time Java API and ISO8601 calendar system.

Frequencies and percentages of subjects will be tabulated for the categorical variables gender, race and ethnicity in the same table by treatment group and overall. Percentages will be based on the total number of subjects in each table pertaining to the FAS, PPS, or IAS.

The demographic listing will be presented for the FAS.

Medical History

A summary of medical history by SOC and PT per MedDRA 19.1 will be produced by treatment group for the FAS.

A medical history listing will be presented for the FAS.

Vaccine Assessment at Screening

A listing of vaccine history and planned vaccination at screening will be presented for all subjects.

3.5.5 Prior and Concomitant Medications

All prior medication will be listed by Anatomical-Therapeutic-Chemical (ATC) class Level 2, Level 3, PT and Generic name per the September 2016 version of World Health Organization Drug Dictionary (WHO-DD) for the FAS population. The listing “Prior medication” includes the medication data where end date is before date of first administration of trial vaccine.
All Concomitant Medication will be summarized by ATC class Level 2 and Level 3 for all subjects in the FAS. A concomitant medication listing will also be presented for the FAS. The table and listing “Concomitant Medication” includes ongoing medication or medication with missing end date or with end date after date of first administration of trial vaccine, as well as medication starting after first administration.

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

3.5.6 Compliance

Compliance will be summarized for the FAS population with respect to:

- Number of subjects who received at least one vaccination
- Number and percentage of subjects who received vaccination 1
- Number and percentage of subjects with memory aid returned at vaccination 1
- Number and percentage of subjects who received vaccination 2
- Number and percentage of subjects with memory aid returned at vaccination 2
- Number and percentage of subjects who received both vaccinations

Separate listings for vaccine administration and memory aid will also be presented.

3.5.7 Immunogenicity Analysis

ELISA, PRNT and ELISPOT

All serum and nasal swab immunogenicity results will be listed for the FAS. Tables will be prepared for the FAS and the PPS. Immunogenicity results from PBMC samples will be summarized for the IAS population.

Primary immunogenicity endpoint: PRNT (A strain) titers

The primary analysis of the primary endpoint is 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.

The primary immunogenicity endpoint will also be summarized descriptively using the geometric mean of fold increase, positivity rates (including associated 95% CI's), and response rates (including associated 95% CI's) for each treatment group, and by age group at each sampling point.

In addition, the following descriptive comparison of the ratios of the GMTs and GMFI's between treatment groups by visit will be calculated along with the corresponding 95% CI by assuming that the log10 PRNT (A strain) titers and log10 PRNT (A strain) Fold Increases 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

As a secondary descriptive analysis for the primary immunogenicity endpoint, an ANOVA model (with dose and age group as independent variables) of the $\log_{10}$ titers for the three doses

using Group 2, Group 4, and Group 5 will be performed. For Group 5 (2 vaccinations of Placebo), a dose value of 1 will be used to facilitate the log transformation of the dose. The dose response relationship will be explored in this analysis using linear and quadratic orthogonal contrasts. 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, then this will be seen as confirmation of a plateau effect in terms of responses for higher dose. This dose response ANOVA will be performed a second time without age group in the model.
As an exploratory analysis, an ANOVA will be conducted on the $\log_{10}$ titers using dose (2 levels), the number of vaccinations (2 levels), and age group (2 levels) as main effects, and dose-by-number of vaccinations as an interaction term. The main effect of dose (2 levels) will not include the placebo treatment group. To further explore whether baseline titers have an effect on dose, a similar ANOVA will be performed where the dependent variable of $\log_{10}$ titers will be replaced with $\log_{10}$ Fold Increase.

All ANOVAs will be performed on the FAS only.

Secondary immunogenicity endpoints
All other immunogenicity results (PRNT strain B, ELISPOT, ELISA IgG/IgA) will be considered as secondary descriptive analyses and will be analyzed similarly to the primary endpoint analysis (by age group results will be included for ELISA IgA only). Note that for secondary immunogenicity endpoints, ANOVAs will be performed only for PRNT strain B, IgA ELISA and IgG ELISA Total. The dose-response ANOVAs will be performed without age group in the model.

Geometric Mean Titers (GMTs)
For all ELISA and PRNT results the GMTs will be calculated by taking the antilogarithm of the mean of the $\log_{10}$ titer transformations.

Descriptive statistics will be derived by visit including number of observations, Min, median, Max, GMT, with 95% CI (derived by the antilogarithm of 95% CI of the $\log_{10}$ titer transformations based on the percentiles of the t-distribution).

Geometric Mean Spot Forming Units (ELISPOT)
SFU/1 x 10^6 PBMC will be reported as whole numbers. Min and Max will be reported as whole numbers. Medians, GMSFUs, and CI will be reported to one decimal place.

A non-parametric percentile based CI (Hahn G and Meeker W (1991) Statistical Intervals: A Guide for Practitioners, New York: John, 1991) will be placed around the median for each treatment group, using the SAS

UNIVARIATE Procedure, i.e.:

```
PROC UNIVARIATE DATA=<dataset_name> CIPCTLDF;
VAR <SFU Variable>;
BY <Treatment Group variable>;
RUN;
```

The calculation of the 95% CI for the Geometric Means will be based upon the assumption that the logarithm of the SFU has a normal distribution.

Seropositivity rates
RSV-specific ELISA and PRNT seropositivity rates will be presented by treatment group for each visit along with the Clopper-Pearson 95% CIs.
Positivity rates (ELISPOT)
Positivity rates will be presented by treatment group for each visit along with the Clopper-Pearson 95% CIs.

Response rates
Response rates for RSV-specific ELISA and PRNT titers will be presented by treatment group for each post baseline visit along with the Clopper-Pearson 95% CIs. Response status is only applicable for subjects with a V1 (baseline) titer available.

The same type of analysis of response rates will be conducted for the ELISPOT results and for IFN-γ and IL-4 results.

Responder rates (ELISPOT)
The responder rates (based on the total number of subjects with responder status available) will also be presented by group with exact Clopper-Pearson 95% CI.

3.5.8 Adverse Events

A summary table by vaccination period and Overall will be presented as an overview of local and general solicited AEs and unsolicited AEs. This summary table will present the number and percentage of subjects who had at least one event in each period as well as the corresponding total number of events for:

- At least one AE documented
- Any TEAE
- Non-serious TEAEs
- SAEs
- Related TEAEs
- TEAEs Graded ≥ 2
- TEAEs Graded ≥ 3
- Related TEAEs Graded ≥ 3

- Related SAEs
- AEs leading to withdrawal from the trial
- AEs leading to withdrawal from second vaccination
- Deaths

The Overall summary is the sum of Period 1 and Period 2 counts.

A similar per subject table will be presented where each subject is counted once per their entire study participation.

For the ATP and FU Phase, all AEs will be listed by subject, including SOC and PT for the FAS. Any AE with onset later than 28 days since the previous vaccination will not be included in summary tables but will be included in the listing and will be flagged accordingly as non-treatment-emergent.

According to the clinical trial protocol no new AEs should be reported during the FU Phase, except SAEs and AEs related to respiratory tract infections, but if any are reported then they will be listed but considered non-treatment-emergent and no statistical testing or summaries will be presented for them.

Serious Adverse Events
All SAEs (solicited and unsolicited) with onset from first vaccination up to and including EAP will be summarized by SOC and PT by vaccination period. Related SAEs will be presented in similar fashion. SAEs which occurred during the FU Phase will be listed.

Related Grade 3 Adverse Events
All Grade 3 or higher related AEs will be summarized by vaccination period by PT for solicited AEs, and by SOC and PT for unsolicited AEs. Individual subject listings for Grade 3 or higher AEs will be presented.

Solicited Local Adverse Events
Solicited local AEs will be summarized by PT after each vaccination, and broken down by maximum intensity. The incidence (i.e., the number of subjects developing a specified solicited local AE on the day of vaccination or over the seven days after each vaccination divided by the number of subjects per respective vaccination period) will be calculated. The incidence will also be calculated for any solicited local AE for each vaccination period, the overall vaccination period, by treatment and by age group. The incidence of Grade 2 or higher AEs will also be calculated as well as the incidence of Grade 3 or higher AEs.

