Clinical Trial Protocol

RSV-MVA-004

A Randomized, Double-blind, Phase 3 Trial to Assess Clinical Efficacy, Safety and Reactogenicity of the Recombinant MVA-BN®-RSV Vaccine in Adults ≥60 Years of Age

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1 General Information

1.1 List of Abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ARD	acute respiratory disease
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BN	Bavarian Nordic
CDC	Centers for Disease Control and Prevention
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRA	clinical research associate
CRO	contract research organization
CSPV	clinical safety and pharmacovigilance
CSR	clinical study report
CTS	clinical trial site
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DS	drug safety
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
ER	emergency room
ePRO	electronic patient reported outcome
EQ-5D-5L	EuroQol 5-dimension 5-level health questionnaire
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FI	formalin-inactivated
FU	follow-up
FU1	follow-up visit 1
FU2	follow-up visit 2
FU-D	follow-up durability
GCP	good clinical practice

GLP	good laboratory practice
GMSFU	geometric mean spot forming unit
GMT	geometric mean titer
HIV	human immunodeficiency virus
IB	investigator's brochure
IBC	institutional biosafety committee
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IM	intramuscular
IMP	investigational medicinal product
Inf.U	infectious units
IRB	institutional review board
IUD	intrauterine devices
IUS	intrauterine systems
IXRS	interactive voice/web-response system
LF	liquid frozen
LRTD	lower respiratory tract disease
MedDRA	Medical Dictionary for Regulatory Activities
MP	medicinal product
MVA	modified vaccinia Ankara strain
MVA-BN®	modified vaccinia Ankara from Bavarian Nordic; also named Jynneos®, Imvamune® or Imvanex®
n/N	number
NIH	National Institutes of Health
NP	nasopharyngeal
OBA	Office of Biotechnology Activities
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PI	principal investigator
PRNT	plaque reduction neutralization test
PT	preferred term
PV	pharmacovigilance
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
RAC	recombinant DNA advisory committee
RiiQ	Respiratory Intensity and Impact Questionnaire
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RVP	respiratory viral panel
PCR	polymerase chain reaction

SADR	serious adverse drug reaction
SAE	serious adverse event
SC	subcutaneous
SCR	screening
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamate pyruvate transaminase
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SV	symptom visit
TBS	tris-buffered saline
$TCID_{50}$	tissue culture infectious dose 50%
TEAE	treatment-emergent adverse event
Th1/Th2	t-helper cells, type 1/type 2
TFI	Tilburg Frailty Indicator (part B only)
UK	United Kingdom
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
V	visit
VACV	vaccinia virus
VE	vaccine efficacy
VACV	vaccinia virus
VE	vaccine efficacy
VL	viral load
WBC	white blood cell count
WOCBP	women of childbearing potential
15D	15-dimension health-related quality of life instrument

1.2 Definitions

RSV season	Currently the onset and end of RSV seasons are changing from the pattern experienced before the COVID pandemic (i.e., peak season in winter months) and cannot be predicted for the coming years. Subjects are followed up for efficacy endpoints for at least 1 RSV season, i.e up to 12 months.
6-month follow-up visit	The visit is performed 6 months after vaccination and, depending on RSV seasonality, might coincide with the end of the first RSV season after vaccination. If applicable, end of season is defined by the Centers for Disease Control and Prevention (CDC) surveillance data.
RSV season 1	First RSV season after first vaccination of approximately 20,000 subjects, who are followed up for efficacy endpoints (RSV-related LRTD for at least this season, up to12 months, after vaccination).
RSV season 2	In case the required number of events (LRTD cases) was not met in the first season and the pre-specified futility boundary was not crossed after season 1, additional subjects (approximately 4000) will be vaccinated and followed up for at least 1 RSV season (up to 12 months after vaccination).
Durability follow-up	Starting 1 year after vaccination, subjects vaccinated before RSV season 1 who are willing to continue to participate in durability follow-up are followed up for at least 6 months and up to 12 months to assess durability of vaccine efficacy by collecting RSV-related ARD/LRTD events. Approximately 16,000 subjects, which allows for a 20% dropout from randomization, will be followed up for durability.
Vaccination	Intramuscular injection with MVA-BN-RSV vaccine or placebo.
ePRO	Electronic device (either subject-owned or provided by vendor) with clinical trial-specific applications including functions for weekly reminders and completion of the memory aid diary, and other patient reported outcome tools if applicable.

1.3 Protocol Synopsis

Title	**A Randomized, Double-blind, Phase 3 Trial to Assess Clinical Efficacy, Safety and Reactogenicity of the Recombinant MVA-BN-RSV Vaccine in Adults ≥60 Years of Age**
Clinical Phase	Phase 3
Sponsor	[redacted]
Coordinating Investigator	[redacted]
Number of Sites and Country/ies	Number of sites: up to 140 Countries: United States of America Germany and UK
Vaccination Dose and Schedule	Each subject will receive a single administration with either 0.5 mL MVA-mBN294B (with a titer of at least 3×10E8 infectious units [Inf.U] per dose; common name MVA-BN-RSV vaccine) or with 0.5 mL placebo at Day 1. MVA-mBN294B is a liquid frozen (LF) suspension. Tris-buffered saline (TBS) will be used as placebo.
Route of Administration	MVA-BN-RSV vaccine/placebo is administered intramuscularly (IM) into the deltoid muscle of the upper arm (preferably the non-dominant arm).
Trial Duration	Up to 24 months per subject (up to 30 months for the total trial)

Primary Objective	To assess the clinical efficacy of MVA-BN-RSV vaccine against lower respiratory tract disease (LRTD) associated with RSV. The estimand corresponding to the primary objective to assess vaccine efficacy is defined as 1 minus the hazard ratio of LRTD associated with RSV infection in the 2 vaccination groups in the population who are randomized and receive the study vaccination, regardless of early termination during the RSV season.
Secondary Objectives	To assess the clinical efficacy of MVA-BN-RSV vaccine against acute respiratory disease (ARD) associated with RSV. The estimand corresponding to this secondary objective of assessing vaccine efficacy is defined as 1 minus the hazard ratio of ARD associated with RSV disease in the 2 vaccination groups in the population who are randomized and receive the study vaccination, regardless of early termination during the RSV season. To assess clinical efficacy of MVA-BN-RSV vaccine against complications or hospitalization related to confirmed RSV disease. To assess safety and reactogenicity of the MVA-BN-RSV vaccine in medically stable subjects ≥60 years of age. To assess the RSV-specific humoral and cellular immunity elicited by MVA-BN-RSV in a subset of the study population.
Exploratory Objectives	Surveillance over a second year after vaccination for subjects vaccinated in the previous season, to assess durability of efficacy. To assess the post-vaccination impact on the burden of RSV disease in the study population. To assess the RSV-specific humoral immunity (IgA) in a subset of the study population. To assess the orthopox-specific humoral neutralizing immunity against the vector backbone MVA-BN in a subset of the study population. To assess healthcare utilization and health-related quality of life. To assess the clinical efficacy of MVA-BN-RSV vaccine against ARD associated with Human Metapneumovirus (hMPV).

	To assess the clinical efficacy of MVA-BN-RSV vaccine against ARD associated with prespecified viral respiratory pathogens. To assess clinical efficacy of MVA-BN-RSV vaccine against hospitalization (all cause, pneumonia, cardiovascular specific) or mortality (all cause, pneumonia, cardiovascular specific) related to confirmed RSV disease.
Primary Endpoints	**Occurrence of LRTD** (≥3 symptoms) associated with RSV until the end of one RSV season (up to 12 months after vaccination). RSV-associated LRTD is defined by the presence of clinical evidence of at least 1 sign or symptom of ARD (see below) and at least 3 of the following signs or symptoms with onset ≥14 days following vaccination until the end of one RSV season (up to 12 months after vaccination), confirmed and documented by a medical professional, together with RSV disease confirmed by polymerase chain reaction (PCR) (nasopharyngeal (NP) swab to be collected within 5 days of symptom onset; preferably within 72 hours of symptom onset). • hypoxemia (oxygen saturation <92% at rest in conjunction with an at least 3% decrease from baseline) • respiratory rate >25 breaths/Min • imaging evidence of new onset of bronchitis, bronchiolitis, or pneumonia • new wheezing or worsening of pre-existing wheezing • new shortness of breath or worsening of pre-existing shortness of breath • new cough or worsening of pre-existing cough new sputum production or worsening of pre-existing sputum production
	Occurrence of LRTD (≥2 symptoms) associated with RSV until the end of 1 RSV season (up to 12 months after vaccination). RSV-associated LRTD is defined by the presence of clinical evidence of at least 1 sign or symptom of ARD (see below) and at least 2 (for less severe disease) of the following signs or symptoms with onset ≥14 days following vaccination until the end of 1 RSV season (up to 12 months after vaccination), confirmed and documented by a medical professional, together with RSV disease confirmed by polymerase chain reaction (PCR) (nasopharyngeal (NP) swab to be collected within 5 days of symptom onset; preferably within 72 hours of symptom onset).

	• hypoxemia (oxygen saturation <92% at rest in conjunction with an at least 3% decrease from baseline) • respiratory rate >25 breaths/Min • imaging evidence of new onset of bronchitis, bronchiolitis, or pneumonia • new wheezing or worsening of pre-existing wheezing • new shortness of breath or worsening of pre-existing shortness of breath • new cough or worsening of pre-existing cough • new sputum production or worsening of pre-existing sputum production
Secondary Endpoints	**Efficacy** **(Key secondary) Occurrence of ARD** associated with RSV until the end of one RSV season (up to 12 months after vaccination). RSV-associated ARD is defined by the presence of either one (1) ARD symptom lasting for at least 24 hours or two (2) simultaneously occurring ARD symptoms (irrespective of duration), with onset ≥14 days following vaccination until the end of one RSV season (up to 12 months after vaccination). RSV disease must be laboratory-confirmed by PCR (NP swab to be collected within 5 days of symptom onset, preferably within 72 hours of symptom onset). ARD symptoms include: • rhinorrhoea • nasal congestion • pharyngitis • earache • new cough or worsening of pre-existing cough • new wheezing or worsening of pre-existing wheezing • new sputum production or worsening of pre-existing sputum production • new shortness of breath or worsening of pre-existing shortness of breath • fever >100°F / >37.8°C (oral temperature) Occurrence of complications related to PCR-confirmed RSV disease. Occurrence of hospitalization due to confirmed RSV disease or due to any complication related to RSV-confirmed respiratory disease.

Occurrence of LRTD (severe LRTD) associated with RSV until the end of one RSV season (up to 12 months after vaccination). RSV-associated LRTD is defined by the presence of clinical evidence of at least 1 sign or symptom of ARD (see above) and at least 1 of the following signs or symptoms with onset ≥14 days following vaccination until the end of one RSV season (up to 12 months after vaccination), confirmed and documented by a medical professional, together with RSV disease confirmed by polymerase chain reaction (PCR) (nasopharyngeal (NP) swab to be collected within 5 days of symptom onset; preferably within 72 hours of symptom onset).

- hypoxemia (oxygen saturation <92% at rest in conjunction with an at least 3% decrease from baseline)
- respiratory rate >25 breaths/Min
- imaging evidence of new onset of bronchitis, bronchiolitis, or pneumonia

Safety

Occurrence of any serious adverse events at any time during the trial period.

Occurrence of any grade 3 or higher adverse events assessed as related to study vaccine within 29 days after vaccination.

Occurrence of solicited local adverse events (pain, swelling, pruritus, erythema, induration) within 8 days after vaccination.

Occurrence of solicited systemic adverse events (body temperature, headache, fatigue, myalgia, nausea, chills) within 8 days after vaccination.

Occurrence of any unsolicited adverse events within 29 days after vaccination.

Immunogenicity (selected sites)

RSV-specific serum IgG antibody titers 2 weeks, 1 year and 2 years after vaccination.

RSV-specific serum neutralizing antibody titers 2 weeks, 1 year and 2 years after vaccination (subtype A and B).

RSV-specific T-cell responses measured 1 week, 1 year and 2 years after vaccination.

Exploratory Endpoints	Occurrence of hospitalization (all cause, pneumonia, cardiovascular specific) or mortality (all cause, pneumonia, cardiovascular specific) related to confirmed RSV disease

Durability

Occurrence of LRTD associated with RSV during a second year after vaccination. Case definition is the same as for the primary, endpoints and severe LRTD endpoint.

Occurrence of ARD associated with RSV during a second year after vaccination. Case definition is the same as for the secondary endpoint.

Overall Vaccine Efficacy for up to 2 Years after Vaccination

Occurrence of LRTD associated with RSV during the entire follow-up period. Case definition is the same as for the primary endpoints, and severe LRTD endpoint.
If 2 events occur in the same individual, only the first event will be counted.

Occurrence of ARD associated with RSV during the entire follow-up period. Case definition is the same as for the secondary endpoint.
If 2 events occur in the same individual, only the first event will be counted.

Burden of Disease

Change in symptoms on the Respiratory Intensity and Impact Questionnaire (RiiQ):

- The area under the curve (AUC) of the change from baseline in RiiQ total and domain-specific symptom scores from onset of symptoms to 6 days later (7 days total) and, in the case of ongoing symptoms, up to 20 days later (21 days total) in participants with confirmed RSV.
- The maximum change from baseline in daily RiiQ total and domain-specific scores for onset of symptoms to 6 days later (7 days total) and, in the case of ongoing symptoms, up to 20 days later (21 days total) in participants with confirmed RSV.

Health-Related Quality of Life

	Change from baseline in the EuroQol 5-dimension 5-level (EQ-5D-5L) health questionnaire utility score at onset of symptoms, day 6 and 1, 3, 6 and 12 months after confirmed RSV. Change from baseline in the 15-dimension (15D) health-related quality of life instrument utility score at onset of symptoms, day 6 and 1, 3, 6, and 12 months after confirmed RSV. Number of stays in the intensive care unit, uses of respiratory/life support, and antibiotic prescriptions due to confirmed RSV disease or due to complications related to RSV-confirmed disease. **Immunogenicity (selected sites)** RSV-specific serum antibody titers 2 weeks, 1 year and 2 years after vaccination assessed by RSV-specific IgA enzyme-linked immunosorbent assay (ELISA). Orthopox-specific serum neutralizing antibody titers 2 weeks, 1 year and 2 years after vaccination. **Efficacy against other respiratory pathogens** Occurrence of ARD associated with hMPV until the end of 1 RSV season. Occurrence of ARD associated with pre-specified viral respiratory pathogens until the end of 1 RSV season.
Sample Size	The expected vaccine efficacy of MVA-BN-RSV vaccine against LRTD with ≥3 symptoms is 80%. For an alpha = 0.05 two-sided test against a null hypothesis of ≤20% vaccine efficacy, a total of 22 events will be required for 90% power. Assuming the rate of LRTD with ≥3 symptoms is 0.2% in the placebo group during an RSV season, approximately 20,000 subjects vaccinated in 2 treatment groups receiving either MVA-BN-RSV vaccine or placebo will allow the observation of at least 22 events. If the number of LRTD with ≥3 symptoms events required for the primary endpoint analysis is accruing slower than anticipated, approximately 4000 additional subjects may be recruited in RSV season 2 (section 11.5). The expected vaccine efficacy of MVA-BN-RSV vaccine against LRTD with ≥2 symptoms is 65%. For an alpha = 0.05 two-sided test against a null hypothesis of ≤20% vaccine efficacy, a total of 53 events will be required for 85% power. Assuming the rate of

	LRTD with ≥2 symptoms is 0.4% in the placebo group during an RSV season, approximately 20,000 subjects vaccinated in 2 treatment groups receiving either MVA-BN-RSV vaccine or placebo will allow the observation of at least 53 events. If the number of LRTD with ≥2 symptoms events required for the primary endpoint analysis is accruing slower than anticipated, approximately 4000 additional subjects may be recruited in RSV season 2 (section 11.5). Assuming the rate of ARD is 1.6% in the placebo group during an RSV season, approximately 240 events will be observed if the vaccine efficacy is 50%. This will result in at least 95% power for an alpha = 0.05 two-sided test against a null hypothesis of ≤20% vaccine efficacy.
Trial Design	Randomized, double-blind, placebo-controlled. In season 1, 20,000 subjects will be randomized into 2 groups. All vaccinated subjects will be followed up for respiratory tract disease starting the day after vaccination until the end of RSV season 1 (for up to 12 months after vaccination). Per definition an RSV season has ended according to the specific RSV surveillance data for the northern hemisphere (e.g., provided by the CDC for US sites https://www.cdc.gov/surveillance/nrevss/rsv/index.htmL) or site- and region-specific surveillance data for sites outside the US. In case of no distinct seasonality, subjects will be followed up for up to 12 months after vaccination, for efficacy endpoint assessment. Futility decision towards the end of RSV season 1: **Scenario 1** If the number of LRTD events met the sample size requirement for the primary endpoint analyses (minimum of 22 LRTD with ≥3 symptoms and minimum of 53 LRTD with ≥2 symptoms) with approximately 6 months of follow-up (depending on the end of the RSV season at different locations) after vaccination of 20,000 subjects, perform primary analyses. Continue if the success criterion for the primary endpoint is met with follow-up of subjects who are willing to continue participation for assessment of durability of protection starting 1 year after vaccination. **Scenario 2** If the number of LRTD events from season 1 did not meet the sample size requirement for the primary endpoints analyses towards the end of the RSV season, perform futility analyses (by an independent vendor). If the futility criterion is not met, continue to enroll,

vaccinate, and follow up further subjects for at least 1 RSV season (for up to 12 months) and continue follow up of subjects from season 1 who are willing to continue participation for assessment of durability of protection starting 1 year after vaccination.

Approximately 4000 additional subjects will be randomized into 2 treatment groups receiving either placebo or MVA-BN-RSV vaccine and will be followed for at least one RSV season (6 months up to 12 months). Exact numbers of subjects required will be based on the number of events already observed and the probability of observing the additional required number of events, conditional on the observed overall event rate in season 1 (section 11.5).

Table 1 Treatment Groups

Group	N	Age [years]	Vaccination	Dose [Inf.U/0.5 mL] IM	Durability Follow up only[b]	Season 2[a]
1	10,000	≥60	Placebo	-	8000[b]	**2000**
2	10,000	≥60	MVA-BN-RSV	at least 3×10E8 Inf.U	8000[b]	**2000**
Total	**20,000 subjects for primary endpoints** Approximately 16,000 (~20% dropout) for second year follow up after vaccination					**24,000**

Abbreviations: IM = intramuscular; Inf.U = infectious units; N = number of subjects per group.

[a] If predefined number of required events is not met, further subjects (e.g., 2000 to 4000) will be enrolled and vaccinated: sample size might be adapted based on number of events after first RSV season.

[b] Subjects vaccinated before RSV season 1 who are willing to participate in the follow up for durability. They will be followed up for respiratory tract disease during a second year after vaccination if trial is not stopped due to futility.

Subjects will be stratified by age into 4 cohorts by years: 60 to 64 (up to 10% of total vaccinated subjects), 65 to 74; 75 to 84 (approximately 25% of subjects) and ≥85 (approximately 5%).

Enrollment should include at least 20% of overall subjects with at least 1 comorbidity associated with higher risk of LRTD, including chronic cardiac diseases and chronic lung diseases (asthma and chronic obstructive pulmonary disease [COPD]), congestive heart failure (CHF), and hypertension. All subjects will complete a frailty index questionnaire at screening/vaccination visit.

Subjects will be followed for disease surveillance via monthly telephone calls and electronic alerts 3× weekly from 2 weeks after vaccination until the end of the RSV season (up to 12 months after vaccination), to trigger a symptom visit (SV) if any respiratory tract symptoms are noted. Surveillance will proceed until up to 12 months with a planned 6-month telephone visit. If the trial continues after the analysis at the end of RSV season 1, subjects will be followed for disease surveillance up to 24 months.

Except for the combined screening and vaccination visit (SCR/V1), symptom visits (SV) for collection of nasopharyngeal swabs for PCR to confirm RSV disease, unscheduled visits (e.g., due to AEs and evaluation of symptoms), and visits for blood draws for immunogenicity testing in a subgroup, all contacts with the subjects will take place by telephone calls.

At the time point of vaccination (Day 1) until Day 8, solicited local and systemic symptoms will be recorded daily in an electronic patient diary. Any symptom(s) will be followed up until resolution.

Starting after vaccination, sites will call subjects monthly (calendar month) to assess for new RSV symptoms (Disease Surveillance Telephone Visits). Telephone assessment includes inquiring of new symptoms, worsening of pre-existing symptoms from prior reported illness, resolution of symptoms, unsolicited adverse events and serious adverse events and follow up after vaccination.

In addition to the telephone calls, subjects will get a text alert 3 times per week from the electronic patient reported outcome (ePRO) application asking about the presence of respiratory symptoms. Additional phone calls will be made in case the subject is not responsive to text alerts for more than a week.

In case of any protocol-defined RSV-related symptoms, an onsite SV will be performed (target is within 72 hours after symptom occurrence, within 5 days is acceptable). Clinical evidence of the signs and symptoms needs to be verified and documented by a medical professional by questioning the subject regarding symptoms and performing specific exams and / or tests assessing, e.g., pharyngitis, oxygen saturation, respiratory rate, imaging evidence of new onset of bronchitis, bronchiolitis, or pneumonia and start of questionnaires EQ-5D-5L and 15D (4.1.4).

A nasopharyngeal swab must be taken to confirm RSV disease by PCR testing at the central lab.

All subjects who experience any RSV-specific symptoms need to complete the RiiQ about their symptoms at symptom onset. The questionnaire is provided to the subjects via the ePRO application and will be filled out for 7 days and up to 20 days in case of ongoing symptoms, independent of whether RSV is confirmed by PCR.

Selected sites:

- Serum and PBMC samples will be taken from a defined sub-population for immunogenicity analysis at specific sites.

Additional specifications after futility analysis and continuation of the trial for follow-up of durability or/and inclusion of further subjects:

Scenario 1 above:
Blinding of subject-level treatment assignment will remain for follow-up of durability starting approximately 12 months after vaccination. A blinded statistician will be assigned to continue to support the operational team.

Scenario 2 above:
The entire team will remain blinded until subjects vaccinated after the first RSV season are followed up until at least the end of the RSV season 2 (up to 24 months after vaccination).