The duration (in days) of the solicited local AEs will be summarized and presented in a listing. A similar table and listing will be presented for relative day of onset for solicited local AEs.

All tables created for solicited local adverse events per vaccination period will be repeated but on a per subject basis, where subjects are counted once per each adverse event experienced.

Solicited General Adverse Events
Solicited general AEs will be summarized in the same manner as solicited local AEs. In addition, a summary table will be produced for general AEs by vaccination period with reasonable possibility of relationship to trial vaccine, where relationship is defined as either possible, probable, definite, or missing. Also, the number of general AE events by intensity and relationship to trial medication will be presented by vaccination period. Each by vaccination period table will be repeated but on a per subject basis where subjects are counted only once per adverse event experienced.

Pre-treatment Adverse Events
AEs recorded after signing of the informed consent form but before the first administration of trial vaccine are considered pre-treatment AEs. These pre-treatment AEs will be presented in a subject listing.

Unsolicited AEs
Treatment-emergent unsolicited AEs in the active trial phase will be summarized by System Organ Class (SOC) and PT, and by vaccination period, and for overall. A similar table will be produced per subject.

Separate tables for related treatment-emergent unsolicited AEs, graded ≥3 treatment-emergent unsolicited AEs, and related graded ≥3 treatment-emergent AEs will be presented by vaccination period and overall.

The total number events and percentages of all treatment-emergent unsolicited AEs will be presented by intensity, relationship, and for related AE intensity.

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

3.5.9 Clinical Laboratory Exams (Hematology, Chemistry)

All measured hematology and chemistry values (and changes from baseline for continuous parameters) will be listed and summarized at each sampling visit using descriptive statistics (mean, SD, median, Min and Max).
Summary tables will be produced for the number of high and low laboratory values at Screening Visit, Visit 2 and Visit 4 by hematology and chemistry parameter. Note that Hepatitis B and C testing, HIV testing, and Troponin I testing are only summarized at the Screening Visit.

In addition, all clinical laboratory values outside the normal range will be listed by subject, gender, age and flagging of abnormal values (LN=Below normal range, HN=Above normal range) with their clinical significance.

Shift tables will be used to evaluate categorical changes from Screening Visit to Visit 2 and Screening Visit to Visit 4 with respect to normal ranges (below LLN, Normal, above ULN) in hematology and biochemistry parameters.

3.5.10 Vital Signs

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

3.5.11 ECGs

ECG Central Assessment results of normal, normal variant, and abnormal will be summarized at Screening Visit, Visit 2, Visit 4, FU1, and FU2 Visits, as applicable. In addition, a similar table for abnormal ECGs as determined by the investigator as clinically significant or not clinically significant will be presented.

All ECGs will be listed.

3.5.12 Pregnancy Test

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

3.5.13 Physical Examination

Subjects with abnormal physical examinations will be listed.

3.6. Alterations in SAP from the Clinical Trial Protocol

The following analysis items are deviations from the trial protocol:

- Section 7.1.1, RSV-specific ELISA, of the protocol states that "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)." Per Bavarian Nordic instruction, this statistic will be deleted from the analysis, and replaced by the Fold Increase.
- Section 9.2, Sample Size Calculation, of the protocol states that "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." and "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." In both regression analyses, age group will be added to the model per direction from Bavarian Nordic.
- RSV-specific memory B cells analyses are not covered in this SAP, but will be addressed in detail in an SAP amendment after further assay development.

4. References

Hahn G and Meeker W (1991) Statistical Intervals: A Guide for Practitioners, New York: John Wiley & Sons.

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Statistical Analysis Plan

RSV-MVA-002 Booster

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

Booster Sub-study

Signature Page

[redacted]

Table of Contents

Abbreviations

Table 1: Abbreviations and Definitions

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical-Therapeutic-Chemical
BATP	Booster Active Trial Phase
BEAP	Booster End of Active Phase
BFAS	Booster Full Analysis Set
BFU	Booster Follow-up visit
BIAS	Booster Immunogenicity Analysis Set
BMI	Body Mass Index
BN	Bavarian Nordic
BV	Booster Visit
CI	Confidence Interval
CSR	Clinical Study Report
DL	Detection Limit
EAP	End of Active Phase
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked Immuno Spot Technique
FU	Follow-up visit
GMFI	Geometric Mean Fold Increase
GMSFU	Geometric Mean Spot Forming Units
GMT	Geometric Mean Titer
HCG	Human Choriogonadotropin
HN	Above normal range
IFN-γ	Interferon-gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL-4	Interleukin 4
LN	Below normal range
Inf.U	Infectious Unit
Log_{10}	Logarithm base 10
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum

MVA-BN	Modified Vaccinia Ankara – Bavarian Nordic
n	Number of Observations
PBMC	Peripheral Blood Mononuclear Cells
PRNT	Plaque Reduction Neutralization Test
PT	Preferred Term
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SFU	Spot Forming Units
SMT	Safety Monitoring Team
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
V	Visit
WBC	White Blood Cells
WHO-DD	World Health Organization Drug Dictionary

General Definitions

Booster Vaccinated/Treated Subjects

A subject is considered vaccinated or treated once they have received any dose of the booster vaccination.

Booster Study Day

For this sub-study, the day of the booster vaccination is defined as Day 0, the following as Day 1, and so on. Equally, the day before the booster vaccination in the screening period is defined as Day -1, and so on. A new study day begins always at midnight regardless of the time of the booster vaccination.

Booster Baseline

If not otherwise specified, "booster baseline" refers to the last measurement prior to the booster vaccination, which is performed on booster visit (BV) 1 (approximately 12 months from the first vaccination in the main study). In case of missing vital event data at the first treatment visit, the booster screening vital event data may be used to impute baseline values. These data will be summarized as baseline data without specifying the visit from which the data were derived. However, in cases where no pre-treatment values exist for a baseline parameter, the subject will be considered as having no baseline, and post-baseline changes will not be able to be calculated and will be excluded from analyses.

Main Baseline

The main study baseline (described as "main baseline" in this document) refers to the last measurement before first vaccination with trial vaccine in the main study. This is either at Visit 1 or at Screening Visit (or latest re-screening) as applicable.

Booster Screening Phase

Time period from the booster screening visit (BV0) until the booster vaccination visit (BV1). This could include any unscheduled visits during the screening period up to the booster vaccination.

Booster Active Trial Phase (BATP)

Time period covering from BV1 until the visit approximately 4 weeks later (Booster End of Active Phase (BEAP)); whether this occurs at the final study visit or at an early termination visit). This could include any unscheduled visits up until final visit of the booster active trial phase. This is also the vaccination period of the booster sub-study.

Booster Follow-Up Trial Phase

Time period between the BEAP and the final study visit. Note that for subjects who do not return for booster sub-study follow-up visits (BFU), there may be no BFU phase data available.

Treatment Emergent Adverse Event (TEAE)

A TEAE is an adverse event with an onset either on or after the day of the booster vaccination, or within the 28 days following the booster vaccination. Note that serious AEs are also considered treatment-emergent after 28 days (see below).

Serious Adverse Events

All Serious Adverse Events (SAEs) from BV1 to the last follow-up visit are considered as treatment-emergent, regardless of the day of onset.

Related AE or Adverse Drug Reaction (ADR)

Treatment-related AEs are defined as TEAEs determined by the investigator to be possibly, probably, or definitely caused by MVA-BN-RSV. TEAEs with an unknown or missing causality also constitute treatment-related AEs. In case of missing causality assessments, a TEAE will be considered as related for the summaries.

Nominal Titer

The MVA-BN-RSV (Respiratory Syncytial Virus) vaccine is formulated at a nominal titer of 5×10^8 Inf.U per dose (0.5 mL). The actual titer will be determined in stability testing.