A detailed visit schedule is provided in the Trial Schedule section 1.4

Analysis and Reports	The primary analyses will occur when at least 53 LRTD (≥2 symptoms) events have been observed. Of those, at least 22 LRTD events need to have at least 3 symptoms. The primary endpoints and the key secondary efficacy endpoint of RSV-associated ARD will then be formally tested. The fixed-sequenced method will be used to control the overall familywise type I error rate. The hypothesis related to vaccine efficacy for LRTD with ≥3 symptoms will be tested against the null hypothesis of ≤20% first, followed by testing the hypothesis related to vaccine efficacy for LRTD with ≥2 symptoms against the null hypothesis of ≤20%. Finally, the hypothesis related to vaccine efficacy for ARD will be tested against the null hypothesis of ≤20%. The main analyses will be based on a Cox proportional hazards regression model with treatment and age groups as fixed factors. Vaccine efficacy is defined as 1 minus the hazard ratio.

	An analysis for vaccine efficacy during the second year after vaccination (durability) and vaccine efficacy up to 2 years since vaccination (2-year vaccine efficacy) will be performed after the last visit is completed. If less than 53 LRTD with ≥2 symptoms events or less than 22 LRTD with ≥3 symptoms events are observed towards the end of the first RSV season, a futility analysis will be performed by an independent unblinded statistical service vendor and assessed by the Data Monitoring Committee (DMC) for the trial. Details can be found in section 4.4 and will be described in the DMC Charter. If the futility boundary is not crossed and the DMC recommends continuing, more subjects will be vaccinated in season 2. However, the number of subjects to be vaccinated in season 2 will be based on the number of events already observed (blinded). Primary analyses will be performed at the end of season 2 with combined data from the 2 seasons. Analysis for durability and two-year vaccine efficacy based on the subjects who are vaccinated in season 1 will also be performed at approximately the same time.
Eligibility Criteria Inclusion Criteria	1. Male and female subjects ≥60 years of age. 2. Informed Consent signed by the subject. 3. Subjects may have one or more chronic medical conditions e.g., mild to moderate underlying illnesses such as chronic cardiac diseases and chronic lung diseases (asthma and chronic obstructive pulmonary disease [COPD]), congestive heart failure (CHF), hypertension, type 2 diabetes mellitus, hyperlipoproteinemia, or hypothyroidism, that is clinically stable as assessed by the investigator. 4. Absence of known, current, and life-limiting diagnoses that render survival to completion of the protocol unlikely. 5. Ability to comply with trial requirements, which necessitates access to transportation to on-site visits, including symptom visits for a nasopharyngeal swab. 6. Willingness and ability to utilize an application on a personal device (i.e., smartphone, tablet, etc.) or a provisioned device to record solicited events and record all per protocol required data during the surveillance period. 7. For women of childbearing potential (WOCBP), agreement to use an acceptable method of contraception during the trial and a negative urine pregnancy test within 24 hours prior to vaccination.

	Note: A woman is considered of childbearing potential unless post-menopausal (defined as ≥12 months without a menstrual period) or who is permanently sterile (i.e., is at least 6 months post-surgical sterilization via hysterectomy or bilateral oophorectomy). Acceptable contraception methods are restricted to abstinence, barrier contraceptives, intrauterine devices (IUD), intrauterine systems (IUS), licensed hormonal products or tubal ligation.
Exclusion Criteria	1. History of or current clinical manifestation of any serious medical condition that in the opinion of the investigator would compromise the safety of the subject, confound data interpretation, or would limit the subject's ability to complete the trial. 2. History of or active autoimmune disease, including diabetes mellitus type I. Vitiligo or hypothyroidism requiring thyroid replacement therapy are not exclusions. Rheumatoid arthritis not requiring immunomodulatory and/or immunosuppressant treatment is not an exclusion. 3. Known or suspected impairment of immunologic functions, including chronic inflammatory bowel disorders. 4. Clinically significant mental disorder that would prevent patients from giving informed consent and complying with study procedures (e.g., completion of the electronic diary). 5. Active or recent (within 6 months before enrollment) history of chronic alcohol abuse. 6. History of a serious reaction to any prior vaccination or Guillain-Barré syndrome (GBS) within 6 weeks of any prior influenza immunization. 7. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine, e.g., tris(hydroxymethyl)-amino methane, chicken embryo fibroblast proteins, gentamycin, ciprofloxacin; this includes: • Known allergy to eggs or aminoglycosides. • History of anaphylaxis or severe allergic reaction to any vaccine. 8. Any administration or planned administration of: • A licensed live or vector-based vaccine within 30 days prior to or after trial vaccine administration. • A licensed inactivated or ribonucleic acid (RNA)-based vaccine within 14 days prior to or after trial vaccine administration. 9. Previous vaccination with an RSV vaccine, or any planned vaccination with an RSV vaccine other than the trial vaccine.

10. Planned chronic, systemic administration (defined as more than 14 days) of >10 mg prednisone (or equivalent)/day or any other systemic use of immune-modifying drugs during a period starting from 3 months prior to first administration of the trial vaccine and ending at the End of Study Visit (EOS). The use of topical, inhaled, ophthalmic and nasal glucocorticoids is permitted.
11. Administration or planned administration of immunoglobulins and/or any blood products during a period starting from 3 months prior to first administration of the trial vaccine and during the trial
12. Known uncontrolled coagulation disorder. Anticoagulant treatment under adequate control for cardiovascular prophylaxis or prophylaxis of thromboembolic disease or stroke in the setting of atrial fibrillation are permitted.
13. Use of any investigational or non-registered drug or vaccine other than the trial vaccine within 30 days prior to the administration of the trial vaccine, or planned administration of such a drug or vaccine between enrollment in the trial and until 4 weeks after the trial vaccine administration.
14. Involvement with this trial as research personnel.
15. Planned leave or holiday of 4 consecutive weeks or more during the RSV season covered by the study, that would prohibit the reporting of ARI cases and attendance at symptom visits.
16. Pregnancy or breast-feeding.

1.4 Trial Schedule

1.4.1 Trial Schedule for Vaccination and Site Follow Up During RSV Season after Vaccination

Visit (V)	**Screening Vaccination**	**Subgroup: Immunogenicity**					
	Visit 1 Screening and Vaccination	**Visit 2a only for PBMC subgroup[a]**	**Visit 2b only for serum subgroup[b]**	**Disease Surveillance Visits[c] (by phone)**	**6-month FU Visit[d] (by phone)**	**End of Study Visit (EOS)[e] (by phone)**	**Symptom Visit (SV)**
Time point	**Day 1**	**Day 7 to Day 10**	**Day 14 to Day 16**	**Monthly until to the EOS Visit starting 1 month after vaccination (+/- 4 days)**	**6 months after vaccination (from wk 26 to wk 28)**	**12 months after vaccination (from wk 52 to wk 54)**	**Within 5 days (target 3 days) of symptom onset**
Informed consent[f]	■[f]						
Complete physical examination[g] measurement of body height and weight, BMI assessment	■						
Eligibility evaluation	■						
Medical history (self-reported)	■						
Assessment for previous RSV, COVID, pneumococcal and influenza vaccination	■						
Targeted physical exam/symptom assessment[h]							■[h]
Vital signs (BP, HR, RR, Temp, SpO_2)	■						■
Recording of prior/concomitant medication	■	■	■	■[i]			■

Visit (V)	Screening Vaccination	Subgroup: Immunogenicity					
	Visit 1 Screening and Vaccination	Visit 2a only for PBMC subgroup [a]	Visit 2b only for serum subgroup [b]	Disease Surveillance Visits [c] (by phone)	6-month FU Visit [d] (by phone)	End of Study Visit (EOS) [e] (by phone)	Symptom Visit (SV)
Time point	**Day 1**	**Day 7 to Day 10**	**Day 14 to Day 16**	**Monthly until to the EOS Visit starting 1 month after vaccination (+/- 4 days)**	**6 months after vaccination (from wk 26 to wk 28)**	**12 months after vaccination (from wk 52 to wk 54)**	**Within 5 days (target 3 days) of symptom onset**
Counseling on avoidance of pregnancy for WOCBP [j]	■						
Download of app or provision of a device for ePRO collection with subject instruction [k]	■						
Randomization	■						
Vaccine administration and subject observation ≥30 minutes	■						
Onsite recording of immediate AEs/SAEs after vaccination	■						
Recording of solicited local and systemic AE for 8 days starting at vaccination / ePRO (see 1.4.3)	■						
Review/discussion of solicited local & systemic symptoms recorded in ePRO application		■ [l]	■ [l]	■ [l]	■ [l]	■ [l]	■ [l]
Recording of unsolicited AEs		■	■	■ [m]	■ [m]	■ [m]	■ [m]
Recording of SAEs/hospitalizations		■	■	■ [n]	■ [n]	■ [n]	■ [n]

Visit (V)	**Screening Vaccination**	**Subgroup: Immunogenicity**					
	Visit 1 Screening and Vaccination	**Visit 2a only for PBMC subgroup [a]**	**Visit 2b only for serum subgroup [b]**	**Disease Surveillance Visits [c] (by phone)**	**6-month FU Visit [d] (by phone)**	**End of Study Visit (EOS) [e] (by phone)**	**Symptom Visit (SV)**
Time point	**Day 1**	**Day 7 to Day 10**	**Day 14 to Day 16**	**Monthly until to the EOS Visit starting 1 month after vaccination (+/- 4 days)**	**6 months after vaccination (from wk 26 to wk 28)**	**12 months after vaccination (from wk 52 to wk 54)**	**Within 5 days (target 3 days) of symptom onset**
Review/discussion of respiratory symptoms [o] and documentation		■	■	■	■	■	
Clinical evaluation of respiratory symptoms							■[p]
X-ray							□[p]
Return of ePRO devices (if provisioned)					■[q]	■[q]	
Laboratory Tests							
Urine pregnancy test for WOCBP	■[r]						
PBMC sample collection[a]	■[a]	■[a]					
Serum sample collection[b]	■[b]		■[b]				
Nasopharyngeal swab collection to confirm RSV disease by PCR							■
Questionnaires							
TFI (via ePRO, see 1.4.3)	■						
EQ-5D-5L, 15D, RiiQ (via ePRO, see 1.4.3)[s]	■				■[s]	■[s]	■[s]

Abbreviations: AE = adverse event; ARD = acute respiratory disease; BMI = body mass index; BP = blood pressure; CDC = Centers for Disease Control and Prevention; COVID = coronavirus disease; ePRO =electronic patient reported outcome; EOS = End of Study Visit; EQ-5D-5L = EuroQol 5-Dimension 5-Level health questionnaire; FU = follow-up; HR = heart rate; IUD = intrauterine device; IUS = intrauterine systems; LRTD = lower respiratory tract

disease; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; RiiQ = Respiratory Intensity and Impact Questionnaire; RR = respiratory rate; RSO = respiratory symptom onset; RSV = respiratory syncytial virus; SAE = serious adverse event; SpO_2 = oxygen saturation; SV = symptom visit; TFI = Tilburg Frailty Indicator; 15D = 15-Dimension health-related quality of life instrument; V = Visit; WOCBP = woman of childbearing potential;

■ = mandatory; ☐ = if indicated/if applicable

[a] A defined sub-population (300 subjects, 150 per study arm) at designated sites will have a PBMC blood draw at Screening, prior to vaccination, and at Visit 2a, an onsite visit 1 week after vaccination (at Day 7 to 10), for collection of 64 mL of blood for immunogenicity analysis.

[b] A defined sub-population (600 subjects, 300 per study arm) at designated sites will have an additional blood draw for serum analysis at Screening, prior to vaccination, and at Visit 2b, an onsite visit 2 weeks after vaccination (at Day 14 to 16), for collection of 8.5 mL of blood for immunogenicity analysis.

[c] Disease surveillance telephone calls to assess onset and symptoms of a respiratory disease. If symptoms are present, subjects need to be called in for symptom visits within 72 hours (up to 5 days is allowed) after first symptoms. Monthly surveillance telephone calls start 1 calendar month (+/- 3 days) after vaccination until the End of Study Visit.

[d] The 6-month FU visit might coincide with the end of the RSV season (defined by the CDC surveillance data, provided by the CDC at https://www.cdc.gov/surveillance/nrevss/rsv/index.htmL) and therefore might be combined with the EOS Visit. The site will confirm any SAEs.

[e] End of Study visit might coincide with the 6 month follow up visit in case the RSV season is over and the number of cases are met (futility analysis) or might coincide with the first visit to follow up for durability FU-D1 see Section 1.4.2 for details.

[f] The informed consent form has to be signed by the subject before any study-related tasks are performed. The allowed time period for informed consent starts 8 days prior to vaccination and can be obtained prior to or on the same day as the vaccine is administered.

[g] Excludes breast, genital, and rectal examinations.

[h] The 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.

[i] Recording of concomitant medication until 29 days after vaccination.

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

[k] Download of the application; if subject does not have a suitable device or does not agree to download the application to their phone, a device with an ePRO application will be provisioned.

[l] Solicited symptoms are reviewed and discussed if symptoms are still ongoing at the times of these visits.

[m] Recording of new, non-serious, unsolicited AEs will be performed until 29 days after vaccination; these symptoms are reviewed and discussed if symptoms are still ongoing at the times of these visits.

[n] New SAEs and ongoing SAEs.

[o] Symptoms associated with potential RSV disease (as defined in the LRTD/ARD definitions) are to be discussed and reported throughout the course of the trial, irrespective of seriousness.

[p] In case of suspected bronchitis, bronchiolitis, or pneumonia when neither the LRTD criteria of hypoxemia nor respiratory rate criteria are met, an x-ray is to be performed for evidence. If the site does not have a radiologist or x-ray device, the subjects need to be transferred to a radiology department for x-ray imaging.

[q] If a provisioned device is used, the device needs to be returned/shipped by the subject (instructions and shipment forms need to be discussed and included in the device package) at the end of the trial.

[r] A urine pregnancy test has to be performed within 24 hours prior to vaccination, only in WOCBP.

[s] All questionnaires will be filled out at baseline prior to vaccination and EQ-5D-5L and 15D will be completed at 6 and 12 month after vaccination. RiiQ will restart at symptom onset (e.g., subject ticks “yes” to symptoms at ePRO reminder or during a site telephone call) and completed from then onward. Completion of EQ-5D-5L and 15D restarts at symptom visit when nasal swab is taken. Further details are given in a study specific instruction.

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

1.4.2 Trial Schedule for Follow-Up for Durability of Protection

This schedule will be followed by all subjects who enter the durability follow-up, which will start approximately 1 year after vaccination and continue until approximately 2 years after vaccination. Potential durability of protection by the MVA-BN-RSV vaccine will be assessed. No further vaccination will be given.

	Fixed Visit Schedule				
Visit (V)	**Durability Follow-up Visit (FU-D1)[a]**	**Disease Surveillance Visit[b] (by phone)**	**6 months FU-D Visit[c] Telephone Visit**	**End of Durability FU-D End of Trial Telephone Visit[n]**	**Symptom Visit (SV)[d]**
Time point	**Day 1 (12 months after vaccination)**	**Monthly (+/- 3 days) until end of durability FU-D**	**6 months after FU (from wk 26 to wk 28) -D1/18 months after vaccination**	**Up to 12 months (from wk 52 to wk 56) after FU-D1/24 months after vaccination**	**Within 5 days (target 3 days) of symptom onset**
General Procedures					
Informed consent confirmation	■				
Targeted physical exam/symptom assessment[e]	■[e]				■[e]
Vital signs[f]	■				■
SAE/hospitalization recording	■[g]	■[h]	■[h]	■[h]	■[h]
Clinical evaluation of respiratory symptoms					■
X-ray					■[i]
Electronic Diary					
Re-Check of ePRO application[j]	■				
Review/discussion of respiratory symptoms		■	■	■	
Return of provided device used for ePRO collection			□[k]	□[k]	

	Fixed Visit Schedule				
Visit (V)	**Durability Follow-up Visit (FU-D1)[a]**	**Disease Surveillance Visit[b] (by phone)**	**6 months FU-D Visit[c] Telephone Visit**	**End of Durability FU-D End of Trial Telephone Visit[n]**	**Symptom Visit (SV)[d]**
Time point	**Day 1 (12 months after vaccination)**	**Monthly (+/- 3 days) until end of durability FU-D**	**6 months after FU (from wk 26 to wk 28) -D1/18 months after vaccination**	**Up to 12 months (from wk 52 to wk 56) after FU-D1/24 months after vaccination**	**Within 5 days (target 3 days) of symptom onset**
Laboratory					
Nasopharyngeal swab collection to confirm RSV disease by PCR					■
PBMC sample collection	■[l]			■[l]	
Serum sample collection	■[m]			■[m]	

Abbreviations: CDC = Centers for Disease Control and Prevention; EOS = end of study; ePRO =electronic patient reported outcome; EQ-5D-5L = EuroQol 5-Dimension 5-Level health questionnaire; FU-D = follow-up durability; LRTD = lower respiratory tract disease; PCR = polymerase chain reaction; RSV = respiratory syncytial virus; SAE = serious adverse event; SV = symptom visit; V = Visit; 15D = 15-Dimension health-related quality of life instrument

■ = mandatory; □ = if indicated/if applicable

[a] FU-D1 might coincide with the -EOS Visit 12 months after vaccination.

[b] Telephone surveillance calls to assess onset and symptoms of a respiratory disease. If yes, subjects need to be called in for symptom visits within 72 hours (up to 5 days accepted) after first symptoms. Monthly telephone calls start 1 calendar (+/- 3days) month after the first visit for durability follow up.

[c] This Visit might coincide with the end of an RSV season (US: defined by the CDC surveillance data, provided by the CDC https://www.cdc.gov/surveillance/nrevss/rsv/index.htmL).

[d] An SV onsite is to be performed within 72 hours (up to 5 days accepted) after onset of any respiratory symptom.

[e] The 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.

[f] Vital signs to be assessed: blood pressure, heart rate, body temperature.

[g] SAEs, occurring from last SAE assessment telephone call/site visit until start visit of subsequent year 2 will be collected retrospectively.

[h] New SAEs and changes to ongoing SAEs, including any hospitalization due to respiratory tract disease.

[i] In case of suspected bronchitis, bronchiolitis, or pneumonia when neither the LRTD criteria of hypoxemia or respiratory rate are met, an x-ray is to be performed for evidence of LRTD. In case the site does not have a radiologist or x-ray device, the subjects need to be transferred to a radiologist department for the x-ray imaging.

[j] Check of previously handed out device or downloaded application to implement any required updates and/or new instructions. If a subject has not fully completed all EQ-5D-5L or 15D questionnaires after a Symptom Visit occurring during season 1, these questionnaires will be continued during the durability part of the trial. No new cycles of questionnaires will be started once the durability part of the trial has begun.

[k] In case that last visit is a telephone visit, the device needs to be shipped back by the subject (instructions and shipment forms need to be discussed and included in the device package).

[l] defined sub-population vaccinated before the first season (300 subjects, 150 per study arm) at designated sites will have a PBMC blood draw at Screening, prior to vaccination, and at Visit 2a, an onsite visit 1 week after vaccination (at Day 7 to 10), approximately 1 year and 2 years after vaccination for collection of 64 mL of blood for immunogenicity analysis.

[m] A defined sub-population vaccinated before the first season (600 subjects, 300 per study arm) at designated sites will have an additional blood draw for serum analysis at Screening, prior to vaccination, and at Visit 2b, an onsite visit 2 weeks after vaccination (at Day 14 to 16), approximately 1 year and 2 years after vaccination for collection of 8.5 mL of blood for immunogenicity analysis.

[n] All subjects participating in the immunogenicity subgroup and need to return for a 2 year blood draw (PBMC/serum) at FU-D

1.4.3 Trial Schedule for Subject Use of ePRO Application

Time point	Day 1 (Vaccination)	Days 2 to 8 after Vaccination						6 Months after SV	12 Months after SV
Instruction on ePRO application[a]	■								
TFI part B completion	■								
Recording of solicited local and systemic symptoms / memory aid[b]	■	■[b]							
RiiQ questionnaire completion[c]	■[d]								
EQ-5D-5L completion[c]	■[d]							■	■
15D completion[c]	■[d]							■	■
Subject with suspected RSV									
			Respiratory Symptom Onset (RSO) Day 1	**Days 2 to 8 from RSO (up to 21 days total)**					
RiiQ questionnaire completion[c]			■	■[e]					
			Symptom Visit (SV) Day 1		**Day 6 from SV**	**1 Month after SV**	**3 Months after SV**	**6 Months after SV**	**12 Months after SV**
EQ-5D-5L completion[f,c]			■		■	■	■	■	■
15D completion[f,c]			■		■	■	■	■	■
Reminders to record any respiratory		<-------	----------	----------	--------	---------	----------	----------	--------->

symptoms (3 times a week)									

Abbreviations: ePRO =electronic patient reported outcome; EOS = end of study; EQ-5D-5L = EuroQol 5-Dimension 5-Level health questionnaire; RiiQ = Respiratory Intensity and Impact Questionnaire; RSO = respiratory symptom onset; SV = symptom visit; TFI = Tilburg Frailty Indicator part B; 15D = 15-Dimension health-related quality of life instrument

[a] If subject does not have a suitable device or does not agree to downloading of the application to their phone, a device with the ePRO application will be provisioned.

[b] Solicited local and general symptoms are recorded for 8 days by the subject. If any symptoms are ongoing, they are recorded until resolution.

[c] Further details on questionnaires are summarized in a study specific instruction.

[d] Baseline evaluation of questionnaires done at screening/vaccination visit before any symptoms occur

[e] RiiQ completion may continue for up to a maximum of 21 days (20 days from symptom onset) as long as symptoms are ongoing and RSV PCR test is confirmed positive.

[f] The long-term schedule of questionnaire completion at 1, 3, 6, and 12 months after a symptom visit will be stopped if/when a subject has another RSV symptom episode/symptom visit, and the whole schedule will be restarted. The schedule should be completed beyond season 1 follow-up for efficacy if the durability part of the trial has started.

2 Background Information and Scientific Rationale

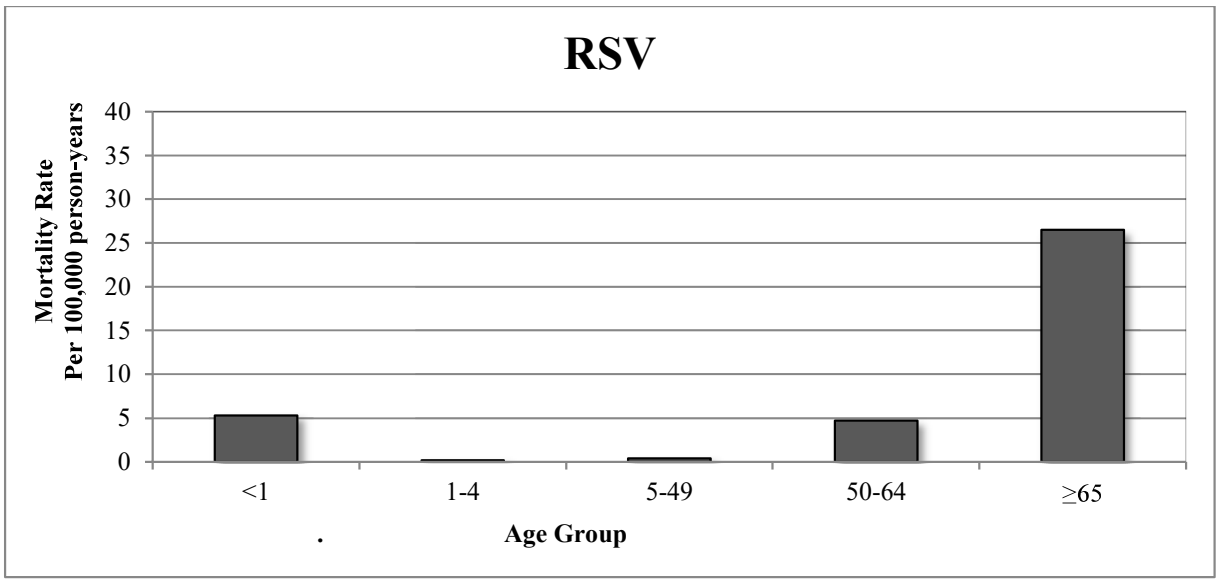
2.1 Introduction to RSV Disease

Respiratory Syncytial Virus (RSV) is a ribonucleic acid (RNA) virus of the Pneumoviridae family. The RSV genome encodes eleven proteins, 2 of which play a key role for pathogenesis and are important antigens for generating protective immunity: Glycoprotein G, responsible for viral attachment, and the fusion protein F, which mediates viral penetration and syncytium formation. There are 2 different subtypes of RSV circulating concurrently, A and B, which are distinguished mainly by variations within the G protein (Hall, 2001).

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

RSV has been recognized as a significant cause of respiratory illness in all age groups. The disease is predominated by febrile upper respiratory tract infections (URTI) in older children and adults and is the leading cause of LRTD in newborns, infants and younger children (Azzari, 2021). While the burden of RSV is highly recognized in the pediatric population, particularly in the very young and those with cardio-respiratory disease, RSV disease is also a serious health concern in the older adults/ elderlies and in immunocompromised adults. Indeed, about 78% of deaths due to RSV-related underlying respiratory and circulatory disease occur among the population ≥65 years of age (Thompson, 2003) (see Figure 1).

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



RSV disease in the older adults, elderly and high-risk adult population in the United States (US) has shown to be a significant health issue. Approximately 170,000 hospitalizations and 10,000 deaths occur annually in people over the age of 65 years (Murata, 2007). Epidemiological surveys performed over several RSV seasons indicate that 3-7% of healthy elderly and 4-10% of high-risk adults are diagnosed with RSV per year (Korsten, 2021). Similar to influenza, RSV disease has been identified as resulting in significant burden in older individuals, causing severe lower respiratory disease such as pneumonia and exacerbation of chronic obstructive pulmonary disease (COPD). COPD patients are even suspected to constitute a reservoir for RSV.

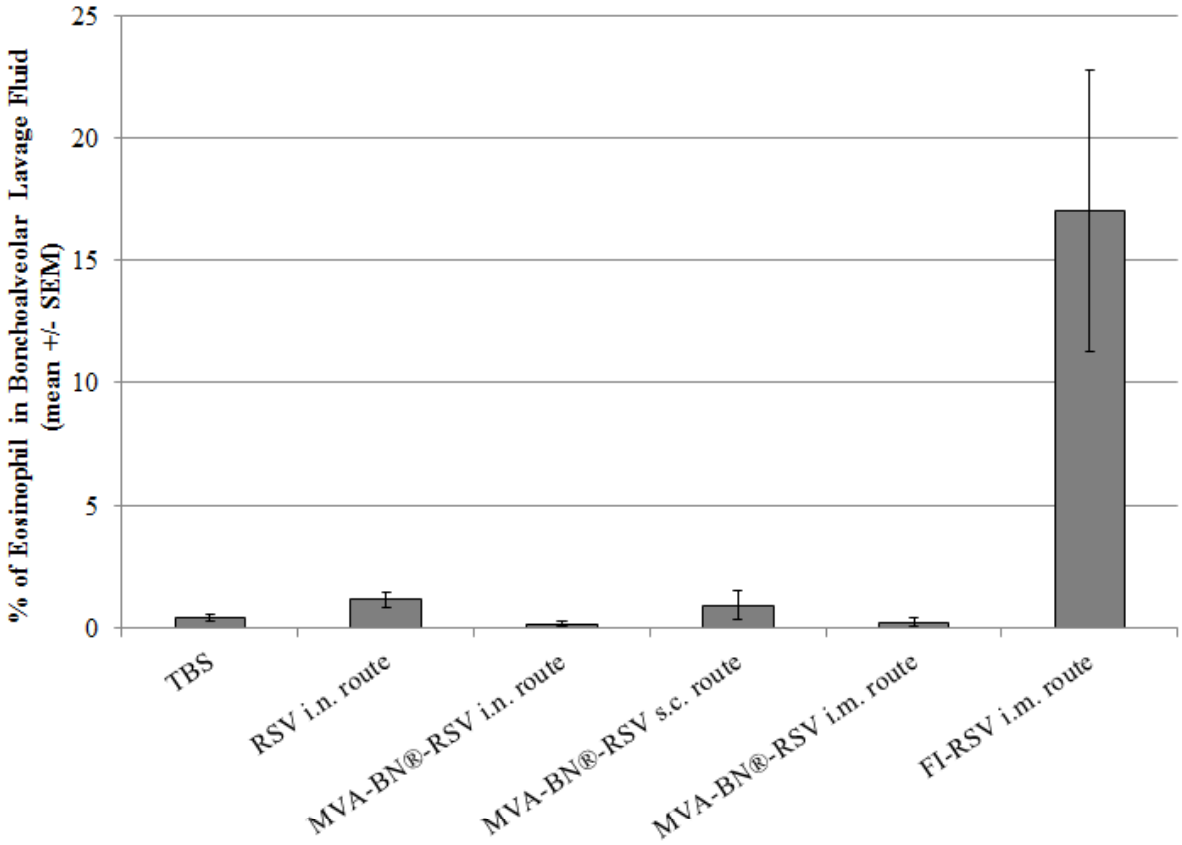
The immunologic factors that are responsible for protection against RSV are not completely understood. RSV infection induces secretory antibodies, serum neutralizing antibodies and T-cell immunity, with some protective effect against LRTD provided by high levels of serum neutralizing antibodies (Groothuis, 1993, Walsh, 2004). The F and G proteins are the main targets for induction of neutralizing antibodies, and whilst there is a trend between higher levels of neutralizing antibodies and protection from severe disease, it is still possible to experimentally re-infect adults with RSV regardless of their systemic antibody levels. A deficiency in RSV F-specific T-cell responses has also been suggested to contribute to susceptibility to severe RSV disease in older adults and the elderly population (Hall, 1991; Cherukuri, 2013). However, naturally acquired immunity is neither complete nor durable (Glezen, 1986; Hall, 2001).

An estimated 90% of the population experiences their first RSV infection within the first 2 years of life (Glezen, 1986; Castilow, 2007). However, immune responses after primary infection in young infants are usually weak and short-lived due to immunological immaturity and suppression by maternal antibodies (Karron, 1999; Power, 2008). Re-infections with RSV are common at all

ages, although of decreasing severity, since with recurring infections the disease becomes more limited to the upper respiratory tract (Glezen, 1986). Morbidity and disease severity increases again in people >50 years (McClure, 2014).

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

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



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

2.2 MVA-BN-RSV Vaccine

Bavarian Nordic (BN) has developed a vaccine candidate against RSV by including RSV surface protein-encoding genes from both circulating RSV subtypes (A and B), as well as conserved internal antigen-encoding genes of the virus, into the MVA-BN vector. The vaccine is designed for a broad reactivity to prevent acute and severe respiratory tract infection caused by RSV (e.g., LRTD such as RSV bronchiolitis and pneumonia) both in the elderly and in adults with

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

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

- The RSV surface proteins F (Fusion) and G (Glycoprotein for subtype A and B), which induce humoral and cell-mediated immunity in animal models (mice and cotton rats).
- Two internal proteins N (Nucleoprotein) and M2-1 (a transcription elongation factor), which are expected to enhance immunogenicity, especially in terms of cytotoxic T-cell responses, but also cross-protection to infection with other subtypes, since these 2 proteins are highly conserved among the different circulating RSV subtypes.

2.3 Origin and Characteristics of MVA-BN Vector Backbone

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

MVA was derived from the serial passage of chorioallantois vaccinia Ankara, a VACV strain used during the smallpox eradication program. During this passaging, MVA suffered a multitude of mutations within its genome, including 6 major deletions, resulting in the loss of 13% (approximately 27 kbp) of original genetic information (Antoine, 1998). The deletions affected a number of virulence and host range genes (Antoine, 1998; Rosel, 1986; Meyer, 1991) and as a consequence, MVA exhibits a severely restricted host range in most mammalian cell types (Sutter, 1992; Carroll, 1997; Blanchard, 1998; Drexler, 1998). Although MVA exhibits strongly attenuated replication in susceptible cell types, its genes are efficiently transcribed, with the block in viral replication occurring at the level of virus assembly and egress (Sutter, 1992; Carroll, 1997).

Bavarian Nordic, an international biopharmaceutical company, has developed a proprietary strain of modified vaccinia Ankara (MVA-BN, trade name IMVANEX in the European Union, IMVAMUNE in Canada, and JYNNEOS in the United States) for use as a prophylactic smallpox vaccine.

MVA-BN is a highly attenuated, purified live vaccine produced under serum-free conditions in chicken embryo fibroblast cells. In contrast to replicating smallpox vaccines, MVA-BN can be administered by subcutaneous (SC) or IM injection, and not by scarification. The standard route and schedule of MVA-BN are 2 subcutaneous injections administered 4 weeks apart. Since MVA-BN is non-replicating in human cells it does not form vesicles (“takes”) (Mayr, 1975).

For IMVANEX, a marketing authorization under exceptional circumstances was granted by the European Commission in July 2013. A marketing authorization for IMVAMUNE® was granted by Health Canada in November 2013, for JYNNEOS in the United States September 2019.

2.4 Summary of Non-clinical Studies with MVA-BN-RSV Vaccine

BN has performed more than 20 good laboratory practice (GLP)-compliant safety studies for either the vector backbone MVA-BN or MVA-BN-based recombinant vaccines. These studies demonstrated that all products investigated are safe and well tolerated. Similarly, the current MVA-BN-RSV vaccine candidate (MVA-mBN294B) was tested in 2 GLP-compliant repeat-dose toxicity and local tolerance studies in rabbits and found to be safe. MVA-BN-RSV was locally well tolerated at the dose of 1×10E8 $TCID_{50}$ (Tissue Culture Infectious Dose 50% corresponding to 1×10E8 infectious units [Inf.U]) even when administered 4 times (in 3-week intervals). There were no MVA-BN-RSV-related mortalities or clinical observations and no vaccine-related findings in the hematology, clinical chemistry, and histopathology. At 2×10E9 Inf.U, a 4-fold higher dose than the maximal human dose of 5×10E8 Inf.U, adverse lesions at injection sites were observed 2 days after the fourth administration with ongoing reversibility after a 28-day recovery period. Again, there were no mortalities or relevant clinical signs. Transient changes in hematology and biochemistry parameters were most likely related to inflammation at the injection site, reflecting induced immune responses by the vaccine. At pathology, there were no systemic findings. Findings were related to the antigenic stimulation by the test item elicited at the injection sites.

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

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

To date, 23 clinical trials evaluating the safety and immunogenicity of MVA-BN have been completed. More than 8900 subjects have been vaccinated with MVA-BN in completed clinical trials, including risk groups with contraindications to conventional smallpox vaccines, such as human immunodeficiency virus (HIV)-infected subjects and subjects with atopic dermatitis. Further, MVA-BN has been evaluated in adults and older adults, i.e., subjects 56 to 80 years of age.

In total, BN has evaluated the safety and immunogenicity of MVA-BN and MVA-BN-based recombinant vaccines in more than 51,000 subjects including healthy subjects, HIV-infected individuals, populations with cancer, and children in completed and ongoing clinical trials. In trials with recombinant MVA vaccines, doses up to 5×10E8 $TCID_{50}$ were administered applying varying schedules of repeat vaccinations. For example, a 3-dose schedule was used for recombinant HIV vaccines, and multiple vaccinations have also been performed in subjects receiving a recombinant therapeutic breast cancer vaccine (MVA-BN-HER2).

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

2.5.1 Safety Overview

In all completed and ongoing clinical trials, vaccinations with MVA-BN or MVA-BN-based vaccines have shown to have a good safety profile and to be well tolerated in all populations tested (healthy, elderly, immunocompromised) and at all doses tested (up to 5×10E8 $TCID_{50}$). No cases of death assessed as being possibly related have been reported for a subject in a clinical trial using MVA-BN or recombinant MVA-BN-based vaccines.

Results obtained from completed phase 1 and phase 2 trials and ongoing trials with several recombinant MVA-BN-based vaccines in healthy adults, children, people infected with HIV, and individuals with cancer demonstrate a similar safety profile as MVA-BN alone.

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

Adverse Drug Reactions (ADRs)

Table 2 summarizes the pooled ADR data of all completed MVA-BN trials. The safety profile of each of the trials with recombinant MVA-BN-based vaccines is comparable to the safety profile displayed in Table 2, as the occurrence of the ADRs is considered to be a reaction to the vector rather than the insert, based on previous experience with recombinant MVA-BN vaccine candidates.

Table 2 Suspected Adverse Drug Reactions Reported by ≥1% of Subjects in the Completed MVA-BN Clinical Trials[a] (N=8992[b])

Preferred Term	No. of subjects	Frequency
Injection site pain	7370	82.0%
Injection site erythema	5875	65.3%
Injection site swelling	4488	49.9%
Injection site induration	3988	44.4%
Injection site pruritus	3573	39.7%
Myalgia	3017	33.6%
Fatigue	2886	32.1%
Headache	2704	30.1%
Nausea	1316	14.6%
Rigors/chills	842	9.4%
Body temperature increased	269	3.0%
Pyrexia	259	2.9%
Injection site nodule	228	2.5%
Appetite disorder	218	2.4%
Arthralgia	209	2.3%
Injection site discolouration	207	2.3%

Pain in extremity	148	1.7%
Injection site haematoma	107	1.2%
Axillary pain	93	1.0%
Injection site warmth	90	1.0%

[a] POX-MVA-001, -002, -004, -005, -006, -007, -008, -009, -010, -011, -013, -023, -024, -027, -028, -029, -030, -031, -036, -037, -03X, HIV-NEF-004 and HIV-POL-002.

[b] 8 subjects exposed but not included in analysis. 7 subjects in POX-MVA-009 received Dryvax either on the same day or within 7 days after MVA-BN administration and were therefore not included to avoid a potential bias in the adverse event reporting. 1 subject in POX-MVA-029 was not vaccinated according to the randomization, therefore removed from analysis set.

[redacted]

The vast majority of these reactions were reported to be mild to moderate in intensity and resolved completely without intervention within the first 7 days following vaccination. To date, no trends have been identified that suggest the occurrence of any particular unexpected adverse reactions or classes of adverse reactions following vaccinations with MVA-BN.

Cardiac Signs and Symptoms

Based on observations with replicating smallpox vaccines, particular attention has been placed on monitoring for cardiac signs and symptoms in all clinical trials using MVA-BN. Despite close cardiac monitoring, no confirmed event indicating a case of myo-/pericarditis has been observed in any completed MVA-BN trial as well as from post-marketing experience so far. Furthermore, no confirmed case of myo-/pericarditis has been observed after administration with MVA-BN-RSV in any of the completed or ongoing studies.

Serious Suspected Adverse Drug Reactions

A total of 7 (7 out of 10,713 vaccinated subjects = 0.07 %) serious suspected ADRs have been reported for MVA-BN smallpox vaccine in completed and ongoing trials. All of them have been thoroughly reviewed by BN and the trial-specific Data Safety Monitoring Boards (DSMB) who concluded that the continued use of MVA-BN in a clinical setting presented no special risks to the subjects. No pattern regarding serious ADRs (SADRs) could be detected.

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

BN has evaluated the safety and immunogenicity of MVA-BN-based recombinant vaccines for several indications such as cancer, HIV, Ebola and measles. Results obtained from these phase 1 to phase 3 trials demonstrate a similar safety profile and vector immunogenicity as compared to MVA-BN alone.

In respect to the MVA-BN-RSV vaccine, subject exposure in the 3 clinical trials RSV-MVA-001, RSV-MVA-002, and RSV-MVA-015 amounted to a total number of 427 subjects. Hence, data were pooled to obtain a better overview of the safety profile of the vaccine.

The safety profile obtained from this pooled safety data analysis is considered as Reference Safety Information for the MVA-BN-RSV vaccine (see also the IB).

The safety population included 427 adult subjects from 18 to ≥70 years of age who were randomized to receive MVA-BN-RSV vaccine in various doses under placebo-controlled conditions. The frequency of the pooled adverse events (AEs) after vaccination with MVA-BN-RSV vaccine or placebo are listed in Table 3 (solicited AEs).

Solicited Adverse Events (8 days following vaccination)

In the analysis of unsolicited AEs, the post-vaccination period was restricted to 8 days following vaccination. The majority of all reported AEs represent solicited local and systemic reactions, such as injection site pain, injection site redness and injection site swelling or muscle pain, headache and fatigue. These findings are in line with those previously observed during the clinical development program of the MVA-BN backbone.

Table 3 Incidence of Solicited Local and Systemic Adverse Events (Per Subject) in Clinical Trials with MVA-BN-RSV[a] for 8 Days Starting at Day of Vaccination

	Treatment Groups						
	MVA-BN-RSV						**Placebo**
	Pooled **(N=424)[a]**	**1×10E7 $TCID_{50}$[b]** **(N=18)[c]**	**1×10E8 $TCID_{50}$/ Inf.U[b]** 18-69 yrs **(N=150)[d]**	**1×10E8 Inf.U** ≥70 yrs **(N=51)[e]**	**5×10E8 Inf.U** 18-69 yrs **(N=154)[f]**	**5×10E8 Inf.U** ≥70 yrs **(N=51)[e]**	**(N=129)[a]**
Preferred Term (MedDRA)	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**
Systemic							
Body Temperature	37 (8.7)	5 (27.8)	8 (5.3)	1 (2.0)	17 (11.0)	6 (11.8)	1 (0.8)
Chills	59 (13.9)	0 (0.0)	14 (9.3)	4 (7.8)	30 (19.5)	11 (21.6)	9 (7.0)
Fatigue	124 (29.2)	3 (16.7)	29 (19.3)	13 (25.5)	57 (37.0)	22 (43.1)	25 (19.4)
Headache	132 (31.1)	6 (33.3)	38 (25.3)	12 (23.5)	59 (38.3)	17 (33.3)	26 (20.2)
Muscle pain	160 (37.7)	2 (11.1)	42 (28.0)	9 (17.6)	86 (55.8)	21 (41.2)	15 (11.6)
Nausea	40 (9.4)	1 (5.6)	13 (8.7)	6 (11.8)	11 (7.1)	9 (17.6)	7 (5.4)
Local							
Induration	71 (16.7)	0 (0.0)	15 (10.0)	8 (15.7)	38 (24.7)	10 (19.6)	6 (4.7)
Itching	63 (14.9)	2 (11.1)	18 (12.0)	9 (17.6)	23 (14.9)	11 (21.6)	7 (5.4)
Pain	300 (70.8)	3 (16.7)	100 (66.7)	28 (54.9)	130 (84.4)	39 (76.5)	19 (14.7)
Redness	129 (30.4)	5 (27.8)	39 (26.0)	9 (17.6)	56 (36.4)	20 (39.2)	26 (20.2)
Swelling	91 (21.5)	1 (5.6)	27 (18.0)	7 (13.7)	45 (29.2)	11 (21.6)	6 (4.7)

Abbreviations: Inf.U = infectious units; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in specified group with available data (i.e., memory aid completed); RSV = respiratory syncytial virus; $TCID_{50}$ = tissue culture infectious dose 50; yrs = years

The number of AEs reported from RSV-MVA-015 may be subject to change after all data cleaning is completed at the end of the study.

[a] RSV-MVA-001, RSV-MVA-002, and RSV-MVA-015

[b] The dose for the phase 1 clinical trial was expressed as $TCID_{50,}$ corresponding to Inf.U

[c] RSV-MVA-001 only

[d] RSV-MVA-001 and RSV-MVA-002

[e] RSV-MVA-002 only

[f] RSV-MVA-002 and RSV-MVA-015

[g] RSV-MVA-002 and RSV-MVA-015

Table 4 Summary of Adverse Events (Per Subject) in Clinical Trials with MVA-BN-RSV[a]

	Treatment Groups						
	MVA-BN-RSV						**Placebo**
	Pooled (N=427)[a]	**1×10E7 $TCID_{50}$[b] (N=18)[c]**	**1×10E8 $TCID_{50}$/ Inf.U[b] 18-69 yrs (N=150)[d]**	**1×10E8 Inf.U ≥70 yrs (N=53)[e]**	**5×10E8 Inf.U 18-69 yrs (N=155)[f]**	**5×10E8 Inf.U ≥70 yrs (N=51)[e]**	**(N=129)[a]**
	Subjects (%)	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**
TEAE	379 (88.8)	15 (83.3)	123 (82.0)	45 (84.9)	148 (95.5)	48 (94.1)	95 (73.6)
Non-serious TEAE	376 (88.1)	15 (83.3)	121 (80.7)	44 (83.0)	148 (95.5)	48 (94.1)	94 (72.9)
SAE	12 (2.8)	0 (0.0)	4 (2.7)	3 (5.7)	3 (1.9)	2 (3.9)	5 (3.9)
Related[g] TEAE	232 (54.3)	8 (44.4)	60 (40.0)	23 (43.4)	104 (67.1)	37 (72.5)	52 (40.3)
TEAE Grade ≥3	56 (13.1)	0 (0.0)	15 (10.0)	6 (11.3)	28 (18.1)	7 (13.7)	6 (4.7)
Related[g] TEAE Grade ≥3	30 (7.0)	0 (0.0)	8 (5.3)	2 (3.8)	16 (10.3)	4 (7.8)	1 (0.8)

Abbreviations: Inf.U = infectious units; N = number of subjects in the specified group; RSV = respiratory syncytial virus; SAE = serious adverse event; TEAE = treatment-emergent adverse event; $TCID_{50}$ = tissue culture infectious dose 50; yrs = years.