Geometric Mean Titer and Geometric Mean Spot Forming Units

The Geometric Mean Titer (GMT) and Geometric Mean Spot Forming Units (GMSFU) are calculated by taking the antilogarithm of the mean of the $\log_{10}$ transformed titers, and Spot Forming Units, respectively.

Detection Limit (DL)

The limit from where a positive signal can be measured in immunogenicity assays. Refer to Appendix 6.1 for DLs of the planned tests.

(Sero)Negative and (Sero)Positive Results

For each immunogenicity assay, a negative result is defined as a titer below the DL, while a positive result is a titer equal to or above the DL.

Response

For each immunogenicity assay, a response to the vaccine (applicable only for post baseline visits) is defined as either the appearance of a positive result for subjects with a negative result at baseline, or an increase by a factor of at least 2 compared to baseline for subjects with a positive result at baseline. Response status is applicable only for post baseline visits and is not calculated for subjects with missing baseline titer. Main study response is defined based on the main baseline. Booster sub-study response is defined based on the booster baseline. Post baseline visits include Visit (V) 1b, V2, V3, V3b, V4, end of active phase (EAP) visit, follow-up visit (FU) 1, and FU2 from the main study; BV1b, BV2, BEAP visit, BFU1, BFU2 and BFU3 from the booster sub-study.

The response rate at each post baseline visit is the percentage of subjects who have a positive response status out of the number of subjects with a non-missing response status at that visit.

Responder

A subject is an ELISPOT responder to the vaccine in a particular test agent (F pool, G(A) pool, G(B) pool, N pool, M2 pool, RSV Virus) if the subject has a response for at least two post baseline visits (V1b, V2, V3, V3b, V4 from the main study; BV1b, BV2 from the booster sub-study) within the same test agent. The responder evaluation applies only to subjects with at least two post baseline results available.

The responder rate for each test agent F pool, G(A) pool, G(B) pool, N pool, M2 pool, RSV Virus) 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.

Individual peak titer

The individual peak titer is the maximum of titers recorded on V1, V2, V3, V4, and EAP visit from the main study, BV2 and BEAP visit from the booster sub-study. Since V1b, V3b, and BV1b samples are only collected for the PBMC subgroup, they will be excluded from the peak titer selection.

Fold Increase

The fold increase is defined as a subject's post Baseline titer at Visit X, divided by the baseline titer. Main study fold increase is defined based on the main baseline. Booster sub-study fold increase can be defined based on the booster baseline or the main baseline.

1 Introduction

This Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the key statistical programming specifications for the booster sub-study of clinical trial RSV-MVA-002. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. The SAP is written based on recommendations from *ICH E3: Structure and Content of Clinical Study Reports*, and *ICH E9: Statistical Principles for Clinical Trials*. Table, figure and listing shells are described in a separate document.

The analyses described here are based on the final clinical trial protocol RSV-MVA-002 Edition 4.0 dated April 26, 2018. Details for the analyses of the main study data are described in the final SAP dated May 31, 2017 and the SAP Addendum dated October 11, 2017. This plan covers analysis details of data collected for the booster sub-study. It will be followed completely for the analysis of data derived from the sub-study. If any unforeseen additional analyses are included in the clinical study report (CSR) they will be clearly described as additional, unplanned analyses.

2 Trial Overview

2.1 Trial Description

This is 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. A total of 420 subjects were recruited into five treatment groups and were vaccinated in the main study (see Table 2).

Table 2 Treatment Groups in the Main Study

Group	N	Age [years]	Volume per dose [mL]	1st vaccination Day 0 [Inf.U]	2nd vaccination Day 28 [Inf.U]	Route
1	78	≥ 55	0.5	1×10^8	Placebo	IM
2	89	≥ 55	0.5	1×10^8	1×10^8	IM
3	80	≥ 55	0.5	5×10^8	Placebo	IM
4	90	≥ 55	0.5	5×10^8	5×10^8	IM
5	83	≥ 55	0.5	Placebo	Placebo	IM
Total	**420**					

Approximately one year after their first vaccination in the main study, 86 subjects in two selected treatment groups of the main study (Group 1 and Group 3) are planned to be recruited to participate in the booster sub-study. They will receive a single booster vaccination using the same MVA-BN-RSV dose they received during the main study. Subjects will be followed up for 12 months after their booster vaccination. Out of these 86 subjects, approximately 26 will be recruited from the PBMC subgroup (approximately 13 subjects for each of the two selected dose

groups). The selection of the treatment groups to be included in the booster sub-study is based on the results of the main study.

2.2 Design Techniques to Avoid Bias

Eligible subjects who have consented to participate in the booster sub-study will be enrolled until a total of 86 is reached. PBMC sites will begin recruitment 1-2 weeks prior to the remaining sites to ensure 13 PBMC subjects per treatment group. Once 46 subjects are enrolled into one treatment group, enrolment for that group will stop to assure an approximately equal number of enrolled subjects in both treatment groups.

2.2.1 Methods of Assigning Subjects to Treatment Groups

Subjects in this booster sub-study will not be randomized. They will get the same dose received during the main study.

2.2.2 Blinding

Subjects in the booster sub-study will not be blinded because they will get the same dose received in the main study, which has already been unblinded.

2.3 Objectives

2.3.1 Primary Objective

The primary objective of the main study is to assess the optimal dose and schedule of the MVA-BN-RSV vaccine in adult and elderly subjects in terms of immunogenicity.

The objective of the booster sub-study 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.

2.3.2 Secondary Objectives

The secondary objectives of the main study are:

- 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.

The secondary objectives of the booster sub-study are:

- To assess the RSV-specific immune responses elicited by the MVA-BN-RSV vaccine (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) of the MVA-BN-RSV vaccine following a one year booster 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

2.4 Study Population

In the main study, subjects were stratified by age into two groups: ≥ 55 to < 70, and ≥ 70 years. At least 20 subjects per treatment group were required in the age stratum ≥ 70 years.

The booster sub-study will enroll approximately 43 subjects from each of the two selected dose groups regardless of age subgroups.

2.5 Inclusion Exclusion Criteria

Subjects who completed all vaccinations of the main trial according to protocol in the selected dose groups and signed the booster sub-study informed consent are eligible to participate in the booster sub-study. A list of exclusion criteria for the booster sub-study is provided in the study protocol. Subjects are required to meet none of the exclusion criteria to enter the sub-study.

2.6 Endpoints

Primary and secondary endpoints for the main study are provided in the study protocol and in the main study SAP and SAP Addendum. Endpoints described in this section are relevant to the booster sub-study only.

2.6.1 Immunogenicity Endpoints

The immunogenicity endpoints for the booster sub-study are:

- 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 booster vaccination immunogenicity serum sampling time points and based on the individual peak titers.

- RSV-specific GMT measured by IgG ELISA at all immunogenicity serum booster sampling time points and based on the individual peak titers.
- RSV-specific antibody response rate measured by Immunoglobulin A (IgA) ELISA at all post booster vaccination immunogenicity serum sampling time points and based on the individual peak titers.
- RSV-specific GMT measured by IgA ELISA at all immunogenicity serum booster sampling time points and based on the individual peak titers.
- RSV-specific antibody response rate measured by PRNT (RSV strain A) at all post booster 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 booster sampling time points and based on the individual peak titers
- RSV-specific antibody response rate measured by PRNT (RSV strain B) at all post booster vaccination 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 booster sampling time points and based on the individual peak titers.
- RSV-specific antibody response rate measured by IgA ELISA at all post booster vaccination 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 booster sampling time points (mucosal IgA) and based on the individual peak titers.
- 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 booster vaccination PBMC sampling time points until BEAP.
- RSV-specific median and geometric mean Spot Forming Units (SFU) measured by IFN-γ / IL-4 ELISPOT at all PBMC booster sampling time points until BEAP.
- RSV-specific memory B cells measured at Booster Follow Up Visit 1 (BFU1) and Booster Follow Up Visit 2 (BFU2).