Serious adverse events are considered treatment-emergent even if they exceed the 29-day follow-up period after each vaccination.

Adverse events (irrespective of seriousness) occurring after inoculation with the RSV challenge virus in trial RSV-MVA-015 are not included.

The number of AEs reported in RSV-MVA-015 may be subject to change after all data cleaning is completed at the end of the study.

[a] RSV-MVA-001, RSV-MVA-002, and RSV-MVA-015

[b] The dose for the phase 1 clinical trial was expressed as $TCID_{50}$, corresponding to Inf.U.

[c] RSV-MVA-001 only

[d] RSV-MVA-001 and RSV-MVA-002

[e] RSV-MVA-002 only

[f] RSV-MVA-002 and RSV-MVA-015

[g] Unsolicited or systemic solicited adverse events the investigator considered to have possible, probable, definite or missing relationship to trial vaccine; although solicited local events are by definition always adverse drug reactions, they are not included here

Unsolicited Adverse Events

In the analysis of unsolicited AEs, the post-vaccination period was restricted to 28 days following vaccination. The most frequently observed unsolicited AEs were URTI in the system organ class (SOC) Infections and Infestations, rhinorrhoea in the SOC Respiratory, Thoracic and Mediastinal Disorders and increased blood potassium in the SOC Investigations (Table 5).

Table 5 Incidence of Treatment-Emergent Unsolicited Adverse Events (Per Subject) in Clinical Trials with MVA-BN-RSV Reported by ≥1% of Subjects

	MVA-BN-RSV Pooled (N=427)[a]
System Organ Class Preferred Term (MedDRA)	**Subjects (%)**
Any Adverse Event	184 (43.1)
Infections and infestations	79 (18.5)
Upper respiratory tract infection	30 (7.0)
Pharyngitis	10 (2.3)
Sinusitis	10 (2.3)
Nasopharyngitis	7 (1.6)
Urinary tract infection	6 (1.4)
Respiratory, thoracic and mediastinal disorders	49 (11.5)
Rhinorrhoea	28 (6.6)
Cough	22 (5.2)
Nasal congestion	18 (4.2)
Productive cough	9 (2.1)
Dyspnoea	5 (1.2)
Investigations	39 (9.1)
Blood potassium increased	12 (2.8)
Blood sodium increased	8 (1.9)
General disorders and administration site conditions	29 (6.8)
Injection site pain	13 (3.0)
Fatigue	7 (1.6)
Injection site swelling	6 (1.4)
Injection site erythema	5 (1.2)
Musculoskeletal and connective tissue disorders	26 (6.1)
Myalgia	13 (3.0)
Gastrointestinal disorders	17 (4.0)
Nausea	6 (1.4)
Nervous system disorders	19 (4.4)
Headache	13 (3.0)
Injury, poisoning and procedural complications	10 (2.3)

Abbreviations: MedDRA = medical dictionary for regulatory activities; N = number of subjects in specified group; RSV = respiratory syncytial virus

Serious adverse events are considered treatment-emergent even if they exceed the 29-day follow-up period after each vaccination including the booster vaccination in the booster sub-study; this table contains unsolicited adverse events that occurred with a frequency of ≥1% on a pooled basis.

Adverse events (irrespective of seriousness) occurring after inoculation with the RSV challenge virus in the trial RSV-MVA-015 are not included.

Numbers of unsolicited adverse events from RSV-MVA-015 may be subject to change after all data cleaning is completed at the end of the study.

[a] RSV-MVA-001, RSV-MVA-002, and RSV-MVA-015

In summary, the majority of the solicited and unsolicited AEs over all clinical studies were mild (Grade 1) or moderate (Grade 2) in intensity, and all were transient in nature and resolved without sequelae. Grade 3 TEAEs were reported in 13.1% of subjects, and related TEAEs (mainly solicited AEs) in 7%. No related serious adverse events were reported so far. The safety and tolerability were generally comparable across different treatment groups and dosages.

2.5.3 Dose Finding for MVA-BN-RSV Vaccine

For MVA-BN, the standard dose and schedule for the general population is 2 doses of at least 5×10E7 $TCID_{50}$ MVA-BN (nominal titer of 1×10E8 $TCID_{50}$ per dose) administered SC 4 weeks apart. A trial in adult and elderly (56-80 years old) vaccinia-experienced subjects indicated that it is sufficient to vaccinate this population only once with MVA-BN (Greenberg, 2016).

In the first clinical trial with the MVA-BN-RSV vaccine (RSV-MVA-001 phase 1 trial), a low dose with a nominal titer of 1×10E7 $TCID_{50}$ per dose was compared against a dose with a nominal titer of 1×10E8 $TCID_{50}$ per dose (see Section 2.6).

In the second RSV trial (RSV-MVA-002 phase 2 trial) different doses and schedules were evaluated: all subjects received 2 vaccinations—either both vaccinations with MVA-BN-RSV vaccine 1×10E8 Inf.U per 0.5 mL, 5×10E8 Inf.U per 0.5 mL, or placebo, or the first vaccination with MVA-BN-RSV vaccine 1×10E8 Inf.U or 5×10E8 Inf.U per 0.5 mL followed by the second vaccination with placebo (Table 7). Please note that the dose was expressed as $TCID_{50}$ for the phase 1 clinical trial with 1×10E8 $TCID_{50}$ per dose corresponding to 1×10E8 Inf.U per dose.

2.6 Clinical Trial Data with MVA-BN-RSV Vaccine

The following clinical trials with the MVA-BN-RSV vaccine have been fully enrolled and final follow-up visits have been completed:

- A randomized, single-blind, placebo-controlled, monocentric phase 1 trial to assess the safety, tolerability, and immunogenicity of the recombinant MVA-BN-RSV vaccine in healthy adult subjects (RSV-MVA-001).

- A randomized, single-blind, placebo-controlled, dose-ranging phase 2 trial in ≥55 year old adults to evaluate the safety and immunogenicity of the recombinant MVA-BN-RSV vaccine (RSV-MVA-002).
- RSV-MVA-015: A phase 2a, randomized, placebo-controlled human challenge trial in which administration of MVA-BN-RSV or placebo was followed by inoculation with an RSV strain known to cause mild to moderate symptoms in healthy adults.

Phase 1: RSV-MVA-001

Safety, tolerability and immunogenicity of the recombinant MVA-BN-RSV vaccine were evaluated in the randomized, single-blind, placebo-controlled phase 1 trial (RSV-MVA-001). In total, 63 healthy adult subjects received 2 vaccinations of placebo, the 1×10E7 $TCID_{50}$ dose, or the 1×10E8 $TCID_{50}$ dose of MVA-BN-RSV vaccine (Table 6).

Table 6 Treatment Groups in Phase 1 Clinical Trial RSV-MVA-001

Group	N[a]	Age (years)	Vaccine: nominal titer per dose ($TCID_{50}$)	Volume per dose [mL]	Schedule (vaccination days)	Route
1	18 + 3	18-49	1×10E7	0.5	0; 28	IM
2	18 + 3	18-49	1×10E8	0.5	0; 28	IM
3	18 + 3	50-65	1×10E8	0.5	0; 28	IM
Total	**63**					

Abbreviations: IM = intramuscular; N = number of subjects per group; $TCID_{50}$ = tissue culture infectious dose 50%

[a] 18 subjects in each treatment group receiving MVA-BN-RSV vaccine and 3 subjects in each treatment group receiving placebo

Data Source: MVA-RSV-001 Clinical Study Report (Ed. 1.0 dated 04 July 2016, Table 1).

To evaluate long-term safety and immunogenicity of the MVA-BN-RSV vaccine, subjects completed a FU visit 6 months after the second vaccination.

Safety Data

The trial demonstrated that a 2-dose regimen of MVA-BN-RSV was well tolerated in adult and elderly subjects receiving either the 1×10E7 $TCID_{50}$ dose or the 1×10E8 $TCID_{50}$ dose of the vaccine, confirming observations previously made during the clinical development programs of the MVA-BN backbone and other recombinant MVA-BN based vaccines. No SAEs or adverse events of special interest (AESI) occurred and no subject discontinued the trial due to an AE. The incidence of solicited local or solicited systemic AEs was generally low and comparable between groups. No clinically significant findings were reported for physical examination assessments.

Immunogenicity Data

Despite the fact that the trial was not powered for statistical analysis of the RSV-specific immunogenicity profile, the results suggest that MVA-BN-RSV increases humoral and cellular immune responses in different doses and across different age groups, including elderly adults.

The humoral immune response was durable for at least 6 months, which is sufficient to cover a full RSV season. The vaccine showed a broad cellular immune response against all vaccine inserts as well as a humoral immune response to both RSV subtypes A and B.

Phase 2 Dose-ranging RSV-MVA-002 Trial

The RSV-MVA-002 was a randomized, single-blind, placebo-controlled, multicenter, dose-ranging phase 2 trial to evaluate safety and immunogenicity of the recombinant MVA-BN-RSV vaccine in adult and elderly subjects ≥55 years of age. The primary endpoint of this trial was to assess the optimal dose and schedule of the MVA-BN-RSV vaccine in adult and elderly subjects in terms of antibody geometric mean titers (GMTs) after 1 or 2 MVA-BN-RSV vaccinations or placebo measured by the Plaque Reduction Neutralization Test (PRNT) against subtype A 2 weeks after the last vaccination.

The immune correlate for protective efficacy against RSV is currently not fully understood. Though neutralizing antibody titers are often used to evaluate potential protection against RSV-related severe disease, recent scientific evidence indicates that the immune responses required to protect against RSV are more complex and will likely also require – in addition to serum antibodies – mucosal antibodies and cell-mediated immune responses.

Clinical efficacy was not evaluated in this dose-ranging trial and sample size was not powered to detect any significant differences in incidence rate of RSV-related respiratory tract disease. However, as the immune correlate for protective efficacy against RSV is currently not fully understood, cellular, humoral and mucosal immune responses induced by the MVA-BN-RSV vaccine were assessed. After completing the active trial phase, all subjects entered a FU phase of 6 months to monitor long-term safety and immunogenicity. Subjects were enrolled into 5 treatment groups (Table 7). In each treatment group, subjects were stratified by age (55 to 70 and ≥70 years of age), and a minimum of 20 subjects per treatment group was required in the age stratum ≥70 years. A subgroup of each treatment group (at least 20 subjects) had additional blood draws for T- and memory B-cell analysis.

Table 7 Treatment Groups in Phase 2 RSV-MVA-002 - Main Part

Treatment Group	N	Age [years]	First Vaccination (Day 1) [Inf.U/0.5 mL]	Second Vaccination (Day 28) [Inf.U/0.5 mL]	Route
1	78	≥55	1×10E8	placebo	IM
2	89	≥55	1×10E8	1×10E8	IM
3	80	≥55	5×10E8	placebo	IM
4	90	≥55	5×10E8	5×10E8	IM
5	83	≥55	placebo	placebo	IM
Total	**420**				

Abbreviations: IM = intramuscular; Inf.U = infectious units; N = number of subjects per group
Data Source: RSV-MVA-002 Clinical Study Report Ed. 3.0, dated 19 November 2018, Table 1.

One year after the last vaccination, subjects from 2 treatment groups having received 1 vaccination with the 1×10E8 Inf.U or the 5×10E8 Inf.U dose of the MVA-BN-RSV vaccine (Groups 1 and 3) were selected to receive an annual booster vaccination of the same dose (Table 8). Those subjects were followed up for another 12 months to evaluate immune responses to the vaccine elicited after a yearly booster vaccination.

Table 8 Treatment Groups in Phase 2 RSV-MVA-002 - Booster Sub-study

Treatment Group	N	N [immunogenicity subset]	Age [years]	Booster vaccination[a] [Inf.U/0.5 mL]	Route
1×10E8 (Group 1)	43	15	≥55	1×10E8	IM
5×10E8 (Group 3)	45	15	≥55	5×10E8	IM
Total	**88[b]**	**30**			

Abbreviations: IM = intramuscular; Inf.U = infectious units; N = number of subjects per group

[a] Same dose as defined in the main trial for respective Groups 1 and 3 of main trial

[b] at least 40 evaluable subjects from the treatment Group 1 (receiving 1×10E8 Inf.U per dose) and Group 3 (receiving 5×10E8 Inf.U per dose) from the main part of the trial (CTP edition 4.0, 26-Apr-2018)

This phase 2 trial has shown that the different MVA-BN-RSV vaccine doses administered once or twice have an acceptable safety profile, were well tolerated, and induced a robust and broad humoral, cellular and mucosal immune response in older and elderly adults:

- The incidences of solicited systemic and local AEs by age group (≥55 to 70 years versus ≥70 years) were low and comparable to that seen overall and across age groups. The incidences of unsolicited treatment-emergent adverse events (TEAEs) were similar among the treatment groups. No relevant differences in hematology and serum chemistry parameters were registered. The data have confirmed the good safety and tolerability profile observed during the phase 1 trial and are in line with the favorable safety profile

observed throughout the clinical development program of the MVA-BN backbone and in clinical trials evaluating other recombinant MVA-BN based vaccines.

- A single administration of the MVA-BN-RSV vaccine is sufficient to induce a robust immune response against both circulating RSV subtypes (A and B), as seen in post-vaccination increases in RSV-specific neutralizing antibodies (PRNT using subtype A and B) and total antibodies (RSV-specific immunoglobulin G [IgG], immunoglobulin A [IgA] ELISA, and RSV G protein-specific IgG ELISA [subtype A and B]).
- A single administration of the MVA-BN-RSV vaccine is sufficient to induce a robust mucosal immune response, as seen in post-vaccination increases in mucosal antibodies using an RSV-specific IgA ELISA.
- Vaccine-induced antibody responses (GMTs and response rates) remained above baseline levels after 30 weeks, indicating durability of humoral immune responses.
- Vaccine-induced antibody responses measured by a variety of serum assays were generally higher after administration of the 5×10E8 dose compared to the 1×10E8 dose, possibly indicating a dose-response effect.
- The MVA-BN-RSV vaccine has been shown to induce a broad, robust, and Th1-biased cellular immune response to all 5 inserts encoded in the vaccine, irrespective of the dose and administration regimen employed.

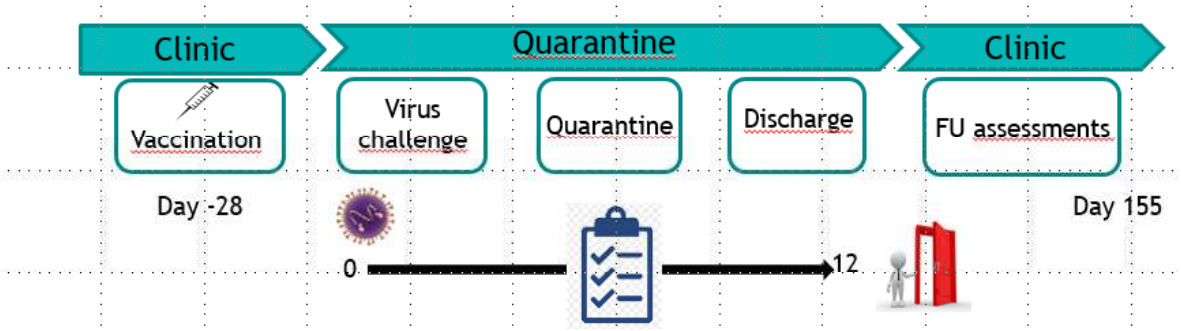
Phase 2a Human Challenge Trial RSV-MVA-015:

Safety, efficacy, and immunogenicity of MVA-BN-RSV against challenge with an RSV virus was assessed in healthy adults in the phase 2a, randomized, placebo-controlled Human Challenge Trial. In total, 73 subjects were vaccinated via IM injection with a single dose (0.5 mL) MVA-BN-RSV (nominal titer 5×10E8 Inf.U per 0.5 mL) or placebo (Table 9). Of these, 63 subjects were then challenged 4 weeks later by intranasal delivery of the RSV-A Memphis 37b strain (total dose of approximately 4.5 $\log_{10}$ plaque forming units) (Figure 3). The primary endpoint was area under the viral load-time curve (AUC), measured from nasal washes obtained from subjects while in quarantine after the RSV-A Memphis 37b challenge. Viral load (VL) for the primary analysis was obtained by quantitative reverse transcriptase PCR (RT-qPCR) from washes collected from 2 days after challenge to discharge from quarantine.

Table 9 Treatment Groups in the Human Challenge Trial

Groups	Number of subjects	MVA-BN-RSV vaccine Dose [Inf.U/0.5mL]	RSV Virus Challenge dose (day 14-28 after vaccination)
1	36	nominal titer 5×10E8	4.5 $\log_{10}$ plaque forming units
2	36	Placebo	4.5 $\log_{10}$ plaque forming units
Total planned	N = 60 (72 vaccinated to account for dropouts)		

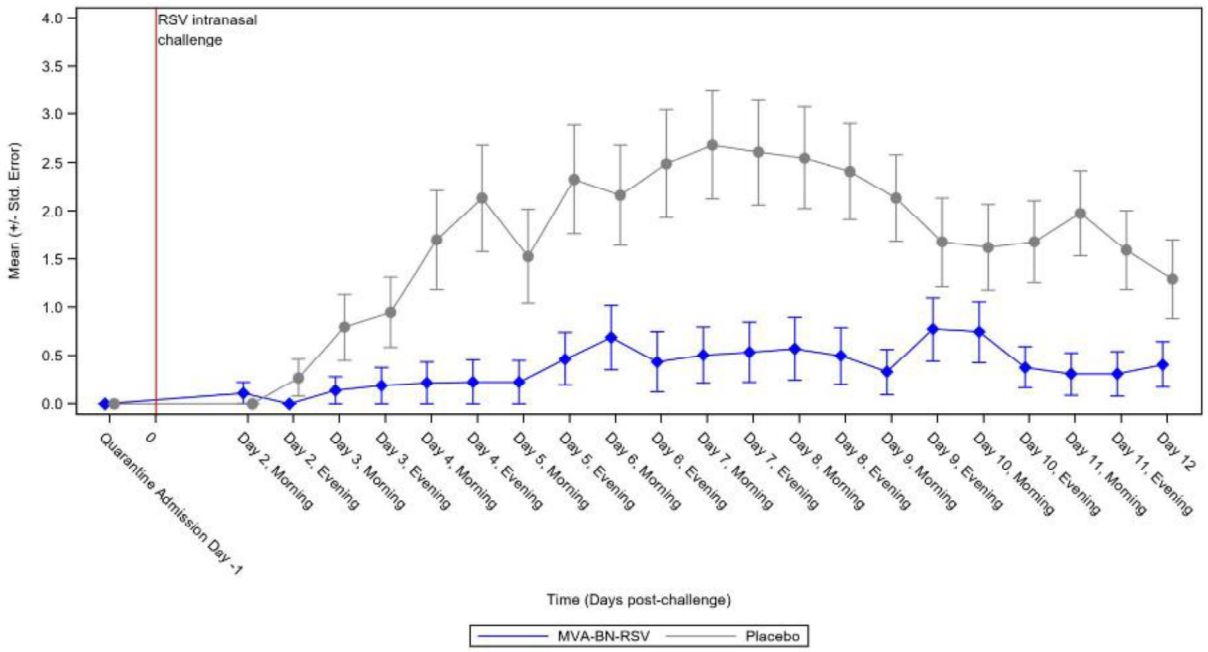
Figure 3 Human Challenge Trial Design (Lambkin; 2018)



The areas under the curve for RSV-A Memphis 37b VL as measured by qRT-PCR are presented in the mean VL plotted over time is illustrated in Figure 4.

The primary endpoint of the trial was met: VL AUC of RSV-A Memphis determined by qRT-PCR was significantly lower for the MVA-BN-RSV group compared to the placebo group (p-value 0.017). The median VL AUC for the vaccine group was 0, while it was 49 for the placebo group. Solicited adverse events reported for 8 days starting at day of vaccination were comparable to results obtained in the completed phase 1 and 2 clinical studies and pooled in Table 3.

Figure 4 Mean Value Over Time in Viral Load of RSV-A Memphis 37b Determined by qRT-PCR from Nasal Washes – Per Protocol Analysis Set



Source: TLFs (23Sep2021), Figure 15.2.1.2.2
Abbreviations: qRT-PCR = quantitative reverse transcription polymerase chain reaction

Therefore, the MVA-BN-RSV vaccine seems to be safe and well tolerated and immunogenic in a population of older subjects considered to be at higher risk of suffering seasonal RSV-related respiratory disease; the inserts contained within the novel MVA-BN-RSV candidate do not induce additional safety concerns in RSV at-risk populations. In addition, vaccine efficacy was demonstrated in the human challenge trial model. Further details on trial data are summarized in the current IB.

2.7 Rationale

RSV is an important cause of serious respiratory disease in all age groups especially in very young infants experiencing their first infection with RSV but also in the older adults and elderly population above 60 years of age. The completed phase 2 clinical trial RSV-MVA-002 generated safety and immunogenicity data of the recombinant MVA-BN-RSV vaccine in healthy adult subjects ≥55 years of age. This trial confirmed safety and immunogenicity results from the phase 1 clinical trial in healthy younger and older adults (RSV-MVA-001). The vaccine had an acceptable safety profile, was well tolerated and able to increase RSV-specific humoral and cellular immune responses in the population tested. Immune responses elicited by the primary MVA-BN-RSV vaccination were durable for at least 6 months and could be boosted by another

MVA-BN-RSV vaccination after 12 months as shown in a booster sub-study of the phase 2 trial. One vaccination with MVA-BN-RSV vaccine was sufficient to raise an immune response without significant additional rise after the second dose. Additionally, immunogenicity results indicated that a higher dose elicits consistently higher antibody titers, which might be beneficial for protection of infection. Efficacy could not be assessed in either in the phase 1 or in the phase 2 trial due to the low sample size of the trial relative to the low incidence rate of a laboratory-confirmed RSV disease. However, efficacy was demonstrated in the phase 2a human challenge trial, which showed significant reduction in VL AUC for the MVA-BN-RSV-vaccinated subjects compared to placebo as well as VL AUC over time, PCR-confirmed RSV disease and total symptom score over time in healthy adults aged 18 to 50.

Hence this placebo-controlled, randomized, double-blind phase 3 trial is designed to assess real-world efficacy after one injection of the MVA-BN-RSV vaccine (corresponding to the higher dose given in the phase 2 trial (nominal titer of 5×10E8 Inf.U)) in the target high-risk population of adult/elderly subjects ≥60 years of age compared to placebo.

Outbreaks of RSV are observed worldwide and follow a seasonal pattern in most parts of the world, with significant occurrence during winter months. Ideally, vaccination for protection against respiratory tract disease caused by RSV would be scheduled shortly before the start of the RSV season. However, sanitary measures, social distancing, and lockdown periods to control the spread of SARS-CoV-2 have also affected the seasonality of RSV, with outbreaks reported in some countries outside of the typical RSV season. Therefore, while it is intended to enroll and vaccinate the trial population before an RSV season and to perform the trial follow-up over the course of that season, because the seasonality of RSV has been disrupted by COVID-19, it is not certain when RSV peaks will occur. For this reason, the follow-up time for subjects is designated as approximately 6 months and up to 12 months, to optimize the likelihood that subjects will be observed during a season of peak RSV infection.

All 20,000 subjects will be enrolled and vaccinated in the phase 3 clinical trial and followed up for PCR-confirmed RSV disease for at least one RSV season (up to 12 months after vaccination). In case the number of events is not met after 6 months after the last vaccination or at the end of the RSV season 1, up to 4000 further subjects will be added and followed up for at least one RSV season (up to 12 months after vaccination). In addition, all subjects from the initial enrollment will be followed up for a second year after vaccination (without any further booster vaccination) to address the question of durability of protection against RSV disease for more than one RSV season and the potential need for a yearly booster vaccination to continuously protect against RSV-related disease.

2.8 Trial Population

Any medically stable ≥60-year-old women and men of any ethnicity who meet all of the inclusion criteria and none of the exclusion criteria are eligible for participation in this trial.

2.9 Risk/Benefit Assessment

2.9.1 Potential Risk

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

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

There is substantial safety data available for the vector backbone MVA-BN and for other MVA-based recombinant vaccines in healthy and immunocompromised subjects as well as the first safety data for the MVA-BN-RSV vaccine (phase 1 clinical trial RSV-MVA-001 in healthy adult subjects; phase 2 clinical trial RSV-MVA-002 in healthy subjects ≥55 years; and phase 2a clinical trial RSV-MVA-015 in healthy adult subjects, see Section 2.6). Adverse reactions in this trial setting are expected to be comparable to adverse reactions previously reported for MVA-BN, MVA-BN-based recombinant vaccines, MVA-BN-RSV, and those typically seen with other vaccines. Main risks involve the development of local reactions at the injection site, e.g., erythema, pain, swelling and induration, and temporary systemic reactions such as headache, fatigue and myalgia.

As with all vaccines, there is a risk of an allergic reaction or an anaphylactic event. Trial site staff will watch subjects for at least 30 minutes after each vaccination, and in the event that a severe allergic reaction and/or dyspnea occurs, appropriate medical treatment and supervision will be readily available.

Nasopharyngeal (NP) swabs are taken in case of respiratory tract disease to assess causality of RSV. This may cause the subject to gag and may cause irritation or dryness at the sampling sites for a short time, usually less than 5 minutes.

2.9.2 Benefit

There will be no direct benefit to the trial participants receiving placebo; however, there is a possibility that the MVA-BN-RSV group may derive benefit from vaccination if the vaccine is proven to be efficacious against RSV-related LRTI. Trial participants will contribute significantly to the testing of an RSV vaccine, which could potentially benefit older and elderly adults and adults with underlying cardiovascular or pulmonary disease by reducing their risk of severe illness and mortality due to infection with RSV. In addition, based on the current immunogenicity and efficacy data collected in non-clinical and clinical studies with MVA-BN, participants may acquire protection against smallpox infection as well as protection against disease symptoms

caused by RSV. The immunogenicity results of the phase 1 and 2 trials with the MVA-BN-RSV vaccine indicate that RSV-specific humoral and cellular immune responses are significantly boosted by the vaccine. However, it cannot be said if the vaccine is efficacious against the disease, as data available up to date are limited and do not allow for conclusions on protection against RSV.

Subjects may also receive IRB/EC-approved stipends for time and travel, depending on the country regulation.

3 Objectives

Please refer to protocol synopsis Section 1.3.

4 Trial Design

4.1 Experimental Design

This is a randomized, double-blind, phase 3 trial to assess clinical efficacy, safety, and reactogenicity of the recombinant MVA-BN-RSV vaccine in adults ≥60 years of age.

It is intended to enroll and vaccinate the trial population before an RSV season and to perform the trial follow-up over the course of that season. Twenty thousand male and female subjects ≥60 years of age are planned to be enrolled and randomized to receive one administration of either placebo or MVA-BN-RSV vaccine. They will be stratified by age into 4 age groups as shown in the table below, with enrollment goals intended to ensure adequate representation of the older age strata. In addition to the age stratification, the trial will also aim to enroll at least 20% of the subjects that meet the definition of "at-risk", i.e., who have at least one comorbidity associated with higher risk of LRTD, including chronic cardiac diseases and chronic lung disease (asthma and chronic obstructive pulmonary disease [COPD]), CHF, and hypertension.

Table 10 Age stratification and Enrollment Target

Age range (years)	Enrollment target
60 to 64	Up to 10%
65 to 74	
75 to 84	Approximately 25% of the enrollment
≥85	Approximately 5% of the enrollment

All subjects will be monitored for lower and upper respiratory tract disease until at least the end of one RSV season (up to 12 months after vaccination). If subjects develop RSV-specific symptoms, they will be scheduled for a symptom visit (SV) at the clinical site, and a NP swab will be collected for RSV PCR testing.

All participants will be asked to complete a questionnaire on respiratory disease-related symptoms (RiiQ), quality of life and frailty questionnaire (Section 4.1.4) at Visit 1 and complete all questionnaires, except the frailty index, also at symptom onset or symptom visit and for a set time period afterwards.

Additionally, serum samples will be collected for immunogenicity testing from a sub-group of approximately 600 subjects (300 per study arm) at pre-defined clinical sites. PBMC samples will also be collected from a sub-group of approximately 300 subjects (150 per study arm) at pre-defined clinical sites. As the clinical trial is double-blind serum and PMBC samples will be collected from both treatment groups (MVA-BN-RSV and placebo).

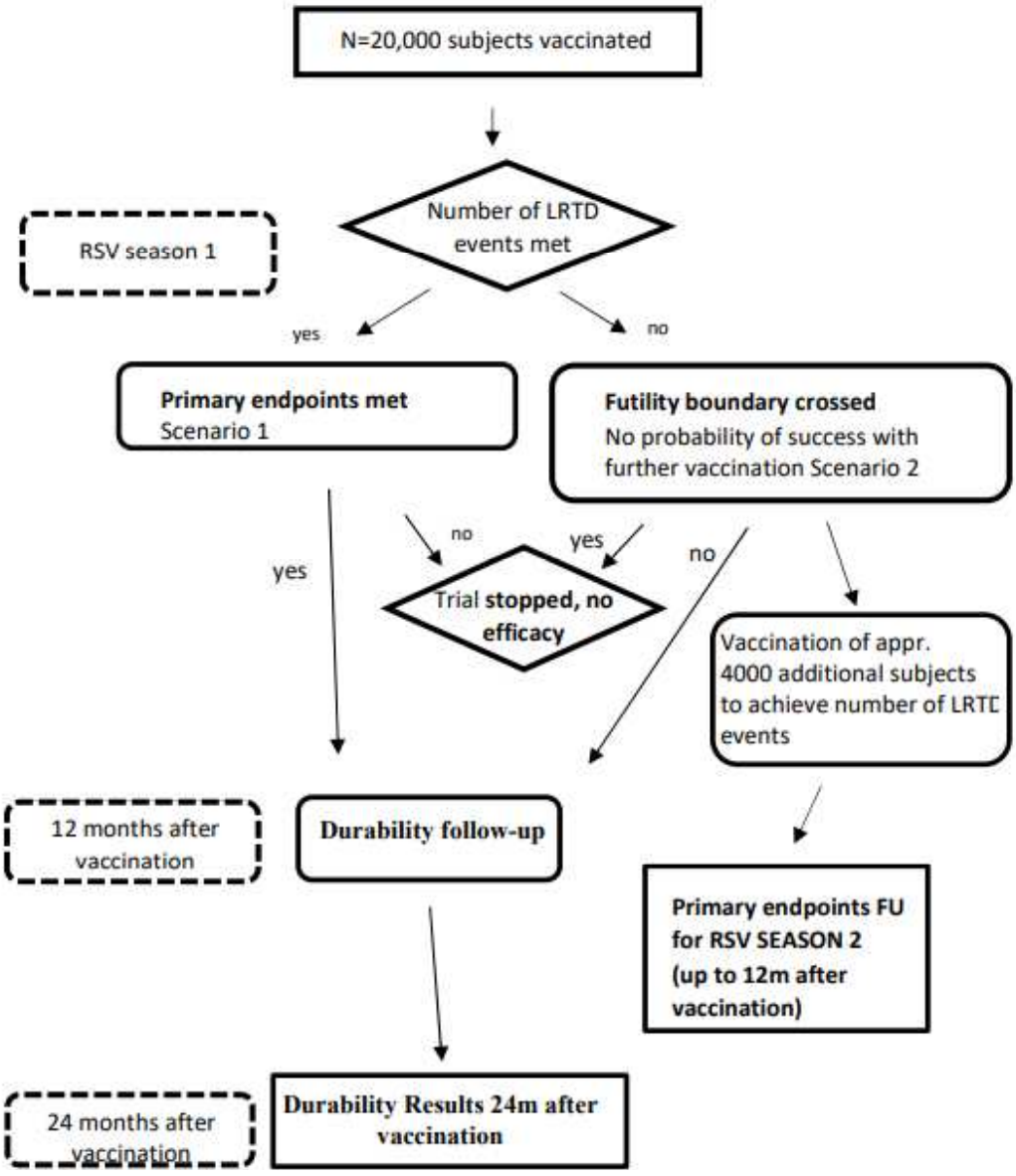
In case both the defined number of LRTD cases required for the primary analysis and the success criteria are met, subjects will be followed up for durability of potential protection against RSV disease up to 24 months after vaccination (scenario 1; Figure 5). It is estimated that approximately 16,000 subjects (accounting for dropouts during follow-up), will participate in this additional monitoring for respiratory tract disease.

In case the defined number of LRTD cases required for the primary analysis is met but not the primary endpoints of efficacy, the trial will be stopped and no further follow up for durability will be done (Figure 5).

In case the defined number of LRTD cases required for the primary analysis is not met after RSV season 1 (less than 53 cases of LRTD with ≥2 symptoms or less than 22 cases of LRTD with ≥3 symptoms) and the futility criterion is not met per the futility analysis, additional (approximately 4000) subjects will be enrolled (scenario 2) and vaccinated (Figure 5). These subjects will be monitored for respiratory tract symptoms until at least the end of 1 RSV season (for up to 12 months after vaccination). Those already enrolled and vaccinated in season 1 will be followed up for durability of potential protection against RSV disease up to 24 months after vaccination.

The trial procedures will be conducted according to the trial procedure schedule (Section 1.4) and as described on the following pages.

Figure 5 Flowchart with 2 Scenarios and Durability



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4.1.1 Screening Visit / Visit 1

All subjects should preferably undergo the screening and vaccination procedures in one day (SCR/V1 on Day 1). If a subject is screened and cannot be vaccinated because of a certain transient condition, then the subject can perform/repeat the respective outstanding visit tasks in one day within a 7-day time period in combination with the vaccination. Vaccination needs to be performed on Day 8 at the latest.

If a subject cannot be vaccinated due to other circumstances (e.g., ongoing wash-out period for a medication or vaccine that is not allowed during the trial) or if the 7-day time period is exceeded, the complete screening process needs to be repeated and a new subject number will be assigned. All subjects must be thoroughly informed of all aspects of the trial (e.g., trial visit schedule, required evaluations and procedures, risks and benefits). Written informed consent must be obtained according to local requirements before any trial-related assessment will be carried out.

All screening tasks will be performed according to the trial procedures outlined in Section 1.4.

Among other visit tasks the inclusion and exclusion criteria need to be checked to assess the eligibility of the subjects. A complete physical examination will be performed only at screening, whereas a targeted physical examination will be performed at all other applicable study visits.

If the subject belongs to one of the immunogenicity subgroups a blood draw will be taken before vaccination.

An ePRO application will be installed onsite on the subjects' smartphone or tablet (in case the subject's personal device is not compatible or they refuse to download the app, a device will be provisioned and the ePRO application instructions will be handed out and a thorough usage training given to the subjects).

All subjects will complete the EQ-5D-5L, RiiQ, 15D and Tilburg Frailty Indicator (TFI) (part B) questionnaires (further details in Section 4.1.4) at the screening/vaccination visit prior vaccination.

Randomized treatment assignments for the subjects will be done at this visit via interactive voice- or web-response system (IWRS) after confirmation of subject's eligibility as outlined above and specified in Section 1.3.

After the subjects are assigned to one specific treatment group, placebo or MVA-BN-RSV vaccine will be administered into the deltoid muscle of the upper arm (preferably the non-dominant arm). The subjects will be kept under close observation at the clinical trial site (CTS) for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the vaccination.

Starting after vaccination the subjects are guided on entering data into the ePRO application to confirm their understanding of the ePRO application entry requirements: an electronic diary (eDiary) must be completed on a daily basis, covering all solicited local and systemic symptoms in the ePRO application until Day 8 after vaccination. For symptoms which are ongoing after Day 8, temperature/symptom measurements should continue to be recorded in the eDiary each day until resolved.

Additionally, the site instructs the subjects to start after vaccination reporting the presence of any symptoms potentially related to a respiratory tract disease caused by RSV into ePRO application immediately after onset of the symptom. Subjects will be reminded of this process 3 times per week by ePRO application notifications and by monthly site calls. Each reporting of symptoms by the subjects will trigger an ePRO application alert to the site staff, who will immediately contact the subjects and schedule an onsite SV within the given time frame (target 72 hours after onset, up to 5 days accepted). Additionally, subjects will be reminded by sites calls if the subject has not responded to notifications in their ePRO device for over a week.

4.1.2 Disease Surveillance and Monthly Telephone Visits

Enrolled and vaccinated subjects will enter the active trial phase. Disease surveillance will start for these subjects with ePRO reminders 3 times per week to report the presence of respiratory symptoms starting after the day of vaccination. The ePRO application will issue an alert to the site in case of a reported symptom, and the site needs to call the subject to schedule an onsite visit.

Additionally, the site staff performs monthly telephone calls to subjects in order to follow up on the presence of any symptoms, to remind the subjects to report symptoms, or to follow up on low compliance with regard to eDiary entries. In case of predefined respiratory tract symptoms, subjects need to be called in for an onsite SV within 72 hours (up to 5 days accepted) after the first symptom occurred (see Section 4.1.3). Subjects are reminded to continuously report any symptom occurrence.

The monthly telephone visits start after vaccination (SCR/V1 (Section 1.4 and 4.1.1)) and will continue until the End of Study (EOS) visit. This time period is expected to cover at least one RSV season (up to 12 months after vaccination).

During the monthly telephone calls from the site, the following items also will be assessed in addition to the occurrence of any respiratory tract symptoms:

- the worsening of pre-existing symptoms from prior reported illness (AEs)
- any needed follow-up on solicited AEs reported via ePRO for the 8-day period (memory aid) beginning with the day of vaccination, until resolution, if still ongoing
- unsolicited AEs, which are to be recorded until 29 days after vaccination, and those which are still ongoing at Day 29 will be followed up until resolved

- new SAEs or changes to existing SAEs will be assessed until the EOS Visit.

The site staff will be trained for making these monthly calls based on standard scripts. If the subject misses any previous call visits and has not responded to the ePRO application reminder, occurrence of any respiratory tract symptoms during this time will be inquired by the site staff. Data cannot be retrospectively entered in the ePRO application, but site can document the start date of symptoms after a telephone call with the subject.

4.1.3 Symptom Visit

Subjects must return for an SV at the site in case they reported the presence of respiratory symptoms as defined in Section 7.3 during the monthly telephone calls or via ePRO application.

Clinical evidence of any of the symptom(s) below must be verified and documented by a medical professional by performing specific exams and/or tests to assess:

- rhinorrhoea
- nasal congestion
- pharyngitis
- earache
- new cough or worsening of pre-existing cough
- new wheezing or worsening of pre-existing wheezing
- new sputum production or worsening of pre-existing sputum production
- new shortness of breath or worsening of pre-existing shortness of breath
- fever >100 °F / >37.8 °C (oral temperature) (High, 2009)
- any other sign or symptom leading to the suspicion of a respiratory disease

Additionally, tests or exams for the below must be performed if appropriate:

- hypoxemia (oxygen saturation <92% at rest in conjunction with an at least 3% decrease from baseline)
- respiratory rate >25 breaths/Min
- imaging evidence of new onset of bronchitis, bronchiolitis, or pneumonia

A NP swab must be taken for PCR testing at the central laboratory to confirm RSV disease. In addition, vital signs, targeted physical examination and presence, onset and/or duration of RSV-specific symptoms will be documented.

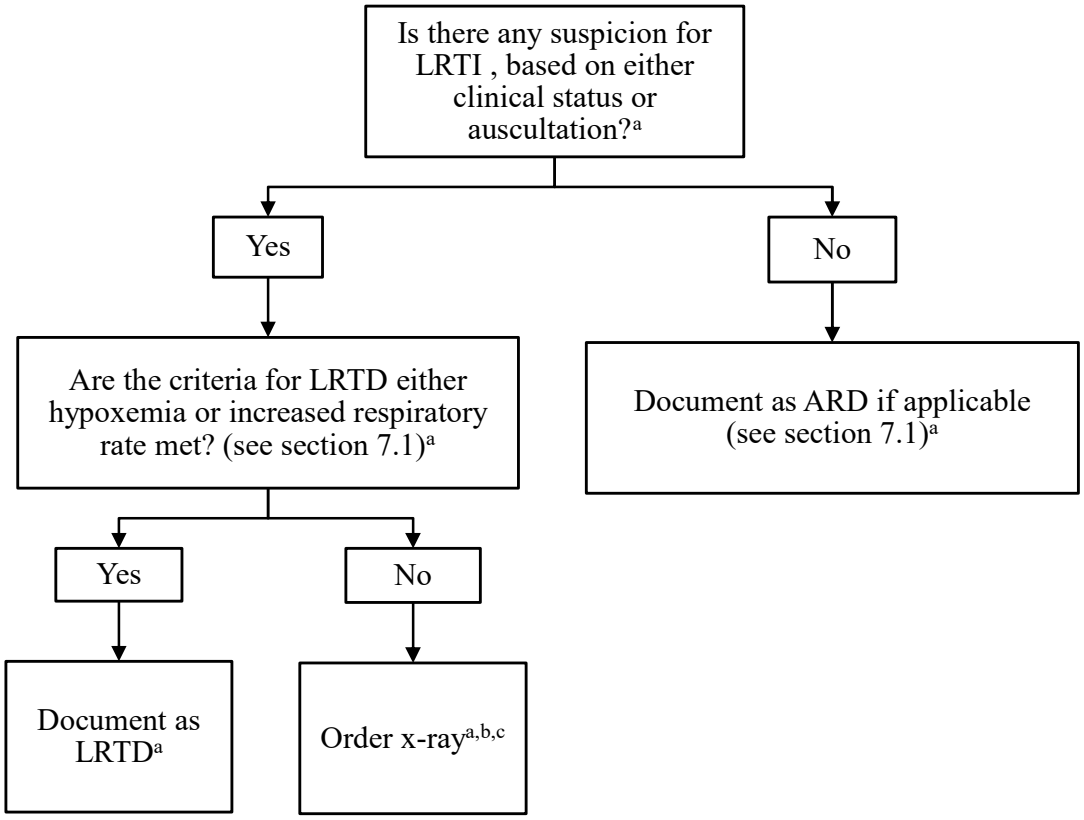
During the SV at the site in addition to the occurrence of any respiratory tract symptoms also the following items will be assessed:

- the worsening of pre-existing symptoms from prior reported illness (AEs)
- concomitant medications if applicable (Section 1.4).
- resolution of symptoms
- any needed follow-up on solicited AEs reported via ePRO for the 8-day period beginning with the day of vaccination, until resolution if still ongoing
- unsolicited AEs, which are to be recorded until 29 days after vaccination and those which are still ongoing at Day 29 will be followed up until resolved
- new SAEs or changes to existing SAEs will be assessed until the EOS visit
- targeted physical examination assessment of vital signs.

4.1.3.1 Imaging

In case of suspicion of severe LRTD based on e.g. clinical status or auscultation an x-ray can be ordered if none of the severe LRTD specific symptoms: hypoxemia and increased respiratory rate (definitions in Section 1.3) are met and medical need as judged by the investigator is present (Figure 6).

Figure 6 Flowchart LRTD (severe) – Decision Tree for X-Rays



[a] A nasopharyngeal swab must be taken in case of presence of respiratory disease symptoms independent of LRTD or ARD determination to confirm presence or absence of RS virus.

[b] maximum timeline for imaging (analog to nasopharyngeal swabbing, ideally within 72 hours **of symptom onset**, but at maximum within 5 days)

[c] X-ray to be performed on investigator's discretion based on medical need

If a subject does not return to the site for an SV and if a respiratory disease triggers a visit to the emergency room (ER), subjects will be provided with a kit including a NP swab and instructions for the ER staff on sampling, storage and how to inform the site. Nasopharyngeal swabs can be taken by the ER staff, sites will be informed accordingly, and transportation for storage at the site will be organized by the site. The procedure describing the process in detail is documented in the laboratory manual handed out to the site.

All documented respiratory tract symptoms with confirmed RSV positive PCR test will be adjudicated to be either ARD, LRTD (three LRTD definitions) or no endpoint at all by an adjudication committee, further described in Section 4.5.

4.1.3.2 Home Healthcare Visits

In case subject cannot return to the site for a symptom visit in the recommend time to assess the RSV-specific symptoms and to take a NP swab for confirmation of RSV-related disease, a home healthcare visit either by the site study team or a contracted specialized provider might be used to collect these assessments.

4.1.3.3 Self-Swabbing by Subject

Only if neither a home healthcare visit nor a visit to the site is feasible, the subject might be provided with a self-swabbing kit. In such as case, detailed swabbing instructions will be provided by the site.

4.1.4 Electronic Patient Reported Outcome (ePRO) Application

Besides serving as reminders for symptom visits and electronic diaries to record reactogenicity following vaccination, the ePRO application will also be used to collect the following patient reported burden of disease and health-related quality of life data.

If the long-term follow-up time points (e.g., 12 months after symptom visit) for the EQ-5D-5L and the 15D questionnaire fall beyond the first 12 months of follow-up after vaccination of the subject, the outstanding questionnaires are to be completed during the durability phase of the trial, if it is conducted.