2.6.2 Safety Endpoints

The safety endpoints are:

- 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 the booster vaccination.
- Occurrence, intensity and duration of solicited local AEs during the 8-day period (day of vaccination and the following 7 days) after the booster 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 the booster vaccination.
- Occurrence, relationship to the trial vaccine and intensity of unsolicited non-serious AEs within 4 weeks after the booster vaccination.

2.7 Interim Analysis

An interim topline analysis is planned when all subjects enrolled in the booster sub-study have completed the BFU1 visit. Refer to Appendix 6.3 for the tables that will be provided for the interim topline analysis.

3 Study Design

Refer to the schedule of events in Appendix 6.2.

4 Statistical Methods

4.1 Planned Sample Size

From two treatment groups selected based on immunogenicity/safety parameters following primary vaccination, approximately 43 subjects will be recruited into the booster sub-study (86 subjects in total). Out of these 86 subjects, approximately 26 subjects (13 subjects for each dose group) will be recruited from the PBMC subgroup.

Based on the variability observed in the $\log_{10}$ titers for PRNT (A strain) 2 weeks after the second vaccination in the main study, the standard deviation (SD) is estimated to be 0.335 for the $\log_{10}$ titers 2 weeks after the booster vaccination. A total 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 1.63 in GMTs. Considering a drop-out rate of 5%, 43 subjects per group will be enrolled to receive a booster vaccination.

The sample size for the main study has been initially estimated based on the need to detect a significant difference between the two doses to select the optimal dose for further development. However, only a descriptive comparison is planned between the two dose groups in the sub-study.

The primary objective of the booster sub-study 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. When the sample size is 40, a paired t-test with a 0.025 one-sided significance level will have >80% power to reject the null hypothesis that the difference in immune response ($\log_{10}$ titers) after the initial vaccination and that after the booster vaccination is 0.08 or farther from zero when the expected difference is 0, assuming that the standard deviation of the differences is 0.168 (log10-scale). This comparison is also considered descriptive.

4.2 Analysis Populations

Two analysis sets are defined for the booster sub-study.

4.2.1 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.

4.2.2 Booster Immunogenicity Analysis Set (BIAS)

This is the subset of subjects in the BFAS who were from 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.

4.3 Data Handling Conventions

4.3.1 Missing Immunogenicity Data

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.

For assay results that are below the detection limit, refer to Appendix 6.1.

4.3.2 Missing or Partial Dates in Adverse Event and Concomitant Medication Data

In the case of incomplete AE and/or medication start and end dates, the following rules will be used to assign AEs to the vaccination period and medications as prior/concomitant:

For analysis purposes of any Prior and Concomitant Medication or any AE, imputation of partial start and end dates will be performed based on the following rules:

Missing	Rule for start date	Rule for end date	Flag for imputation
Day	First day of month	Last day of month	D
Month†	January 1	December 31	M
Year†	Vaccination date	Last BATP visit date	Y

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

Partial/Missing Start Date

- If day is missing, then impute the 1st of the month as in the table above, but if the month is the same as the month of the booster vaccination date then assign the imputed start date as the vaccination date.

- If month and day are missing, then impute as above to January 1 unless the year is the same as for the vaccination date then assign imputed start date as the vaccination date.
- If the date is completely missing, then impute the vaccination date unless the end date indicates that the AE/medication could have started/been taken prior to this in which case the date is imputed to January 1 of the same year as the start date.

Partial/Missing End Date

- If day is missing, then impute the last day of the month as in the table above unless the month is the same as the month of the last BATP visit date then impute the end date as the last BATP visit date.
- If month and day are missing, then impute as above to December 31 unless the year is the same as the last BATP visit date then assign imputed end date as the last BATP visit date.
- If the date is completely missing, check if AE/medication is ongoing before imputing a date and when the AE/medication started in relation to vaccination date. If the ongoing flag is missing, then assume that the AE/medication is still ongoing/medication is still being taken. In this case, do not impute the date. If the AE/medication stopped and the start date is prior to the last BATP visit date, then impute with the last BATP visit date. If the AE/medication started on or after the last BATP visit date, then impute an end date which is one day after the last BATP visit date.

These imputation methods will be used for assigning AEs to the vaccination period, and medications as prior/concomitant. Listings will display the original dates as captured in the eCRF.

4.3.3 Assignment of AEs to Trial Phase

Each AE will be assigned to the booster active trial phase (BATP) or booster follow-up (BFU) phase using date/time of vaccination and date/time of onset of the AE:

- All AEs starting at or after the booster vaccination but before the BEAP visit will be assigned to the booster active trial phase. For subjects who missed the BEAP visit, AEs within the booster vaccination + 28 day will also be assigned to the BATP.
- Any AEs starting after the booster vaccination but are not assigned to the BATP belong to the BFU period.

If onset time is missing and start date of AE coincides with the date of vaccination, the AE will be assigned to the BATP.

Each AE starting on or after the booster vaccination not matching the definition of a solicited AE is defined as an unsolicited AE. If a solicited AE begins outside of the 8-day period following the booster vaccination it will be considered an unsolicited AE regardless of the preferred term (PT). If start time of the AE is missing and start date coincides with date of vaccination, it will be

regarded as a treatment-emergent AE. If the start date is (partially) missing the AE will be regarded as a treatment-emergent AE following the worst-case principle.

Worst-case principle:

To avoid a potential misclassification of an AE to the BATP, if an imputed start date corresponds to the first of the month or to the first of the year, and matches the month and year of the booster vaccination date, then the AE will be assigned to the BATP. If the AE cannot be assigned to either phase because of a (partially) missing start date then it will be assigned to the BATP.

4.3.4 General Considerations for AEs

Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 will be used for coding of AEs.

Duration of an AE will be calculated as follows:

For Unsolicited AEs: expressed in [days]

- End date – start date of AE + 1 day. Note that duration can be calculated even if time of day is missing for either start or end dates, or if time is missing for both.
- In case of partially missing start date (month and/or day missing) or partially missing end date (month and/or day missing), duration will not be calculated.
- In case of an ongoing AE, the duration will not be calculated.

For Solicited AEs: expressed in [days]

- End date of AE – start date of AE + 1, where end date is the last day in which the symptom is defined as an AE, and start date is the first day in which the symptom is defined as an AE (disregarding if the AE occurred continuously between first and last day).
- In case of an ongoing AE, the duration will not be calculated.

Relative day of onset between vaccination and start of AE will be calculated as follows:

For Unsolicited AEs: expressed in [days]

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

For Solicited AEs: expressed in [days]

- The relative day is calculated as the day of first symptom intensity recording > 0.

- Start date of AE – booster vaccination date, where start date is the first day a symptom is defined as an AE; booster vaccination day corresponds to booster sub-study Day 0.

4.4 Analysis Variables

4.4.1 Demographic and other Baseline Characteristics

Demographics

- Age (years)
- Age Group (≥ 55 to < 70, ≥ 70)
- Gender (male, female)
- Race (White/Caucasian, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Other, Missing)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Missing)
- Height [cm]
- Body weight [kg]
- Body Mass Index (BMI)

Other baseline characteristics

- Medical history
- Prior and concomitant medications
- Pre-vaccination AEs

Age will be calculated based on date of informed consent for the booster sub-study. For weight and BMI, updated data will be obtained from the booster screening visit. Additional demographics and baseline characteristics will be obtained from the main study.

Demographics tables will be presented by treatment group for the BFAS and BIAS. Other baseline characteristics will be summarized by treatment group for the BFAS only. Demographics and other baseline characteristics will be presented in separate subject listings.

4.4.2 Safety Variables

Physical examination (complete examination at Booster Screening Visit and targeted physical examination at BV1, BV2, BEAP, BFU1 and BFU2 Visits).

A targeted physical examination is guided by any signs or symptoms previously identified or any new symptoms that the subject has experienced since the last visit. A subgroup of subjects who are from the PBMC subset will have targeted physical examination at BV1b.

Only abnormal physical examinations will be listed.

Vital signs (at Booster Screening, BV1, BV2, BEAP, BFU1 and BFU2 Visits)

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

The PBMC subgroup also has vital signs reported at BV1b.

Booster baseline, actual and change from booster baseline vital sign parameters will be summarized and individual subject listings will be presented.

12-lead electrocardiogram (ECG) data will not be collected for the booster sub-study.

Safety laboratory data (at Booster Screening Visit, BV2 and if clinically indicated at BFU1 or BFU2 Visits)

The safety laboratory measurements are performed at a central laboratory. Laboratory normal ranges are provided by the central laboratory.

Serum chemistry:

- Total Bilirubin (mg/dL)
- Alkaline Phosphatase (AP) (U/L)
- Aspartate Aminotransferase (AST) (U/L)
- Alanine Aminotransferase (ALT) (U/L)
- Creatinine (mg/dL)
- Sodium (mmol/L)
- Potassium (mmol/L)
- Calcium (mg/dL)

Hematology:

- Red blood cell count (x 10^6/µL)
- Hemoglobin (g/dL)
- Total and differential White Blood Cell count (WBC) (x 10^3/µL)
- Platelet count (x 10^3/µL)
- Hematocrit (%)
- Mean corpuscular volume (MCV) (fL)
- Mean corpuscular hemoglobin (MCH) (pg)
- Mean corpuscular hemoglobin concentration (MCHC) (g/dL)
- Red blood cell distribution width (RDW) (%)

Booster baseline, actual values at each visit, and change from booster baseline safety laboratory parameters (serum chemistry and hematology) will be summarized and individual subject listings will be presented.

Shift tables will also be presented for serum chemistry and hematology using the categories of Missing, Below Lower Limit of Normal, Normal, and Above Upper Limit of Normal.

Pregnancy Test (BV1)

A urine β-human choriogonadotropin (HCG) pregnancy test will be conducted for all women of childbearing potential at BV1 prior to the booster vaccination. Pregnancy test results will be presented as individual subject listings.

Solicited local AEs reported in the subject memory aid (on day of booster vaccination and during the following 7 days)

- Injection Site Erythema (0 = 0, 1 denotes < 30 mm, 2 denotes ≥ 30 - < 100 mm, 3 denotes ≥ 100 mm)
- Injection Site Swelling (0 = 0, 1 denotes < 30 mm, 2 denotes ≥ 30 - < 100 mm, 3 denotes ≥ 100 mm)
- Injection Site Induration (0 = 0, 1 denotes < 30 mm, 2 denotes ≥ 30 - < 100 mm, 3 denotes ≥ 100 mm)
- Injection Site Pruritus (0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe)
- Injection Site Pain (0 = Absent, 1 = Painful to Touch, 2 = Painful when limb is moved, 3 = Spontaneously painful / prevents normal activity)

Solicited local AEs will be summarized by maximum intensity. Individual subject listings for solicited local AEs will also be presented.

Solicited general AEs reported in the subject memory aid (on day of booster vaccination and during the following 7 days)

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)

MedDRA coded Preferred Term General AEs	Grade	Maximum Severity
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).

Solicited general AEs will be summarized by maximum intensity. Individual subject listings for solicited general AEs will also be presented.

Other safety variables include:

- Unsolicited TEAE
- Unsolicited SAEs
- Unsolicited Related TEAEs
- Unsolicited TEAEs Graded ≥ 3
- Unsolicited Related TEAEs Graded ≥ 3
- Unsolicited Related SAEs
- Unsolicited AEs leading to withdrawal from the trial

4.4.3 Immunogenicity Variables

Antibody titers (at BV1, BV1b [PBMC subgroup only], BV2, BEAP, BFU1, BFU2, BFU3 [serum samples only])

- Serum RSV-specific antibodies (IgG ELISA)
- Serum RSV-specific antibodies (IgA ELISA)
- Serum RSV-strain A G protein specific antibodies (IgG ELISA)
- Serum RSV-strain B G protein specific antibodies (IgG ELISA)
- Serum RSV-strain A specific neutralizing antibodies (PRNT)
- Serum RSV-strain B specific neutralizing antibodies (PRNT)
- Mucosal RSV-specific antibodies ELISA (IgA ELISA)

ELISPOT SFU/1x10^6 PBMC (at BV1, BV1b, BV2 for PBMC subgroup only)

- IFN-γ RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)
- IL-4 RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)

(Sero)positivity ELISA and PRNT (yes/no) (at BV1, BV1b [PBMC subgroup only], BV2, BEAP, BFU1, BFU2, BFU3 [serum samples only])

- Serum RSV-specific antibodies (IgG ELISA)
- Serum RSV-specific antibodies (IgA ELISA)

- Serum RSV- strain A G protein specific antibodies (IgG ELISA)
- Serum RSV-strain B G protein specific antibodies (IgG ELISA)
- Serum RSV-strain A specific neutralizing antibodies (PRNT)
- Serum RSV-strain B specific neutralizing antibodies (PRNT)
- Mucosal RSV-specific antibodies ELISA (IgA ELISA)

Positivity ELISPOT (yes/no) (at BV1, BV1b, BV2 for PBMC subgroup only)

- IFN-γ RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)
- IL-4 RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)

Response ELISA and PRNT (yes/no) (at BV1b [PBMC subgroup only], BV2, BEAP, BFU1, BFU2, BFU3 [serum samples only])

- Serum RSV-specific antibodies (IgG ELISA)
- Serum RSV-specific antibodies (IgA ELISA)
- Serum RSV-strain A G protein specific ELISA (IgG ELISA)
- Serum RSV-strain B G protein specific ELISA (IgG ELISA)
- Serum RSV-strain A specific neutralizing antibodies (PRNT)
- Serum RSV-strain B specific neutralizing antibodies (PRNT)
- Mucosal RSV-specific antibodies ELISA (IgA ELISA)

Response ELISPOT (yes/no) (at BV1b, BV2 for PBMC subgroup only)

- IFN-γ RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)
- IL-4 RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)

ELISPOT RSV-specific Responder Status (yes/no) (per subject, BV1b and BV2 for PBMC subgroup only)

- IFN-γ RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)
- IL-4 RSV Peptide pool (pool F, G(A), G(B), N, M2, RSV virus)

Refer to Section 4.5.7 for details of immunogenicity analyses.

4.5 Analysis and Presentation of Methods

4.5.1 Listings and Descriptive Statistics

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

For all ELISA and PRNT titers descriptive statistics will be based on number of observations (n), Geometric Means, confidence intervals (CI), minimum (Min), median, and maximum (Max). Other continuous measurements will be summarized using descriptive statistics (i.e., number of

observations (n), arithmetic mean, standard deviation (SD), Min, median, and Max. Categorical data will be summarized by means of frequency tables (i.e., count and percentages), if not stated otherwise. Unless otherwise stated, the Min and Max will be reported with the same number of decimal places as the individual values are recorded. CIs, Means, Medians, and SD will be reported to one additional decimal place.

Descriptive statistics for the SFU values will be based on both the GMSFU and the median (with associated CI) and Min and Max.

Titers will be reported as whole numbers. Min and Max will be reported as whole numbers. Medians, GMTs, and CI will be reported to one decimal place.

A non-parametric percentile based CI (Hahn, 1991) will be presented for the median using the SAS UNIVARIATE Procedure, i.e.:

PROC UNIVARIATE DATA=<dataset_name> CIPCTLDF; VAR SFU; BY GROUP; RUN;

Repeated assessments/measurements and unscheduled assessments/measurements will be included in the Individual Subject Data Listing. All tables and listings will be sorted by scheduled visit with unscheduled visits listed in-between scheduled visits (and by subject, if appropriate).

All tables will be presented by treatment groups. Solicited AEs will be presented by treatment group. For immunogenicity analysis, only PRNT strain A and ELISA IgA will be presented by treatment and age group (≥55 to <70 and ≥70 years) for GMT and fold increase analyses by treatment groups. The remaining ELISA immunogenicity analyses will be presented by treatment group only.