4.1.4.1 RiiQ

Subjects will need to complete a questionnaire on respiratory disease-related symptoms (RiiQ) at screening/vaccination visit. This questionnaire will also be activated via the ePRO application at symptom onset and for 7 days after (8 days total), or until either symptom resolution or a maximum of 20 days after onset of symptoms (21 days total) is reached.

4.1.4.2 EQ-5D-5L

An EQ-5D-5L Questionnaire will completed by all subjects at screening/vaccination visit, at the symptom visit if an NP swab is obtained, and on day 6 and at 1, 3, 6, and 12 months after the symptom visit.

4.1.4.3 15D

The 15-dimension health-related quality of life instrument (15D) will be filled out at screening/vaccination visit, at the symptom visit if an NP swab is obtained, and on day 6 and at 1, 3, 6, and 12 months after the symptom visit.

4.1.4.4 Tilburg Frailty Indicator

TFI part B only will be assessed at screening for all subjects.

4.1.5 6-month Follow-up Visit

The 6-month follow-up visit (per telephone) will be scheduled at 6 months after vaccination. The visit might coincide with the end of the first RSV season, which will be determined by the sponsor but informed by country-specific RSV surveillance data (e.g. US: defined by the CDC surveillance data, https://www.cdc.gov/surveillance/nrevss/rsv/index.htmL and RKI Robert Koch Institute, https://survstat.rki.de/). BN will continuously monitor regional RSV data related to clinical sites of the trial.

For US, the end of season can be declared by BN at the earliest when at least 3 out of 5 regions have an RSV test percent positivity rate below 10% both with antigen and PCR testing. It will be declared at the latest when all 5 regions have RSV test percent positivity rate below 5% both with antigen and PCR testing.

For Germany and UK, available surveillance data relating to the regions and/or clinical trial sites in the respective countries will be monitored and based on either national criteria or CDC criteria to determine the end of RSV season (up to 12 months after vaccination).

At the 6-month FU visit, new SAEs and changes to SAEs/AEs ongoing at Day 29 need to be recorded. In case of 6-month FU visit and EOS visit are at the same day please also follow procedure listed under Section 4.1.6.

4.1.6 End of Study Visit

The end of study visit (per telephone) will be scheduled at approximately 12 months after vaccination. Only in case the trial is terminated early (due to lack of efficacy) this visit will be scheduled soon after the futility analysis.

If number of events for the primary endpoints is not met by the end of season 1, disease surveillance and monthly calls will continue until the sponsor notifies sites to conduct the EOS visits.

At the EOS visit, new SAEs and changes to SAEs/AEs ongoing at Day 29 need to be recorded. Any provisioned device for ePRO application needs to be returned by the subject to the site directly or shipped according to instructions provided at clinical trial start if the subject is not proceeding to the durability part of the trial.

4.1.7 Immunogenicity Visit / Visit 2a/2b / Visit FU-D1 / Visit FU-D

For the PBMC immunogenicity subgroup of 300 subjects (150 per study arm) at designated sites, a blood draw will be performed at the combined SCR/V1 before vaccination and one additional onsite blood draw 1 week after vaccination (at Day 7 to 10) (Visit 2a).

For the serum immunogenicity subgroup of 600 subjects (300 per study arm) at designated sites, a blood draw will be performed at the combined SCR/V1 before vaccination and one additional onsite blood draw 2 weeks after vaccination (at Day 14 to 16) (Visit 2b).

For PBMC and serum immunogenicity subgroup vaccinated before the first RSV season onsite blood draws will be performed approximately 1 year after vaccination at Durability Follow-up Visit (FU-D1) and approximately 2 years after vaccination at End of Durability Follow Up Visit (FU-D) (Section 1.4.2). Only subjects in the immunogenicity subgroup will therefore have an onsite visit FU-D for scheduled 2 year blood draw for either serum or PBMC.

In addition, the following procedures will be done at the immunogenicity visits:

- the worsening of pre-existing symptoms from prior reported illness (AEs)
- concomitant medications if applicable (Section 1.4).
- any needed follow-up on solicited AEs reported via ePRO for the 8-day period beginning with the day of vaccination, until resolution if still ongoing
- unsolicited AEs, which are to be recorded until 29 days after vaccination and those which are still ongoing at Day 29 will be followed up until resolved
- new SAEs or changes to existing SAEs

4.1.8 Unscheduled Visits

Additional visits may be necessary between scheduled visits based on a subject's health status and the investigator's clinical opinion (SAEs, worsening of AEs, worsening of RSV-specific symptoms). Examinations performed at unscheduled visits will be documented in the source documents as well as in the respective electronic case report form (eCRF) sections for unscheduled visits. Assessment of RSV-specific symptoms will be done if present at that visit.

4.1.9 Early Discontinuation

Reasons for early discontinuations:

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

- An AE/SAE that, in the opinion of the investigator, makes it impossible or unsafe for the subject to continue with the trial routine or to receive the single vaccination after randomization
- Clinical need for concomitant or ancillary therapy not permitted in the trial as outlined in Section 9.2.2
- Subject's request to discontinue
- Subject's unwillingness or inability to comply with trial requirements, e.g., usage of ePRO application, returning to the site for SVs
- Any reason that, in the opinion of the investigator, requires early discontinuation of a subject

Handling of early discontinuations:

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

If a subject discontinues early for any reason, every attempt should be made to document the reason for the discontinuation.

4.1.10 Durability Follow Up (FU-D1) – During Second Year after Vaccination

Based on the number of LRTD cases observed until end of RSV season 1 (up to 12 months after vaccination) and results of the futility analysis, the trial may be:

1. terminated if the futility criterion is met, or
2. additional subjects (approximately 4000) will be vaccinated if the number of LRTD cases is less than 53 (≥2 symptoms) or 22 (≥3 symptoms) and the futility criterion is not met. Already enrolled subjects will continue to be followed-up for RSV-related diseases until up to 2-year post-vaccination to assess durability of protection against RSV disease. (Section 11.5.1).
3. if the number of LRTD cases is at least 53 (≥2 symptoms) and 22 (≥3 symptoms), the study may continue until end of RSV season 1 for the primary analysis. If the primary success criterion is met, subjects will continue to be followed-up during a second year post-vaccination to assess durability.

If the decision is made to continue the trial, subjects vaccinated in season 1 who are willing to participate in the durability follow-up part of the trial (starting approximately 12 months and up to 24 months after vaccination) will be scheduled for this visit. Approximately 1 year after vaccination, subjects will return to the site for a start of durability visit. The visit should coincide with the EOS Visit for season 1.

This onsite visit starts at Day 1 (approximately 12 months after vaccination); vital signs and symptoms will be assessed, and a targeted physical examination performed.

Any SAEs occurring from the last SAE assessment (telephone call or onsite visit) until the start of the durability follow up visit will be collected retrospectively.

During the first visit, the site personnel need to re-check the functionality of the ePRO application and the device or provide a new device in case the subject had returned the provisioned device at a prior visit. Subjects are reminded to report the presence of any respiratory disease-specific symptoms in ePRO application.

If the long-term follow-up time points (e.g., 12 months after symptom visit) for the EQ-5D-5L and the 15D questionnaire fall beyond the 12 months of follow-up after vaccination of the subject, the outstanding questionnaires are to be completed during the durability phase of the trial, if it is conducted.

The subjects are notified that respiratory disease symptom assessment via monthly calls is performed for disease surveillance and will be supported by ePRO reminders 3 times per week, asking for presence of respiratory symptoms.

All ePRO application entries will be monitored remotely (and at potential onsite visits) for compliance and reactions.

4.1.11 Durability 6-Month Follow-Up Visit (FU) / 18 months after vaccination (6 months after FU-D1)

The Durability 6-month follow up visit (per telephone) will be scheduled approximately 18 months after vaccination corresponding to 6 months after the durability start visit.

4.1.12 Durability End of Trial / approximately 24 months after vaccination (12 months after FU-D1)

The durability end of trial visit (per telephone) will be scheduled approximately 24 months after vaccination. Only for subjects participating in the immunogencity subgroup this visit will be an onsite visit in case a blood draw is performed (see section 4.1.7).

At this visit new SAEs and changes to SAEs/AEs ongoing at Day 29 need to be recorded. Any provisioned device for ePRO application needs to be returned by the subject to the site directly or shipped according to instructions provided at clinical trial start.

4.2 Emergency Unblinding

Unblinding for adverse events should only be performed in emergencies where knowledge of the subject's group assignment is essential for further management of the subject's medical care.

Unblinding a subject's group assignment under any other circumstances will be considered a protocol violation. In case of an emergency, the Principal Investigator (PI) has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. The investigator must also immediately notify the Sponsor and the Medical Monitor that the code has been broken. If possible, the Sponsor should be consulted before the code is broken, but this will only occur if the safety of the participant will not be compromised. Although the Medical Monitor should be contacted, the subject's treatment code should not be communicated to the Medical Monitor. Emergency unblinding for adverse events will be performed through an IXRS. All calls resulting in an unblinding event are recorded and reported by the IXRS. Emergency unblinding must also be appropriately documented at the trial site. The Medical Monitor will receive notification of unblinding from IXRS but will not be notified of the subject's treatment assignment.

As emergency unblinding is performed via electronic systems (IXRS) unblinding of treatment will be provided. The detailed process for emergency unblinding will be described in a trial-specific procedure.

Subjects who become unblinded for any reason during their participation in the trial will not be replaced and will be withdrawn from the trial.

BN Clinical Safety and Pharmacovigilance (CSPV) and Pharmacovigilance (PV) Vendor will have appointed designee(s) that may receive the unblinded data should a subject be unblinded due to safety concern / SAE (i.e., when regulatory reporting is required). This will be described in the Safety Management Plan.

4.3 Trial Duration

The overall duration of the trial is approximately 24 months. For the potential additional subjects that will be enrolled in RSV season 2 the trial duration would only be approximately 12 months.

RSV season 1 – approximately 6 months (starting from screening of first subject of RSV season 1 to the end of this RSV season (up to 12 months)).

RSV season 2 (if applicable) – approximately 6 months (starting from screening of first subject enrolled in season 2 to the end of this RSV season (up to 12 months)).

Durability follow up – starting approximately 12 months after vaccination for subjects enrolled in season 1 until up to 24 months after vaccination.

4.4 Data Monitoring Committee

The data monitoring committee (DMC) is an independent board that will oversee the safety of subjects participating in the trial, evaluate the efficacy data, and make the recommendation to

either discontinue or continue to RSV season 2 based on pre-specified decision rules if the number of LRTD events is less than 53 (≥2 symptoms) or 22 (≥3 symptoms) at the end of season 1. The members of the DMC are independent, i.e., are not involved as investigators in any MVA-BN-RSV trials and have no direct or indirect financial interests in BN or the Contract Research Organization (CRO) managing the trial. The primary responsibilities of the DMC are to periodically review and evaluate the accumulated trial data for participant safety, efficacy of the vaccine, trial conduct and progress, and to make recommendations to BN, the Coordinating Investigator, and PIs concerning the continuation, modification, or termination of the trial program. The DMC considers trial-specific data as well as relevant background knowledge about the disease, test agent, and subject population under study.

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

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

4.5 Adjudication Committee

The adjudication committee is an independent board that oversees the adjudication of ARD and LRTD for cases of confirmed RSV infection for primary and key secondary efficacy endpoints. The committee will consist of 3 members including a medical expert in infectious diseases or pulmonologist, a radiologist, and an internal medicine physician who are blinded to the trial treatment subjects received. One of them will act as a chairperson with responsibilities described in a charter.

The adjudication committee will receive on an ongoing basis case packages of all diagnosed ARD and LRTD with confirmed RSV infection. Case packages will at a minimum include PCR test results, respiratory tract symptom documentation, and x-ray (if present). The radiologist of the adjudication committee will always rate the x-rays and check for confirmation of LRTD diagnosis. The adjudication committee will review all case packages in a timely manner and adjudicate whether cases are ARD or/and LRTD (≥3 symptoms, ≥2 symptoms or/and severe LRTD). Details of the procedures, responsibilities and timelines will be specified in Section 7.4 and in an adjudication manual.

4.6 Trial Halting Rules

At the end of season 1, if the number of LRTD cases observed is less than 53 (≥2 symptoms) or 22 (≥3 symptoms) (the minimum number of cases for the primary analysis), a futility analysis will be performed. Based on the results of the futility analysis recruitment and durability surveillance during a second year after vaccination may move forward or be terminated. If the number of LRTD cases observed is at least 53 (≥2 symptoms) and 22 (≥3 symptoms), durability

surveillance for RSV during the second year after vaccination depends on results of the primary analysis at the end of season 1. Details and decision rules are described in Section 11.8.

A temporary halting or termination for the trial may also be decided by the DMC in case of an occurrence of:

- A vaccine-related SAE; or
- An unexpected (i.e., not listed in the current IB) grade 3 or higher systemic reaction or lab toxicity as defined in Appendix 1.

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

If an event that meets the trial halting criteria reaches the investigator's attention, the investigator is required to alert the responsible PV Department immediately (within 24 hours) and provide a comprehensive documentation of the event. Contact details of the responsible PV Department are provided in Section 9.3.1.

5 Selection of Subjects

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

For subjects not fulfilling the eligibility criteria, the minimum information documented in the eCRF is confirmation of informed consent form (ICF) signature, demographics, eligibility criteria, adverse and serious adverse events, and reason for screen failure (Section 12.2).

Subjects who participate in the trial during RSV season 1 will be encouraged by the site to continue with the trial during a second year after vaccination. They will be called by the site 4 to 6 weeks prior the start of the durability portion of the trial. Subjects' agreement or discontinuation will be entered into the eCRF.

5.1 Recruitment Procedure

Subjects will be recruited actively. Recruitment strategies, including IRB-approved advertisements, will be evaluated by the Sponsor. Subjects identified as potential participants in the trial will be provided with all necessary information required to make an informed decision about their participation in the trial.

5.2 Inclusion Criteria

Please refer to Protocol Synopsis Section 1.3.

5.3 Exclusion Criteria

Please refer to Protocol Synopsis Section 1.3.

6 Investigational Medicinal Product

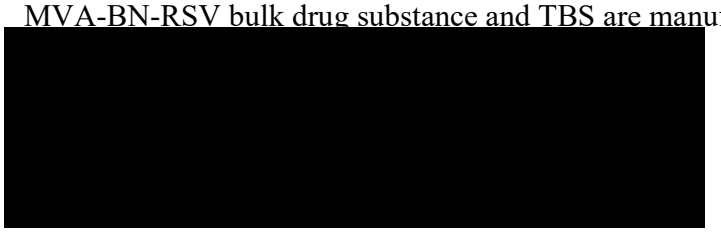
MVA-mBN294B (common name MVA-BN-RSV vaccine) is a highly attenuated, live recombinant virus based on the viral vector MVA-BN. It is supplied in single use vials at a dose level of nominal titer of at least 3×10E8 Inf.U (0.5 mL volume) if used undiluted, provided as a LF formulation. It is administered as an intramuscular injection.

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

Placebo consists of TBS. TBS will be provided in liquid aliquots of 0.5 mL. One dose of 0.5 mL placebo contains 0.605 mg trometamol (tris-hydroxymethyl-amino methane) and 4.09 mg sodium chloride. It is administered as an intramuscular injection.

6.1 Production, Packaging and Labeling

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



The packages and vials of liquid frozen MVA-BN-RSV vaccine and placebo are labeled taking into consideration the regulatory requirements for the respective countries.

6.2 Shipment, Storage and Handling

MVA-BN-RSV vaccine and placebo are packed separately in an open-labeled manner and will be shipped under temperature control and monitoring to the warehouse and from the warehouse to the CTSs. At the CTS, the package is handed over to the unblinded personnel in charge of vaccine preparation, e.g., the pharmacist. At the CTS, the unblinded personnel are the only individuals with knowledge as to which vaccine formulation subjects receive. They are not allowed to disclose this information. Upon receipt the unblinded CTS personnel are responsible for proper storage of vaccine and placebo.

MVA-BN-RSV vaccine is shipped and stored at -4°F ± 9°F (-20°C ± 5°C) avoiding direct light. A vial must not be re-frozen once it has been thawed. Details on shipment, storage and handling

of the LF formulation of MVA-BN-RSV vaccine are provided in trial-specific shipment/storage and vaccination instruction.

Placebo must be shipped and stored at 36°F to 46°F (+2°C to +8°C).

6.3 Preparation, Administration and Dosage

The preparation of the vaccine will be performed by authorized, unblinded personnel only. The unblinded personnel must not be involved in the trial treatment and/or the evaluation of the trial subjects. The administration of the vaccine will be performed by authorized, blinded personnel only.

Trial-specific vaccination instructions detailing the preparation and application procedure will be provided to the CTS.

6.4 Accountability and Disposal

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

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

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

Hazardous materials such as used syringes and needles with hazardous content should be discarded immediately in a safe manner, e.g., autoclaved or incinerated and discarded at the CTS according to local regulations and will therefore not be retained for accountability purpose.

6.5 Randomization and Blinding

This is a double-blind clinical trial with blinding and unblinding procedures governed by a study specific manual. A third party is responsible for creating and maintaining the randomization

schedule, as well as implementing the randomization system. Details will be described in a trial-specific charter.

Subjects will be randomized in a 1:1 ratio to either the MVA-BN-RSV group or the placebo group stratified by age group (60 to 64, 65 to 74, 75 to 84, ≥85 years) and by CTS after confirmation of subject's eligibility.

Since MVA-BN-RSV vaccine and placebo are packed in an open-labeled manner, dedicated team members at the CRO and the sponsor will form an unblinded trial team to oversee all aspects of handling, preparation and accountability of IMP. At the CTS, the unblinded personnel are the only individuals with knowledge related to which substance subjects receive. The unblinded CTS personnel will be in charge of IMP handling, preparation and accountability at the site. Syringes will be labeled in a way that subjects cannot see the content.

Unblinded team members are not allowed to disclose this information. Communication between the unblinded and blinded team members will be outlined in a trial-specific procedure.

When at least 53 (≥2 symptoms) and 22 (≥3 symptoms) LRTD events have been observed at the end of RSV season 1, the biostatistics (including statistical programming) team at the statistical service provider will be unblinded and the primary analyses will be performed. The operational team, including data management, clinical operations, and at least one statistician who will support the operational team will remain blinded until the decision concerning follow-up for durability during a second year after vaccination is made.

If the success criterion for the primary endpoints is met at the end of RSV season 1, the trial will continue to follow-up of subjects for durability of protection. The operational team, including data management and clinical operations will remain blinded on subject-level randomization or vaccination information until the end of RSV season 2 and the clinical database is locked. A blinded statistician will be assigned to continue to support the operational team during the period of follow-up for durability. However, no major protocol amendment that may affect the primary and secondary efficacy endpoints will be allowed.

If the success criterion for the primary endpoints is not met at the end of season 1, the trial will be terminated.

If the number of LRTD events from season 1 did not meet the sample size requirement for the primary endpoints, a futility analysis will be performed by an independent vendor. If the futility criterion is not met as determined by the DMC, the trial will continue and enroll/vaccinate further subjects. No one will be unblinded.

The clinical database will be locked after proper data cleaning and the entire clinical trial team will be unblinded after the decision to terminate the trial is made.

7 Assessment of Efficacy

7.1 Signs and Symptoms of Respiratory Tract Disease

The presence of signs and symptoms for respiratory illness will be collected via an eDiary starting the day after vaccination to end of at least 1 RSV season (i.e., up to 12 months after vaccination), details in Section 4.1.2

Lower Respiratory Tract Disease (LRTD; ≥3 or ≥2 symptoms)

RSV-associated LRTD is defined by the presence of clinical evidence of at least 1 sign or symptom of ARD (see below) and at least 3 (or 2) of the following signs or symptoms with onset ≥14 days following vaccination, confirmed and documented by a medical professional, and RSV infection confirmed by PCR analysis of NP swab collected within 5 days (preferably 72 hours) of symptom onset.

- hypoxemia (oxygen saturation <92% at rest in conjunction with an at least 3% decrease from baseline)
- respiratory rate >25 breaths/Min (High, 2009)
- imaging evidence of new onset of bronchitis, bronchiolitis, or pneumonia
- new cough or worsening of pre-existing cough
- new wheezing or worsening of pre-existing wheezing
- new sputum production or worsening of pre-existing sputum production
- new shortness of breath or worsening of pre-existing shortness of breath

Lower Respiratory Tract Disease (severe LRTD)

RSV-associated LRTD is defined by the presence of clinical evidence of at least 1 sign or symptom of ARD (see below) and at least 1 of the following signs or symptoms with onset ≥14 days following vaccination, confirmed and documented by a medical professional, and RSV infection confirmed by PCR analysis of NP swab collected within 5 days (preferably 72 hours) of symptom onset.

- hypoxemia (oxygen saturation <92% at rest in conjunction with an at least 3% decrease from baseline)
- respiratory rate >25 breaths/Min (High, 2009)
- imaging evidence of new onset of bronchitis, bronchiolitis, or pneumonia

Acute Respiratory Disease (ARD)

RSV-associated ARD is defined by the presence of either 1 ARD symptom lasting for at least 24 hours or 2 simultaneously occurring ARD symptoms (irrespective of duration), with onset starting ≥14 days following vaccination, with RSV infection confirmed. NP sample collection for PCR and targeted physical exam must be completed amongst other procedures within 5 days (preferably 72 hours) of symptom onset.

- rhinorrhea
- nasal congestion
- pharyngitis
- earache
- new cough or worsening of pre-existing cough
- new wheezing or worsening of pre-existing wheezing
- new sputum production or worsening of pre-existing sputum production
- new shortness of breath or worsening of pre-existing shortness of breath
- fever >100°F / >37.8°C (oral temperature) (High, 2009)

7.2 Respiratory Pathogen Panel

Whether ARD or LRTD is associated with RSV or not is assessed via respiratory viral panel (RVP) testing. Samples for the RVP need to be collected preferably within 72 hours but no later than 5 days of symptom onset.

In case of any symptoms indicating a respiratory tract disease (Section 1.3) following vaccination to end of RSV season, the subject needs to return to the CTS and a NP swab will be obtained at the onsite SV to assess if a current RSV disease is underlying. This determination will be done in the central laboratory by running an RVP differentiating also between RSV subtype A and B in addition to several other pathogens (to account for e.g. multiple infections) utilizing a technology which will be specified in the laboratory manual. Subjects need to be instructed to return to the site preferably within 72 hours but not later than 5 days after start of symptoms. The results of the RVP will not be available to the site for immediate treatment decisions. If needed in the context of further subject treatment, the site is encouraged to additionally perform a locally available test.