4.5.2 Software

All statistical summaries and analyses of safety and immunogenicity data will be performed using SAS® 9.4 or higher (Statistical Analysis System, SAS-Institute, Cary, NC, USA) on a Windows 2016 server.

4.5.3 Disposition of Subjects

All subjects screened for the booster sub-study will be accounted for.

A summary table will be presented specifying:

- The number of subjects screened (i.e., signed informed consent)
- The number of subjects who received the booster vaccination
- The number and percentage of subjects eligible for the BFAS
- The number and percentage of subjects eligible for the BIAS
- The number and percentage of subjects who completed the BATP

- The number and percentage of subjects prematurely discontinuing from the trial before BEAP as well as the frequency and percentage of the reason for withdrawal from the trial
- The number and percentage of subjects attending BFU1, BFU2, BFU3
- The number and percentage of subjects who discontinued from the BFU Phase as well as the frequency and percentage of the reason for withdrawal from the BFU Phase

Other than the number of subjects screened, the percentages will be based on the number of subjects who received the booster vaccination.

A listing for all subjects in the BFAS will present the following:

- Completion Status for the BATP (Yes/No)
- If completion status is No, then the listing will present the Sub-study Premature Discontinuation Date, relative day and Reason
- Receipt (Yes/No) and date of booster vaccination
- Completion of BFU1, BFU2 and BFU3 (Yes/No)

A listing will present all violations of the inclusion criteria for the BFAS. Similarly, a listing will present all exclusion criteria fulfilled for the BFAS.

4.5.4 Demographic and Other Baseline Data

Demographics

Descriptive statistics for the demographics will be produced for the BFAS and BIAS. Continuous variables include: age at booster screening (years), height at main study screening (cm), weight at booster screening (kg) and BMI at booster screening (kg/m^2). If there is a full rescreening then the information from the rescreening visit will be used.

Frequencies and percentages of subjects will be tabulated for the categorical variables gender, race and ethnicity in the same table by treatment group and overall. Percentages will be based on the total number of subjects in each table pertaining to the BFAS or BIAS.

The demographic listing will be presented for the BFAS.

Medical History

A summary of medical history by System Organ Class (SOC) and PT per MedDRA 19.1 will be produced by treatment group for the BFAS. A medical history listing will be presented for the BFAS.

Medical history refers to disease or symptoms presented prior to first MVA-BN-RSV vaccination in the main study. Any SAEs since the last follow-up visit in the main study will be listed separately.

4.5.5 Prior and Concomitant Medications

All prior medication will be listed by Anatomical-Therapeutic-Chemical (ATC) class Level 2, Level 3, PT and Generic name per the September 2016 version of World Health Organization Drug Dictionary (WHO-DD) for the BFAS population. Prior medication is defined as medications with end date that is before date of first administration of trial vaccine in the main study. Medications taken since the last follow-up visit in the main study and have ended prior to the booster sub-study are only to be captured in case the concomitant medication is related to a SAE.

All Concomitant Medications taken during the booster sub-study will be summarized by ATC class Level 2 and Level 3 for all subjects in the BFAS. A concomitant medication listing will also be presented for the BFAS. The table and listing "Concomitant Medication" includes ongoing medication or medication with missing end date or with end date after date of administration of the booster vaccine, as well as medication starting after administration of the booster vaccine.

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

4.5.6 Compliance

Compliance will be summarized and listed for the BFAS population with respect to number and percentage of subjects with memory aid completed.

4.5.7 Immunogenicity Analysis

ELISA, PRNT and ELISPOT

All serum and nasal swab immunogenicity results will be listed for the BFAS. Immunogenicity results from PBMC samples will be summarized for the BIAS population.

PRNT (A strain) titers

The primary analysis of the endpoint is Geometric Mean Titers (GMTs) after a single booster MVA-BN-RSV vaccination measured by Plaque Reduction Neutralization Test (PRNT; against strain A) 2 weeks post vaccination.

PRNT (A strain) titers will also be summarized descriptively using the geometric mean of fold increase, positivity rates (including associated 95% CI's), and response rates (including associated 95% CI's) for each treatment group, and by age group at each sampling point. In order to compare immune responses after initial vaccination in the main study and after booster vaccination in the booster sub-study, the summary will include data from all sampling points in the main study as well as those in the booster sub-study for the BFAS. Fold increase and response rates in the main study visits will be based on the main baseline; fold increase and

response rates in the booster visits will be based on the booster baseline. In addition, fold increase for post booster baseline time points will also be summarized based on main baseline.

Descriptive comparison of the ratios of the GMTs and GMFI's between the two treatment groups (Group 3 / Group 1) by visit will be calculated along with the corresponding 95% CI by assuming that the log10 PRNT (A strain) titers and log10 PRNT (A strain) Fold Increases are normally distributed:

Pair differences in $\log_{10}$ titer (main study $\log_{10}$ titer - booster sub-study $\log_{10}$ titer) and fold increase from booster sub-study at similar post-vaccination time points will be calculated, as well as their 95% CI. This will be presented as ratio and the corresponding 95% CI in the original scale. Fold increase in the main study visits will be based on the main baseline; fold increase in the booster visits will be based on the booster baseline.

Other immunogenicity endpoints

All other immunogenicity results (PRNT strain B, ELISPOT, ELISA IgG/IgA) will be considered as secondary descriptive analyses and will be analyzed similarly to PRNT (A strain) titers. Fold increases will not be calculated or analyzed for ELISPOT assays.

Geometric Mean Titers (GMTs)

For all ELISA and PRNT results the GMTs will be calculated by taking the antilogarithm of the mean of the $\log_{10}$ titer transformations.

Descriptive statistics will be derived by visit including number of observations, Min, median, Max, GMT, with 95% CI (derived by the antilogarithm of 95% CI of the $\log_{10}$ titer transformations based on the percentiles of the t-distribution).

Geometric Mean Spot Forming Units (ELISPOT)

SFU/1 x 10^6 PBMC will be reported as whole numbers. Min and Max will be reported as whole numbers. Medians, GMSFUs, and CI will be reported to one decimal place.

A non-parametric percentile based CI (Hahn, 1991) will be placed around the median for each treatment group.

The calculation of the 95% CI for the Geometric Means will be based upon the assumption that the logarithm of the SFU has a normal distribution.

Seropositivity rates

RSV-specific ELISA and PRNT seropositivity rates will be presented by treatment group for each visit along with the Clopper-Pearson 95% CIs.

Positivity rates (ELISPOT)

Positivity rates will be presented by treatment group for each visit along with the Clopper-Pearson 95% CIs.

Response rates

Response rates for RSV-specific ELISA and PRNT titers will be presented by treatment group for each post main study baseline visit and post booster sub-study visit along with the Clopper-Pearson 95% CIs. Response status is only applicable for subjects with a baseline titer available. Response rates in the main study visits will be based on the main baseline; response rates in the booster visits will be based on the booster baseline. The same type of analysis of response rates will be conducted for the ELISPOT results (IFN-γ and IL-4 results).

Responder rates (ELISPOT)

The responder rates (based on the total number of subjects with responder status available) will also be presented by group with exact Clopper-Pearson 95% CI.

4.5.8 Adverse Events

A summary table will be presented as an overview of local and general solicited AEs and unsolicited AEs during the BATP. This summary table will present the number and percentage of subjects who had at least one event as well as the corresponding total number of events for:

- At least one AE documented
- Any TEAE
- Non-serious TEAEs
- SAEs
- Related TEAEs
- TEAEs Graded ≥ 2
- TEAEs Graded ≥ 3
- Related TEAEs Graded ≥ 3
- Related SAEs
- AEs leading to withdrawal from the trial
- Deaths

For the BATP and BFU Phase, all AEs will be listed by subject, including SOC and PT for the BFAS. Any non-serious AE with onset later than 28 days after the booster vaccination will not be included in summary tables but will be included in the listing and will be flagged accordingly as non-treatment-emergent.

According to the clinical trial protocol no new AEs should be reported during the BFU Phase, except SAEs, but if any are reported then they will be listed but considered non-treatment-emergent and no summary will be presented.

Serious Adverse Events

All SAEs (solicited and unsolicited) with onset from booster vaccination up to and including BEAP will be summarized by SOC and PT. Related SAEs and SAEs which occurred during the BFU Phase will be presented in a similar fashion.

Related Grade 3 Adverse Events

All Grade 3 or higher related AEs during the BATP will be summarized by PT for solicited AEs, and by SOC and PT for unsolicited AEs. Individual subject listings for Grade 3 or higher AEs will be presented.

Solicited Local Adverse Events

Solicited local AEs will be summarized by PT after vaccination, and broken down by maximum intensity. The incidence (i.e., the number of subjects developing a specified solicited local AE on the day of vaccination or over the seven days after vaccination divided by the number of subjects with memory aid completed) will be calculated. The incidence will also be calculated for any solicited local AE by treatment group. The incidence of Grade 2 or higher AEs will also be calculated as well as the incidence of Grade 3 or higher AEs.

The duration (in days) of the solicited local AEs will be summarized and presented in a listing. A similar table and listing will be presented for relative day of onset for solicited local AEs.

Solicited General Adverse Events

Solicited general AEs will be summarized in the same manner as solicited local AEs. In addition, a summary table will be produced for general AEs with reasonable possibility of relationship to trial vaccine, where relationship is defined as either possible, probable, definite, or missing. Also, the number of general AEs by intensity and relationship to trial medication will be presented.

Pre-treatment Adverse Events

AEs recorded after signing the informed consent form, but before administration of the booster vaccine, are considered pre-treatment AEs. These pre-treatment AEs will be presented in a subject listing.

Unsolicited AEs

Treatment-emergent unsolicited AEs in the BATP will be summarized by SOC and PT.

Separate tables for related treatment-emergent unsolicited AEs, Grade ≥3 treatment-emergent unsolicited AEs, and related Grade ≥3 treatment-emergent AEs will be presented.

The total number of events and percentages of all treatment-emergent unsolicited AEs will be presented by intensity, relationship, and for related AE intensity.

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

4.5.9 Clinical Laboratory Exams (Hematology, Chemistry)

All measured hematology and chemistry values (and changes from booster baseline for continuous parameters) will be listed and summarized at each sampling visit using descriptive statistics (mean, SD, median, Min and Max).

Summary tables will be produced for the number of high and low laboratory values at BV0, booster baseline, BV2 and BEAP by hematology and chemistry parameter.

In addition, all clinical laboratory values outside the normal range will be listed by subject, gender, age and flagging of abnormal values (LN=Below normal range, HN=Above normal range) with their clinical significance.

Shift tables will be used to evaluate categorical changes from booster baseline to BV2 with respect to normal ranges (LN, Normal, HN) in hematology and biochemistry parameters.

Booster baseline is defined as last available measurements prior to the booster vaccination. This will be different from the booster screening measurement when the subject has missing screening value or has multiple screening values.

4.5.10 Vital Signs

Measured vital sign values and changes from booster baseline will be summarized at each applicable time point using descriptive statistics. All measured values will be listed.

4.5.11 Pregnancy Test

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

4.5.12 Physical Examination

Subjects with abnormal physical examinations will be listed.

4.6 Alterations in SAP from the Clinical Trial Protocol

RSV-specific memory B cells analyses are not covered in this SAP, but will be addressed in detail in an SAP amendment after further assay development.

5 References

1. International Conference on Harmonisation (July 1996). E3 Structure and Content of Clinical Study Reports.
2. International Conference on Harmonisation (September 1998). E9 Statistical Principals for Clinical Trials.
3. Hahn G and Meeker W (1991) Statistical Intervals: A Guide for Practitioners, New York: John Wiley & Sons.

6 Appendix

6.1 Detection Limits (DL)

Test	Detection Limit (DL)	Negative values reported
PBMC RSV-specific IFN-γ ELISPOT (pool F, G(A), G(B), N, M2 or RSV virus) PBMC RSV-specific IL-4 ELISPOT (pool F, G(A), G(B), N, M2 or RSV virus)	50	25 (half of the DL)
Serum RSV-specific PRNT Strain A Serum RSV-specific PRNT Strain B	20	10 (half of the DL)
Serum RSV-specific IgG ELISA	63	31.5 (half of the DL)
Serum RSV-specific IgA ELISA	100	50 (half of the DL)
Mucosal RSV-specific IgA ELISA (nasal swabs)	2	1 (half of the DL)
Serum RSV (strain A) G protein - specific IgG ELISA Serum RSV (strain B) G protein- specific IgG ELISA	no detection limit applies	negative reported as 50
RSV-specific B cell Fluorospot *IgG and IgA*	no detection limit applies	a measured percentage is considered a positive result

6.2 Trial Schedule Booster Sub-study

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]			◆	■				
Collection 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**
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 Protocol 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)

6.3 Tables and Listings

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15.1.2	Overall Assessment: Reason for Premature Discontinuation – All Subjects	
15.1.3.1	Demographic Data – BFAS	✓
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Number	Title	Topline
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15.2.6.5	Serum RSV-strain B G protein-specific IgG ELISA: Geometric Mean Titer Ratios Between Dose Groups – BFAS	✓
15.2.6.6	Serum RSV-strain B G protein-specific IgG ELISA: Geometric Mean Titer Ratios Between Booster Sub-study and Main Study – BFAS	✓

Number	Title	Topline
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15.2.7.9	Mucosal RSV-specific IgA ELISA: Geometric Mean Fold Increase Ratios Between Booster Sub-study and Main Study – BFAS	✓
15.2.8	**PBMC RSV-specific IFN-γ ELISPOT Peptide Pools**	
15.2.8.1	PBMC RSV-specific IFN-γ (ELISPOT Peptide Pools/RSV): Positivity rates – BIAS	
15.2.8.2	PBMC RSV-specific IFN-γ (ELISPOT Peptide Pools/RSV): Response rates – BIAS	✓
15.2.8.3	PBMC RSV-specific IFN-γ (ELISPOT Peptide Pools/RSV): Median and Geometric Mean SFU – BIAS	✓
15.2.8.4	PBMC RSV-specific IFN-γ (ELISPOT Peptide Pools/RSV): Responder Rates – BIAS	✓
15.2.8.5	PBMC RSV-specific IFN-γ (ELISPOT Peptide Pools/RSV): Responders to 1, 2, 3, 4 or 5 Peptide Pools – BIAS	✓
15.2.9	**PBMC RSV-specific IL-4 ELISPOT Peptide Pools**	
15.2.9.1	PBMC RSV-specific IL-4 (ELISPOT Peptide Pools/RSV): Positivity rates – BIAS	
15.2.9.2	PBMC RSV-specific IL-4 (ELISPOT Peptide Pools/RSV): Response rates – BIAS	
15.2.9.3	PBMC RSV-specific IL-4 (ELISPOT Peptide Pools/RSV): Median and Geometric Mean SFU – BIAS	✓