7.3 RSV-specific Symptoms and Complications

RSV-specific symptoms are defined by any case of rhinorrhea, nasal congestion, pharyngitis, cough (or worsening of), earache, wheezing (or increase in baseline wheezing), sputum production (or increase / change in nature of baseline sputum production), new (or worsening of) shortness of breath or fever >100°F / >37.8°C (oral temperature) plus RSV disease confirmed by

the PCR testing (Section 7.1) from nasopharyngeal swabs collected preferably within 72 hours but no later than 5 days of symptom(s) onset. The presence of RSV-specific symptoms are collected during the symptom visit starting after vaccination until up to 12 months later (Section 4.1.2).

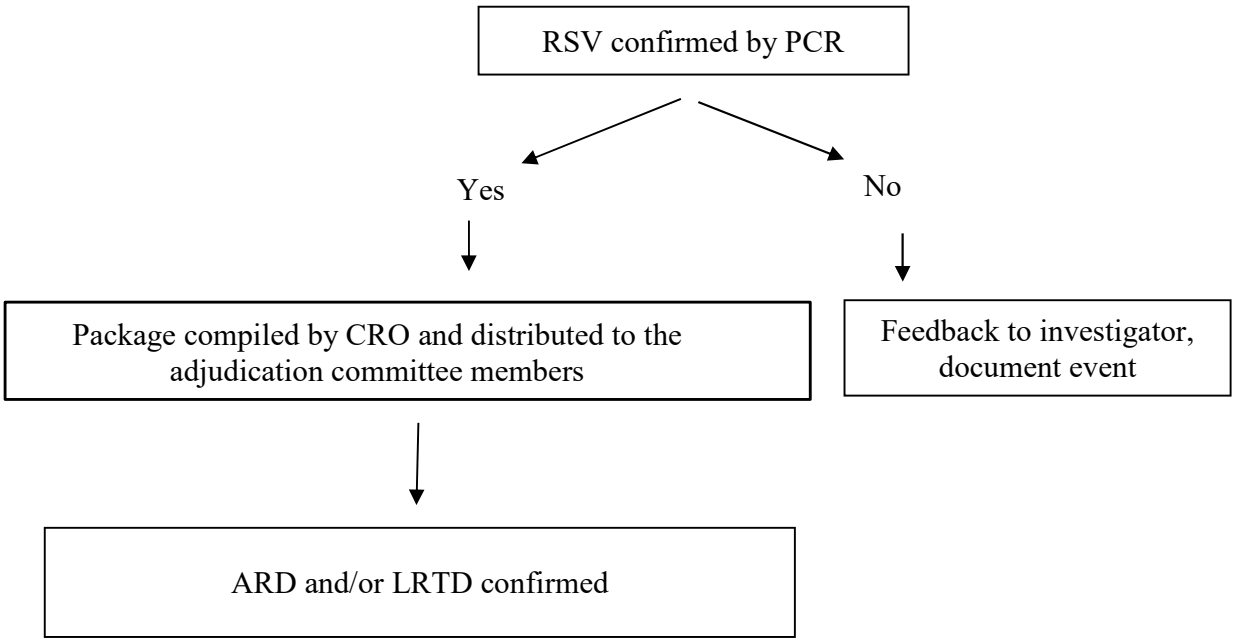
RSV-specific complications include presence of acute clinical consequences of RSV infection, such as pneumonia (incl. bacterial superinfection), sepsis, positive blood culture, and pneumothorax as well as longer term consequences of RSV-specific symptoms, such as persistent worsening of chronic conditions (e.g. COPD), new onset of persistent medical conditions (e.g. chronically impaired lung function, asthma) or a worsening of the functional status of the patient, e.g. new onset of nursing or assisted living need.

7.4 Adjudication Committee for Efficacy Endpoints

The adjudication committee (refer to Section 4.5) will adjudicate all cases of RSV laboratory-confirmed respiratory tract disease and rate if criteria – for the primary endpoints LRTD with ≥3 symptoms, primary endpoint LRTD with ≥2 symptoms, the secondary endpoints severe LRTD and ARD – are met (Figure 7). The committee will work continuously during the whole trial. Processes, responsibilities, set up of the committee and decision making are described in the adjudication committee charter. Based on described decision rules, the adjudication committee will decide whether criteria for primary or secondary efficacy endpoints are met. The adjudication committee will receive blinded information only as specified in the charter. Any deviation from the charter will be documented and corrective actions will be established. The radiologist in the adjudication committee will perform an independent read out of the available x-rays obtained for suspected LRTD cases.

The adjudication committee will receive only those cases with confirmed positive RSV PCR.

Figure 7: Flowchart LRTD/ARD – Process Adjudication Committee



The adjudication committee should review all cases with positive RSV panel to ensure alignment on symptom assessment and discuss all ARD and LRTD (≥3 or ≥2 symptoms or severe LRTD) cases with positive RSV PCR. The committee will consist of three members: an infectious disease expert, an internal medicine physician, and a radiologist.

8 Immunogenicity Assessment

8.1 Systemic Humoral Immune Responses

Serum samples will be collected from a subset of subjects as outlined in the trial procedure schedule in Section 1.4. Samples for immunogenicity testing will be obtained at the vaccination visit prior to vaccination and approximately 2 weeks after vaccination (Day 14 to 16). Additional samples will be taken from the same subgroup approximately 1 and 2 years after vaccination (Section1.4.2).

RSV-specific (e.g. by IgG/IgA ELISA or PRNT assays) and vaccinia-specific antibody responses will be assessed in vaccinated subjects. Serum assays will be performed at Bavarian Nordic [redacted].

The procedures for collection, preparation, storage and shipment of serum samples are specified in separate Study Specific Instructions, which will be provided to the investigators / clinical trial site personnel as well as to the processing laboratories before recruitment commences.

Additionally, the personnel will be trained on the procedures during the investigator meeting / site initiation visit for the sites participating in the immunogenicity sampling.

8.2 Cellular Immune Responses

PBMC samples will be collected from a subset of subjects as outlined in the trial procedure schedule in Section 1.4. Samples for immunogenicity testing will be obtained on the vaccination visit prior to vaccination and approximately 1 week after vaccination (Day 7 to 10). Additional samples will be taken from the same subgroup approximately 1 and 2 years after vaccination Section (1.4.2).

RSV-specific cellular immune responses will be assessed in vaccinated subjects. PBMC assays will be performed at Bavarian Nordic [redacted]

The procedures for collection, preparation, storage and shipment of PBMC samples are specified in separate Study Specific Instructions, which will be provided to the investigators / clinical trial site personnel as well as to the processing laboratories before recruitment commences. Additionally, the personnel will be trained on the procedures during the investigator meeting / site initiation visit for the sites participating in the immunogenicity sampling.

8.3 Future Use of Lab Specimen

Serum samples will be stored for future testing as described above in Section 8.1 and for supporting the licensure path of MVA-BN-RSV vaccine and other recombinant MVA-BN vaccines. Future testing will facilitate the bridging of trial results to animal immunogenicity results and/or to immune response data collected from subjects vaccinated with competitor vaccines. Further, remaining samples might be used for assay development and controls. Subjects will be asked to consent to storage / future use of samples and will be informed about data protection measures. Specimens will be stored in BN's secured laboratory area or at an external storage facility in a coded, pseudonymized manner to ensure data protection. Genetic testing will not be performed.

9 Safety and Reactogenicity

Safety will be monitored by collection of medical history including onset of new chronic disease and by performing physical examinations including vital signs when appropriate. Reactogenicity for local and systemic solicited AEs will be collected for 8 days post vaccination via an eDiary as application on ePRO. Ongoing symptoms after day 8 will be collected until resolution.

9.1 Definitions

9.1.1 Medical History

Symptoms and conditions present before or at SCR/V1 will be documented in the medical history.

9.1.2 Adverse Events

AEs are defined as any untoward (undesirable) occurrence of a medical event in a clinical trial subject temporally associated with the administration of an IMP or a medicinal product (MP) which does not necessarily have a causal relationship with this IMP/MP. Any new signs, symptoms or changes in health starting after ICF signature are documented in the subjects' records and the AE section of the eCRF (data collection requirements for screen failures see Section 12.2). AEs are recorded based on unsolicited and solicited questioning (Section 9.1.2.1 and 9.1.2.2).

9.1.2.1 Unsolicited AEs

Unsolicited AEs are defined as AEs which are not pre-listed on the eDiary/memory aid. AEs (e.g., feeling of ill-health, subjective symptoms and objective signs, intercurrent diseases, accidents, etc.) observed by the investigator and/or reported by the subject must be recorded in the eCRF regardless of the assessment of causality in relationship with the IMP/MP.

The investigator should ask the subjects if they have experienced any AEs or visited a medical care provider since their last visit. All intercurrent diseases reported by the subject need to be recorded by the investigator in the appropriate section of the eCRF.

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

9.1.2.2 Solicited AEs

In this clinical trial protocol solicited AEs are defined as all local and systemic symptoms specifically listed in the eDiary/memory aid provided to the subjects following the vaccination. After vaccination, the subjects are requested to monitor and record local symptoms (i.e., erythema, swelling, induration, pruritus and pain at the injection site) as well as systemic

symptoms (i.e., body temperature, headache, chills, myalgia, nausea and fatigue) in the eDiary/memory aid daily for the day of vaccination and the following 7 days (Days 1 to 8, 8-day period) or until resolution if still ongoing at Day 8.

9.1.2.3 SAEs

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening

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

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

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

9.2 Assessments

9.2.1 Relevant Medical History

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

9.2.2 Prior and Concomitant Medication

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

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

Exclusionary medications or medication use where washout periods need to be adhered to are (see also eligibility criteria in Section 1.3):

- Vaccinations or planned vaccinations with a licensed live or vector-based vaccine within 30 days prior to or after trial vaccine administration or with a licensed inactivated or RNA-based vaccine within 14 days prior to or after trial vaccine administration.
- Chronic systemic use (defined as more than 14 days) of >10 mg prednisone (or equivalent) per day or any other systemic use of immune-modifying drugs. during a period starting from 3 months prior to first administration of the trial vaccine and ending at the EOS. The use of topical, inhaled, ophthalmic and nasal glucocorticoids will be permitted.
- Administration or planned administration of immunoglobulins and/or any blood products during a period starting from 3 months prior to first administration of the trial vaccine and ending at the last visit of the EOS.
- Uncontrolled anticoagulant treatment. Anticoagulant treatment under adequate control for cardiovascular prophylaxis or prophylaxis of thromboembolic disease or stroke in the setting of atrial fibrillation are not excluded.
- Use of any investigational or non-registered drug or vaccine other than the trial vaccine within 30 days preceding the administration of the trial vaccine, or planned administration of such a drug between enrollment in the trial and until the end of the clinical trial including follow-up.
- Prior or planned vaccination with an RSV vaccine/vaccine candidate.

9.2.3 Physical Examination

Complete physical examination

A complete physical examination will be performed at screening (including body height and weight, body mass index (BMI) assessment). Complete or targeted physical exams may be performed at visits other than those indicated based on investigator's discretion.

Any clinically significant findings at the baseline physical examination will be recorded as medical history events, and any new or worsening of clinically significant findings post-treatment will be captured as adverse events. The only data captured in the eCRF for the physical examination itself will be the date it was performed.

Targeted physical examination

A targeted physical examination, guided by any signs or symptoms previously identified or any new symptoms that the subject has experienced since the last visit, is required at all SV. Any new or worsening of clinically significant findings from the treatment period physical examinations will be recorded as AEs.

9.2.4 Vital Signs

At all visits, saturation of peripheral oxygen, respiratory rate, blood pressure and pulse rate will be taken after the subject has been sitting upright for approximately 2 minutes. Body temperature will be measured orally.

9.2.5 Unsolicited AEs

All intercurrent diseases reported when the investigator actively questions the subject will be documented and all required details (e.g., start and stop date, intensity) will be assessed. Unsolicited AEs will be reported in the subject's medical record and respective AE eCRF (requirements for screen failures see Section 12.2).

Unsolicited AEs will be assessed and documented from ICF signature to end of active trial phase corresponding to 29 days post vaccination and if ongoing, followed until resolution or until the subject's last trial visit.

SAEs and new AEs related to potential RSV respiratory disease (as defined in the ARD/LRTD definitions) will be assessed and documented at all trial visits until EOS. SAEs will be followed up until resolution or achievement of stable clinical conditions.

Assessment of Intensity

For all unsolicited AEs not represented in the toxicity scale for Laboratory Values (Appendix 1), the maximum intensity will be based on the following descriptions:

Grade 1	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with daily activities.
Grade 2	An AE which is sufficiently discomforting to interfere with daily activities.
Grade 3	An AE which prevents daily activities. Such an AE would, for example, prevent attendance at work and would necessitate corrective therapy.
Grade 4	Life-threatening, causing hospitalization, or disabling.
Grade 5	Fatal

Assessment of Causality

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

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

Probable The pharmacological properties of the IMP or substance class, and/or the course of the AE after discontinuation of the IMP and possible subsequent re-exposure, and/or specific findings (e.g. positive allergy test or antibodies against the IMP / metabolites) suggest a (concomitant) causal connection with / worsening of the AE resulting from the IMP, however another cause cannot completely be ruled out.

Definite The pharmacological properties of the IMP or substance class and/or the course of the AE after discontinuation of the IMP and possible subsequent re-exposure, and/or specific findings (e.g. positive allergy test or antibodies against the IMP / metabolites) definitely indicate that there is a (concomitant) causal connection with / worsening of the AE resulting from the IMP and there are no indications of other causes.

9.2.6 Solicited AEs

After the vaccination, subjects receive an eDiary/memory aid to record solicited local and systemic AEs most likely to occur on the day of vaccination and the following 7 days (Days 1 to 8; 8-day period). Local and systemic symptoms still ongoing after Day 8 will be measured or examined each day until resolution or until no further change can reasonably be expected and will be documented in the eDiary/memory aid.

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

The investigator will discuss this information during the following scheduled visits and will perform an assessment of the events including causality (for solicited systemic AEs), seriousness, outcome, and any intervention required.

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

9.2.6.1 Solicited Local AEs

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

Assessment of Intensity

Injection site erythema, swelling, and induration will be assessed based on the longest diameter as measured by the subject in mm and recorded in the memory aid. Subjects are asked to document the solicited local AEs in the memory aid as described in Table 11 below.

Table 11 Grading of Local Symptoms from the Subject's Memory Aid

		Grading for Analysis	Grading in Former Version of the Protocol
MedDRA coded Preferred Term Local Adverse Events	**Grade**	**Severity Measure[a]**	**Severity Measure**
Injection site erythema, Injection site swelling, and Injection site induration[b] (longest diameter measured in mm)	0	<25 mm	0 mm
	1	≥25 mm - <50 mm	<30 mm
	2	≥50 – <100 mm	≥30 – <100 mm
	3	≥100 mm	≥100 mm
Injection site pruritis	0	Same as assessed at diary review	Absent
	1		Mild
	2		Moderate
	3		Severe
Injection site pain	0	Same as assessed at diary review	Absent
	1		Painful on touch
	2		Painful when limb is moved
	3		Spontaneously painful/prevents normal activity

[a] Per FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in preventive Vaccine Clinical Trials (September 2007). Available at https://www.fda.gov/media/73679/download

[b] Per FDA Guidance injection site swelling and induration are combined (ie. injection site swelling/induration).

Assessment of Causality

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

9.2.6.2 Solicited Systemic AEs

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

Assessment of Intensity

Subjects are asked to document the solicited systemic AEs in the memory aid as described in Table 12 below. In the subject's memory aid, the grading of maximum symptom intensity is described in basic, easily understood language based on the following descriptions:

Table 12 Grading of Systemic Symptoms from the Subject's Memory Aid

		Grading for Analysis	Grading in Former Version of the Protocol
MedDRA coded Preferred Term Systemic AEs	**Grade**	**Severity Measure [a]**	**Severity Measure**
Body temperature (oral) [b]	0	<100.4°F (<38.0°C)	<99.5°F (<37.5°C)
	1	100.4°F – 101.1°F (38.0°C – 38.4°C)	≥99.5 – <100.4°F (≥37.5 – <38.0°C)
	2	101.2°F – 102.0°F (38.5°C – 38.9°C)	≥100.4 – <102.2°F (≥38.0 – <39.0°C)
	3	102.1°F – 104°F (39.0°C – 40°C)	≥102.2 – <104.0°F (≥39.0 – <40.0°C)
	4	>104°F (>40°C)	≥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

[a] Per FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in preventive Vaccine Clinical Trials (September 2007). Available at https://www.fda.gov/media/73679/download

[b] Pyrexia is defined as oral temperature ≥100.4°F (≥38.0°C), which is fever Grade ≥1 by FDA grading and oral temperature Grade ≥2 as originally collected

Assessment of Causality

Causal relationship between solicited systemic AEs and the vaccine will be assessed by the investigator using the same categories as for unsolicited AEs (see Section 9.2.5).

9.2.7 Laboratory Measurements

Laboratory measurements will be performed if clinically indicated in the investigator's opinion e.g. in the course of an SAE. In this case CTS local laboratory will be used.

9.2.8 Pregnancy

It is unlikely that female subjects will be of childbearing potential, given the age criteria for the trial. However, as per inclusion criteria, any women of childbearing potential must have a negative urine pregnancy test performed within 24 hours prior to the vaccination. In addition, they must have used an acceptable method of contraception for 30 days prior to the vaccination, must agree to use an acceptable method of contraception during the trial, and must avoid becoming pregnant for at least 28 days after the vaccination. Nevertheless, IMP-exposed pregnancies (participating females and female partners of participating males) cannot be excluded with certainty. Subjects who become pregnant during the active trial period (up to and including one month [minimum 28 days] after receiving the vaccination) may continue other trial procedures at the discretion of the investigator. All cases where the embryo or fetus may have been exposed to the vaccine should be followed-up until delivery in order to collect information on the outcome of the pregnancy.

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

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

9.3 Reporting

9.3.1 Reporting of SAEs

All SAEs (collection starts at signing of ICF) occurring throughout the entire course of the trial have to be entered in the eCRF within 24 hours of awareness by the investigators, which triggers a notification to the Drug Safety (DS) Department of the contract research organization (CRO).

In case the eCRF is unavailable, a manual paper SAE report form is to be completed and sent via email to the DS Department of the CRO within 24 hours of becoming aware of the SAE. The SAE must still be reported in the electronic data capture (EDC) eCRF as soon as it is availableCRO:

[redacted]

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

- the reporter (investigator's name and contact information)
- the subject
- involved IMP
- (S)AE(s)
- seriousness criterion
- date of onset

BN is responsible for expedited as well as periodic reporting to the involved regulatory authorities (e.g., Food and Drug Administration (FDA)) according to applicable laws and guidelines. Regulatory authorities will be notified as soon as possible but no later than 7 days after first knowledge of a fatal or life-threatening unexpected SAE with an at least possible relationship to the IMP (Suspected Unexpected Serious Adverse Reaction (SUSAR)) and no later than 15 days after knowledge of any other SUSAR. The investigator is responsible for reporting to the Ethics Committees or IRBs.

9.3.2 Reporting of Pregnancies

All reports where the embryo or fetus may have been exposed to the trial product (either through maternal exposure or transmission of trial product via semen following paternal exposure) should be followed-up until delivery in order to collect information on the outcome of the pregnancy.

If a female subject or female partner of a male subject becomes pregnant during the active trial phase (up to and including 1 month [minimum 28 days] after receiving the trial vaccination), the positive pregnancy test result must be recorded on the Pregnancy Test eCRF and also reported on the manual paper Pregnancy Report Form, within 24 hours of the investigator becoming aware of the pregnancy, and forwarded to [redacted] The female partner of a male study participant should sign the Pregnant Partner Informed Consent Form for follow up.

A pregnancy will be followed to its outcome to include any premature terminations. The investigator should collect details pertaining to the pregnancy outcome to include, but not limited to the health status of the mother and child including date of delivery and the child's sex and

weight, etc. Within 24 hours of awareness of the pregnancy outcome, the pregnancy outcome should be reported on the manual Pregnancy Outcome Follow-up Form and forwarded to [redacted]

Any event during pregnancy fulfilling the criteria for an SAE will be reported as an SAE (Section 9.3.1). However, hospitalization for delivery is a prospectively planned hospitalization and is not considered an SAE per se.

10 Burden of Disease Assessments

10.1 Respiratory Intensity and Impact Questionnaire (RiiQ)

RiiQ is a respiratory illness specific questionnaire (Falsey, 2021) covering 3 domains: upper respiratory (nasal congestion, sore throat), lower respiratory (coughing, wheezing, shortness of breath, and sputum), and systematic symptoms (headache, fever, neck pain, body aches, fatigue, sleep problems, and appetite loss). The symptoms in each domain are measured at 4 levels of severity—the mean of the symptom scores gives the domain scores, the mean of the domain scores gives the total score.

The RiiQ will be completed at Screening and symptom onset and for 7 days after (8 days total). If symptoms continue and RSV PCR test is confirmed positive, the RiiQ will continue to be filled out until symptoms resolve or 21 days are completed, whichever comes first. Further details are summarized in a study specific instruction.

10.2 EuroQoL 5-Dimension 5-Level (EQ-5D-5L) Questionnaire

The EQ-5D-5L questionnaire is a generic preference-based measure of health covering 5-dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) measured at 5 levels of severity. The health states will be converted into a single score representing a participant's quality of life measured between 0 (death) and 1 (full health).

The EQ-5D-5L questionnaire will be completed at Screening, at 6 and 12 months for all subjects and at a symptom visit if an NP swab is taken, and on day 6 and at 1, 3, 6, and 12 months after the symptom visit.

If the long-term follow-up time points (e.g., 12 months after symptom visit) fall beyond the first 12 months of follow-up after vaccination of the subject, the outstanding questionnaires are to be completed during the durability phase of the trial, if it is conducted. Further details are summarized in a study specific instruction.

10.3 15-Dimension (15D) Health-related Quality of Life Instrument

The 15D questionnaire is a generic preference-based measure of health covering 15-dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity). Each dimension is measured at 5 levels of severity. The health states will be converted into a single score representing a participant's quality of life measured between 0 (death) and 1 (full health).

The 15D questionnaire will be completed at Screening, at 6 and 12 months for all subjects and at symptom visit if an NP swab is taken, and on day 6 and at 1, 3, 6, and 12 months after symptom visit.

If the long-term follow up time points (e.g., 12 months after symptom visit) fall beyond the first 12 months after vaccination of the subject, the outstanding questionnaires are to be completed during the durability phase of the trial, if it is conducted. Further details are summarized in a study specific instruction.