Number	Title	Topline
15.2.9.4	PBMC RSV-specific IL-4 (ELISPOT Peptide Pools/RSV): Responder Rates – BIAS	
15.3	**14.3 Safety**	
15.3.1	**14.3.1 Adverse Events**	
15.3.1.1	Overview of Solicited and Unsolicited Adverse Events During the Booster Sub-study Active Trial Phase – BFAS	✓
15.3.1.2	**Solicited Local Adverse Events**	
15.3.1.2.1	Solicited Local Adverse Events During the Booster Sub-study Active Trial Phase: Incidence by Maximum Intensity – BFAS	
15.3.1.2.2	Solicited Local Adverse Events During the Booster Sub-study Active Trial Phase: Any Grade, Grade ≥ 2 and Grade ≥ 3 TEAEs – BFAS	
15.3.1.2.3	Solicited Local Adverse Events During the Booster Sub-study Active Trial Phase: Summary of Duration – BFAS	
15.3.1.2.4	Solicited Local Adverse Events During the Booster Sub-study Active Trial Phase: Summary of Relative Day of Onset – BFAS	
15.3.1.3	**Solicited General Adverse Events**	
15.3.1.3.1	Solicited General Adverse Events During the Booster Sub-study Active Trial Phase: Incidence by Maximum Intensity – BFAS	
15.3.1.3.2	Solicited General Adverse Event Related to Vaccination during the Booster Sub-study Active Trial Phase: Incidence by Maximum Intensity – BFAS	
15.3.1.3.3	Solicited General Adverse Events During the Booster Sub-study Active Trial Phase: Summary of Duration – BFAS	
15.3.1.3.4	Solicited General Adverse Events During the Booster Sub-study Active Trial Phase: Summary of Relative Day of Onset – BFAS	
15.3.1.4	**Unsolicited Adverse Events**	
15.3.1.4.1	Treatment-Emergent Unsolicited Adverse Events During the Booster Sub-study Active Trial Phase: Incidence by System Organ Class and Preferred Term – BFAS	✓
15.3.1.4.2	Related Treatment-Emergent Unsolicited Adverse Events During the Booster Sub-study Active Trial Phase: Incidence by System Organ Class and Preferred Term – BFAS	
15.3.1.4.3	Grade ≥ 3 Treatment-Emergent Unsolicited Adverse Events During the Booster Sub-study Active Trial Phase: Incidence by System Organ Class and Preferred Term – BFAS	
15.3.1.4.4	Related Grade ≥ 3 Treatment-Emergent Unsolicited Adverse Events During the Booster Sub-study Active Trial Phase: Incidence by System Organ Class and Preferred Term – BFAS	

Number	Title	Topline
15.3.1.4.5	Treatment-Emergent Unsolicited Adverse Events During the Booster Sub-study Active Trial Phase: Summary of Intensity and Relationship to Trial Medication – BFAS	
15.3.2	**Serious Adverse Events**	
15.3.2.1	Serious Adverse Events During the Booster Sub-study Active Trial Phase: Incidence by System Organ Class and Preferred Term – BFAS	
15.3.2.2	Related Serious Adverse Events During the Booster Sub-study Active Trial Phase: Incidence by System Organ Class and Preferred Term – BFAS	
15.3.3	**Laboratory, Vital Signs, and ECG Safety Data**	
15.3.3.1	Laboratory Data (Mean Values): Hematology – BFAS	
15.3.3.2	Laboratory Data (Mean Values): Biochemistry – BFAS	
15.3.3.3	Laboratory Abnormalities: Hematology – BFAS	
15.3.3.4	Laboratory Abnormalities: Biochemistry – BFAS	
15.3.3.5	Laboratory Data (Shift Table): Hematology – BFAS	
15.3.3.6	Laboratory Data (Shift Tables): Biochemistry – BFAS	
15.3.3.7	Vital Signs – BFAS	

LIST OF LISTINGS

Number	Title
16.2.1	**Discontinued Subjects**
16.2.1.1	Violation of Inclusion Criteria – BFAS
16.2.1.2	Exclusion Criteria Fulfilled – BFAS
16.2.1.3	Informed Consent – BFAS
16.2.1.4	Overall Assessment – BFAS
16.2.1.5	Disposition – BFAS
16.2.2	**Protocol Deviations**
16.2.2.1	Protocol Deviations – BFAS
16.2.2.2	Sample Handling Deviations – BFAS
16.2.3	**Subjects not Eligible for the Trial**
16.2.3.1	Eligibility for Trial Participation – Subjects not Eligible for the Trial
16.2.4	**Demographic Data and Other Baseline Characteristics**
16.2.4.1.1	Demographic Data – BFAS
16.2.4.1.2	Medical History – BFAS
16.2.4.1.3	Pre-treatment Adverse Events and Serious Adverse Events Since Last Follow-up Visit in the Main Study – BFAS
16.2.4.1.4	Abnormal Physical Examinations at Booster Screening – BFAS
16.2.4.2	**Prior and Concomitant Medication**
16.2.4.2.1	Concomitant Medication – BFAS
16.2.4.2.2	Prior Medication - BFAS
16.2.5	**Compliance and/or Drug Concentration Data**
16.2.5.1	Dates of Visits and Blood and Mucosal Sampling – BFAS
16.2.5.2	Investigational Product Administration – BFAS
16.2.5.3	Memory Aid – BFAS
16.2.6	**Individual Immune Response Data**
16.2.6.1	RSV-specific Serum IgG, Serum IgA Analysis: Titer, Positivity, Response Status, and Fold Increase per Subject by Visit – BFAS
16.2.6.2	RSV-specific PRNT (Strain A and B): Titer, Positivity, Response Status, and Fold Increase per Subject by Visit – BFAS
16.2.6.3	ELISPOT IFN-γ: SFU per Subject by Visit – BIAS
16.2.6.4	ELISPOT IFN-γ: Positivity per Subject by Visit – BIAS
16.2.6.5	ELISPOT IFN-γ: Response Status per Subject by Visit – BIAS

16.2.6.6	ELISPOT IFN-γ: Responder Status per Subject – BIAS
16.2.6.7	ELISPOT IL-4: SFU per Subject by Visit – BIAS
16.2.6.8	ELISPOT IL-4: Positivity per Subject by Visit – BIAS
16.2.6.9	ELISPOT IL-4: Response Status per Subject by Visit – BIAS
16.2.6.10	ELISPOT IL-4: Responder Status per Subject – BIAS
16.2.6.11	RSV-specific Mucosal IgA Analysis: Titer, Positivity, Response Status, and Fold Increase per Subject by Visit – BFAS
16.2.7	**Adverse Event Listings**
16.2.7.1.1	Unsolicited Adverse Events – BFAS
16.2.7.1.2	Related Unsolicited Adverse Events – BFAS
16.2.7.1.3	Grade ≥ 3 Unsolicited Adverse Events – BFAS
16.2.7.1.4	Grade ≥ 3 Related Unsolicited Adverse Events – BFAS
16.2.7.1.5	Adverse Events Leading to Discontinuation from the Sub-study – BFAS
16.2.7.1.6	Solicited Local Adverse Events: Injection Site Pain – BFAS
16.2.7.1.7	Solicited Local Adverse Events: Injection Site Erythema – BFAS
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16.2.7.1.9	Solicited Local Adverse Events: Injection Site Induration – FAS
16.2.7.1.10	Solicited Local Adverse Events: Injection Site Pruritus – BFAS
16.2.7.1.11	Solicited General Adverse Events: Body Temperature Increased – BFAS
16.2.7.1.12	Solicited General Adverse Events: Headache – BFAS
16.2.7.1.13	Solicited General Adverse Events: Myalgia – BFAS
16.2.7.1.14	Solicited General Adverse Events: Chills – BFAS
16.2.7.1.15	Solicited General Adverse Events: Nausea – BFAS
16.2.7.1.16	Solicited General Adverse Events: Fatigue – BFAS
16.2.7.1.17	Examination of Injection Site – BFAS
16.2.7.2	**Serious Adverse Events**
16.2.7.2.1	Serious Adverse Events – BFAS
16.2.7.2.2	Related Serious Adverse Events – BFAS
16.2.8	**Listings of Individual Laboratory Measurements by Subject**
16.2.8.1.1	Laboratory Data: Hematology – BFAS
16.2.8.1.2	Laboratory Data: Hematology – Abnormal Values – BFAS
16.2.8.1.3	Laboratory Data: Biochemistry – BFAS
16.2.8.1.4	Laboratory Data: Biochemistry – Abnormal Values – BFAS
16.2.8.1.5	Laboratory Data: Pregnancy Test Results (Female Subjects Only) – BFAS
16.2.8.1.6	Laboratory Data: Laboratory Normal Ranges

16.2.8.2	**Other Safety Data**
16.2.8.2.1	Vital Signs – BFAS
16.2.8.2.2	Abnormal Physical Examination – BFAS