10.4 Tilburg Frailty Indicator

In addition to the assessments already described above, the TFI part B only will be assessed at screening for all subjects.

The TFI questionnaire is a frailty index. The frailty components include 15 questions - 8 describe physical components of frailty, 4 describe psychological components, and 3 describe social components. Typically, respondents who are described by 5 or more of the frailty components are considered frail (in GFI, the cut-off is at four).

11 Statistical Analysis Plan

This section outlines statistical methodologies and procedures to be used for the clinical trial.

11.1 Randomization and Unblinding Procedure

Please refer to Section 6.5 for further details.

11.2 Primary Trial Hypothesis

Vaccination with MVA-BN-RSV will reduce the incidence of LRTD associated with RSV in adults ≥60 years of age.

The success criterion for the two primary endpoints is that the lower bound of the 95% (two-sided) confidence interval (CI) is greater than 20% for the estimated vaccine efficacy against LRTD (≥3 or ≥2 symptoms), respectively.

11.3 Endpoints

Please refer to Protocol Synopsis (Section 1.3).

11.4 Multiplicity

If the number of LRTD events does not meet the sample size requirement, a futility analysis will be conducted towards the end of RSV season 1 before proceeding to durability follow-up of subjects or further enrollment and vaccinations in case needed (refer to Section 11.8). There is only one efficacy analysis of the primary and the key secondary efficacy endpoints to confirm the trial hypotheses.

A hierarchical testing strategy will be employed and no multiplicity adjustment will be made. At first, the hypothesis related to vaccine efficacy for LRTD with ≥3 symptoms will be tested against the null hypothesis of ≤20% at the two sided significance level α=0.05, or equivalently based on the two-sided 95% CI. If the success criterion is met, the hypothesis related to vaccine efficacy for LRTD with ≥2 symptoms will be evaluated in a confirmatory manner against the null hypothesis of ≤20% at the same nominal significance level. Finally, if vaccine efficacy is confirmed for both primary endpoints, the key secondary efficacy endpoint related to RSV-associated ARD will be tested in a confirmatory manner against the null hypothesis of ≤20%. This is consistent with the Gatekeeping procedure, and the type I error rate will not be inflated.

No multiplicity adjustment will be made for the analyses related to the other secondary and exploratory endpoints due to their descriptive nature.

11.5 Sample Size Calculation

11.5.1 Efficacy Analysis

Vaccine Efficacy (VE) is defined as $1 - \frac{Risk\ (Vaccinated\ Subjects)}{Risk\ (Unvaccinated\ Subjects)}$, where the measure of risk can be the incidence rate, hazard rate, or cumulative incidence (attack rate) conditional on equal exposure to infection. The primary analysis of VE will be based on the hazard rate, and therefore, the Cox proportional hazard model will be used.

In general, the incidence rate will be reported as number of cases in person-time. Since we consider the RSV season as unit of 1, cumulative incidence and incidence are the same and will only be referred to as incidence.

The expected vaccine efficacy of MVA-BN-RSV vaccine against LRTD with ≥3 symptoms is 80%. For an alpha = 0.05 two-sided test against a null hypothesis of ≤20% vaccine efficacy, a total of 22 events will be required for 90% power. Assuming the rate of LRTD with ≥3 symptoms is 0.2% in the placebo group during an RSV season, approximately 20,000 subjects vaccinated in 2 treatment groups receiving either MVA-BN-RSV vaccine or placebo will allow the observation

of at least 22 events. If the number of events (LRTD with ≥3 symptoms) required for the primary efficacy analyses is lower than 22 at the end of RSV season 1, approximately 4000 additional subjects will be recruited prior to RSV season 2 such that the total number of events (LRTD with ≥3 symptoms) will be at least 22, conditional on the blinded observed incidence in season 1 with probability of at least 80% to observe the additional required number of events.

The expected vaccine efficacy of MVA-BN-RSV vaccine against LRTD with ≥2 symptoms is 65%. For an alpha = 0.05 two-sided test against a null hypothesis of ≤20% vaccine efficacy, a total of 53 events will be required for 85% power. Assuming the rate of LRTD is 0.4% in the placebo group during an RSV season, approximately 20,000 subjects vaccinated in 2 treatment groups receiving either MVA-BN-RSV vaccine or placebo will allow the observation of at least 53 events. If the number of events (LRTD with ≥2 symptoms) required for the primary endpoint analyses is lower than 53 at the end of RSV season 1, approximately 4000 additional subjects will be recruited prior to RSV season 2 such that the total number of events (LRTD with ≥2 symptoms) will be at least 53, conditional on the blinded observed incidence in season 1 with probability of at least 80% to observe the additional required number of events.

Assuming the rate of ARD is 1.6% in the placebo group during an RSV season, approximately 240 events will be observed if the vaccine efficacy is 50%. This will result in 95% power for an alpha=0.05 two-sided test against a null hypothesis of ≤20% vaccine efficacy.

11.5.2 Immunogenicity Analysis

In season 1 a subgroup of about 300 subjects per group will have serum sample draws, and 150 subjects per group will have PBMC sample draws for immunogenicity analysis prior to vaccination (baseline titer) as well as 1 week or 2 weeks thereafter. Additional blood draws will be taken from the same subgroup 1 and 2 years after vaccination.

Moreover, the samples will be stored for potential future analysis to assess immunogenicity in MVA-BN-RSV vaccinated subjects, e.g., whether immune responses from different target populations in other MVA-BN-RSV trials are non-inferior to those obtained in this phase 3 study population. The sample size is chosen to ensure adequate power for future analyses.

11.6 Analysis Sets

Analysis sets will be defined for the analyses of the clinical trial data.

The full analysis set (FAS) will be defined as subjects who are randomized to any treatment arm and receive the study vaccination. This is the primary analysis set for efficacy assessments and will be based on the treatment group to which the subject is randomized.

The safety set will include subjects who receive any MVA-BN-RSV vaccine or placebo. This is the primary analysis set for safety evaluation and will be based on the actual treatment the subject

received. The list, reporting if actual treatment was received, will be maintained by the third party vendor who is maintaining the randomization and vaccine distribution system and will be provided to the biostatistics teams upon unblinding for interim (unblinded team) or final analyses (blinded team).

Two immunogenicity analysis sets will be defined to assess the humoral and cellular immunity, respectively. They will be subsets of the FAS and include those subjects who were selected for the respective immunogenicity analysis.

11.7 Analysis Methods

11.7.1 Efficacy

11.7.1.1 Population Level Summary and Analysis of Primary Endpoints

The primary efficacy endpoints, the incidence of LRTD (≥3 or ≥2 symptoms) associated with RSV during a single RSV season, are defined as the number of PCR-confirmed LRTD (≥3 or ≥2 symptoms) cases from vaccination plus 2 weeks to the end of RSV season 1 (up to 12 months from vaccination). The case definitions are provided in the Protocol Synopsis Section 1.3.

For the primary analysis, vaccine efficacy of LRTD is defined as the relative reduction of the hazard rate of LRTD associated with RSV in the MVA-BN-RSV vaccinated group compared with that in the placebo group. The statistical hypotheses for the VE of LRTD associated with RSV are H_0: $VE_{LRTD} \leq 20\%$ versus H_1: $VE_{LRTD} > 20\%$.

For each of the two primary endpoints, a Cox proportional hazards regression model based on the FAS stratified by age groups (60 to 64, 65 to 74, 75 to 84, ≥85 years) will be used as the primary analysis to establish VE against LRTD in the MVA-BN-RSV vaccinated group compared with the placebo group. If the "≥85 years" age group is too small (e.g., <10%), it will be combined with the "75 to <85 years" age group. The follow-up time for subjects who develop LRTD associated with RSV will be defined as (first LRTD onset date – vaccination date +1), and LRTD onset will be defined as the date when LRTD symptoms are observed, and the later-obtained sample is positive for RSV by PCR. Subjects who do not develop any LRTD event will be censored at time of dropout (if applicable) or at the end date of RSV season 1. A large number of ties is expected due to end of surveillance. Efron's method will be used to handle ties in the Cox regression model.

The 95% (two-sided) CI of VE obtained from the Cox regression model will be presented. The success criterion is met if the lower bound of the 95% CI is greater than 20% for the estimated VE.

11.7.1.2 Analysis of Secondary Efficacy Endpoints

The key secondary efficacy endpoint is the incidence of ARD associated with RSV during a single RSV season, defined as the number of PCR-confirmed ARD cases from vaccination plus 2 weeks to the end of at least one RSV season (up to 12 months after vaccination). Case definition is provided in the Protocol Synopsis Section 1.3.

For the primary analysis of this secondary efficacy endpoint, VE of ARD is defined as the relative reduction of the hazard rate of ARD associated with RSV in the MVA-BN-RSV vaccinated group compared with that in the placebo group. The statistical hypothesis for VE of ARD associated with RSV is H_0: $VE_{ARD} \leq 20\%$ versus H_1: $VE_{ARD} > 20\%$.

A Cox proportional hazards regression model based on the FAS stratified by age groups (60 to 64, 65 to 74, 75 to 84, ≥85 years) will be used as the primary analysis to establish VE against ARD in the MVA-BN-RSV vaccinated group compared with the placebo group. ARD onset will be defined as the date when ARD symptoms are observed, and the later-obtained sample is positive for RSV by PCR. Other aspects of the analysis related to follow-up time, censoring, and tie handling are identical to the primary analysis of the primary efficacy endpoint.

The 95% (two-sided) CI for VE obtained from the Cox regression model will be presented. The success criterion for the secondary efficacy endpoint is met if the success criteria for the primary efficacy endpoints are met ($VE_{LRTD} > 20\%$) and the lower bound of the 95% CI of VE_{ARD} is greater than 20%.

Formal tests for the other secondary endpoints are not planned. Incidence of complications related to RSV-confirmed respiratory diseases, or hospitalization due to RSV-confirmed diseases or due to complication related to RSV-confirmed respiratory diseases will be summarized and vaccine efficacy will be estimated in a similar manner as the primary endpoints.

RSV-specific serum antibody titers and T-cell responses will be summarized descriptively for the respective immunogenicity subset by timepoint and treatment group presenting geometric mean titers (GMT)/geometric mean spot forming units (GMSFU) along with the 95% CI. Post-baseline results will be compared between the 2 treatment groups using an analysis of covariance (ANCOVA) model on the $\log_{10}$-transformed titers/spot forming units for each of the scheduled post-baseline time points, respectively. The model will include the treatment group and age group as fixed effects and the $\log_{10}$-transformed pre-vaccination titer/spot forming unit as covariate. An adjusted difference in least square means (on the $\log_{10}$ scale) between the 2 treatment groups will be calculated along with the 95% CI and back-transformed to obtain the adjusted GMT/GMSFU ratio with 95% CI. If there is subject in the serum subset experiences any confirmed RSV diseases, the subject will be excluded from the immunogenicity analysis for timepoints after onset of RSV diseases. If there are enough cases in this subset, correlation between RSV diseases and immune responses will be explored.

11.7.1.3 Handling of Potential Intercurrent Events for the Primary and Secondary Efficacy Endpoints

Subjects who terminated trial participation after any confirmed RSV LRTD (for the primary efficacy endpoints) or ARD (for the key secondary efficacy endpoint) will not be considered as having missing data for the primary or secondary efficacy endpoints. Since subjects will only receive a single vaccination prior to the start of the RSV season, early termination due to vaccine-related AE or lack of efficacy is expected to be minimal. Reasons for termination can be related to clinical trial procedures (e.g., burden of participation) or other reasons unrelated to the trial vaccine, which are expected to have no or minimal effect on estimating the vaccine efficacy. Therefore, the treatment-policy strategy will be used to address this type of potential intercurrent events. Vaccine efficacy (defined as 1 minus the hazard ratio of the 2 vaccination groups) against LRTD or ARD associated with RSV disease in the target population will be assessed regardless of whether early termination prior to the end of the RSV season has occurred.

Dual enrollers are defined as subjects who are enrolled more than once in different clinical trial sites for the same RSV trial, or for a different RSV trial during season 1 (from 30 days prior to screening and until end of season 1). This type of intercurrent events can have significant impact on assessment of vaccine efficacy as the subject can receive both an RSV vaccine and a placebo. The while-on-treatment strategy will be used to address this intercurrent event. Subjects will be censored at time of the 2nd enrollment. If the subject is enrolled in another RSV trial prior to this trial, the subject will be censored on Day 1.

11.7.1.4 Supplementary and Sensitivity Analyses of Primary and Secondary Efficacy Endpoints

An unstratified Cox model will also be used to estimate VE of LRTD and ARD in the FAS.

One of the sensitivity analyses is to estimate VE_{LRTD} and VE_{ARD} based on incidences. Incidences of LRTD and ARD at the end of each season will be provided by the vaccination group. A log binomial model will be used to estimate the relative risk in subjects who receive the MVA-BN-RSV vaccine compared to subjects who receive placebo. This is a generalized linear regression model with log-link, incidence of LRTD or ARD as a binary response variable, age group, risk of LRTD, geographic region, and vaccination group as independent variables.

In addition, the primary Cox proportional hazard model will be repeated for both RSV subtypes separately, i.e., the vaccine efficacy will be calculated for RSV subtype A and RSV subtype B, respectively if there are sufficient number of cases by subtype.

11.7.1.5 Subgroup Analysis of Primary and Secondary VE Endpoints

VE_{LRTD} and VE_{ARD} will also be summarized by age group (60 to 64, 65 to 74, 75 to 84, ≥85 years), comorbidities associated with LRTD, sex, race, frailty, and by geographic region based on

the FAS using the Cox regression model as the primary analysis without stratifying by age group. Because the subgroups can be small, the 95% confidence intervals will be considered descriptive and exploratory.

11.7.1.6 Analysis on the Durability of VE

To evaluate the durability of vaccine efficacy, subjects who were vaccinated in season 1 will be followed up for ARD or LRTD (≥3 or ≥2 symptoms) events in season 2. The incidence of ARD or LRTD (≥3 or ≥2 symptoms) will be summarized by vaccination group for the FAS. A similar Cox model as for the primary analysis will be used to estimate VEs and the corresponding 95% CIs by post-vaccination RSV season. VE is considered to be "lost" if the lower bound of the 95% CI for VE_{ARD} is ≤20%, or the lower bound of the 95% CI for VE_{LRTD} is ≤20%. Subjects who had confirmed RSV infection in season 1 will be excluded from the durability analyses.

Due to potential dropouts during the RSV follow-up season, the estimates will be less precise, and the 95% confidence intervals are expected to be wider. The criteria for "loss" of VE are not considered confirmatory. They will provide supportive evidence of VE durability. Subjects who are vaccinated in season 2 (if any) will not be included in these analyses.

11.7.1.7 Analysis on Overall Vaccine Efficacy for Two RSV Seasons

A combined analysis with LRTD (≥3 or ≥2 symptoms) or ARD occurred in 2 RSV seasons will also be performed. In the event of 2 events occurring in the same individual, only the first event will be counted. Subjects who are vaccinated in season 2 (if any) will also be included in these analyses.

The overall incidence of LRTD or ARD will be summarized by vaccination group for the FAS. A similar model as for the primary analysis will be used to estimate VEs.

11.7.1.8 Analysis on Vaccine Efficacy Against Other Respiratory Pathogens

The occurrence of ARD associated with other respiratory pathogens (e.g. hMPV) tested by the central laboratory (Section 7.2) will also be investigated in a descriptive manner. Incidences will be summarized by vaccination group for the FAS. For pathogens for which a sufficiently high number of ARD events is reported, VE will be estimated based on a Cox proportional hazards regression model similar to the primary analysis.

11.7.1.9 Handling of Missing Data for Efficacy Analysis

Subjects will receive ePRO alerts 3 times per week and monthly telephone calls from the site to assess the occurrence of any potential RSV-related symptoms. If the subject has not responded to the ePRO application reminder for more than a week, the subject will receive additional telephone calls from the site. Unless the subject terminates clinical trial participation, missing a

monthly call will not be considered missing data for the estimation of the primary and secondary estimand.

Since subjects with RSV disease typically have symptoms that are similar to other acute respiratory diseases, missing or inadequate nasopharyngeal PCR results for subjects whose documented symptoms meet the ARD or LRTD case definitions will be considered missing data. Every effort will be made to ensure proper nasopharyngeal samples are collected within 72 hours (and no later than 5 days) of symptom onset.

In the primary analyses of VE based on hazard ratios (Cox model), subjects who withdrew from the clinical trial prior to having the event will be censored at time of withdrawal and thus early termination will be accounted for in the analyses. For subjects who had documented symptoms that meet the primary LRTD case definitions, but PCR results are missing, the test result will be assumed to be negative for RSV (since it is not confirmed by PCR) for the primary analysis. The following sensitivity analyses will also be performed.

1. Missing PCR results will be considered RSV positive
2. Best case scenario: PCR results will be considered positive in the placebo group but negative in the MVA-BN-RSV group
3. Worst case scenario: PCR results will be considered negative in the placebo group but positive in the MVA-BN-RSV group

In the sensitivity analyses of VE based on relative risk (log binomial model), subjects who withdrew prior to having the event will be considered as having no RSV disease during the season.

For analysis on durability of VE, subjects who do not continue to participate in the surveillance during the subsequent season(s) will be excluded.

11.7.2 Safety

11.7.2.1 Reactogenicity

Recording of solicited local and systemic symptoms will occur on Day 1 to Day 8 after vaccination.

Local and systemic solicited AEs will be summarized by categories (local versus systemic) and by vaccination group. The risk differences on these solicited AEs between the 2 vaccination groups and the corresponding 95% CI on the risk difference will be provided using the Miettinen and Nurminen method (Miettinen, 1985).

Similarly, solicited AEs with intensity ≥ grade 3, related systemic solicited AEs, and related systemic solicited AEs with intensity ≥ grade 3 will also be summarized.

For solicited AEs, the duration and relative day of onset (in days) will be summarized.

11.7.2.2 Unsolicited AEs

Non-serious AEs will be monitored until 29 days post-vaccination, but serious AEs will be monitored throughout the RSV season.

The incidence of unsolicited AEs will be summarized descriptively by vaccination group and Medical Dictionary for Regulatory Activities (MedDRA) SOC and preferred term (PT) in descending frequency based on the active vaccination group. The summaries will be provided for any TEAEs (defined as AEs occurring on or after date of vaccination and up to the end of the post-vaccination observational period for the respective AEs), non-serious TEAEs, related TEAEs, TEAEs with intensity grade ≥3, related TEAEs with intensity grade ≥3, AEs leading to withdrawal from the trial, SAEs, and related SAEs.

11.7.2.3 Data Handling

Effort will be made to ensure the same event is not recorded multiple times. It is possible that similar local reaction AEs and systemic symptom AEs are also recorded as unsolicited AEs.

Although non-serious AEs will be reported until 29 days post-vaccination, AEs reported up to the end of the post-vaccination observational period will also be considered TEAEs.

If an unsolicited AE has missing or partial onset date or AE end date, relative day to onset or duration of AE will not be computed.

If an unsolicited AE has missing or partial onset date, the event will be considered treatment-emergent unless the year and month of onset are clearly before date of vaccination.

Secondary safety endpoints will also be summarized by subgroups specified in Section 11.7.1.5.

11.7.3 Burden of Disease and Health-Related Quality of Life

RiiQ is a respiratory illness specific questionnaire covering 3 domains: upper respiratory (nasal congestion, sore throat), lower respiratory (coughing, wheezing, shortness of breath, and sputum), and systematic symptoms (headache, fever, neck pain, body aches, fatigue, sleep problems, and appetite loss). The symptoms in each domain are measured at 4 levels of severity; the mean of the symptom scores gives the domain scores; the mean of the domain scores gives the total score.

For subjects with confirmed RSV disease, AUC of the change from baseline in RiiQ total score (defined as mean of all scores) and domain-specific symptom scores, maximum daily change from baseline in RiiQ total and domain-specific symptom scores, and duration of any symptoms will be summarized descriptively.

Besides descriptive summary, the AUC of the change from baseline in RiiQ total score, and the maximum daily change from baseline in RiiQ total score will be compared between the 2 treatment groups. If the score is skewed, transformation of the raw data may be considered.

The EQ-5D-5L questionnaire is a generic preference-based measure of health covering 5-dimensions (mobility, self--care, usual activities, pain/discomfort, and anxiety/depression) measured at 5 levels of severity. The health states will be converted into a single score representing a participant's quality of life measured between 0 (death) and 1 (full health). The EQ-5D-5L data collected in this study will be used for health economic modeling. The analysis and results will not be reported in the CSR.

The 15D questionnaire is a generic preference-based measure of health covering 15-dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity). Each dimension is measured at 5 levels of severity. The health states will be converted into a single score representing a participant's quality of life measured between 0 (death) and 1 (full health). The 15D data collected in this study will be used for health economic modeling. The analysis and results will not be reported in the CSR.

11.8 Safety Monitoring and Futility Analysis (if applicable)

The DMC will monitor safety data closely from enrollment, vaccination to end of the study. There is a planned safety data analysis and safety data review meetings at the end of every season, unless there are specific safety concerns raised during the trial when an ad-hoc DMC meeting will need to be called based on a joint decision of the DMC Chair and the sponsor. In the event that SAEs, or vaccine-related death are suspected, the DMC may recommend stopping the trial.

If the number of LRTD events does not meet the sample size requirement, a futility analysis will be conducted at the end of season 1 before proceeding to season 2. Upon review of the results from the futility analysis, the DMC may recommend to 1) terminate the trial (futility) or 2) continue to enroll additional subjects and to follow up subjects in season 2.

The DMC will consist of clinicians and an experienced statistician who is not associated with the sponsor and is experienced and familiar with futility analyses and decision rules. Specific futility rules and distribution of unblinded information, including list of personnel and contents for distribution, will be described in the DMC charter.

12 Data Management and Electronic Records

12.1 Data Management

Clinical Data Management activities will be performed by a CRO, with oversight by BN. All data management procedures will be detailed in a Data Management Plan (DMP).

12.2 Electronic Case Report Forms

Subject data will be entered into an eCRF in a 21 CFR 11-compliant electronic data capture (EDC) database. The eCRF data will combined with data transmitted from other external systems (e.g., lab data). All data transmissions will be secure. Personal identifiers will not be used when collecting and storing data.

All eCRFs will be completed by authorized clinical trial personnel at the site. Trial personnel will be appropriately trained in the use of eCRFs and application of electronic signatures before being given access to the EDC system. Access to EDC is managed by the CRO or an authorized representative.

All effort will be made by trial personnel and PI to enter the eCRFs within the contractually agreed upon timeframe of each subject's visit. It is the PI's responsibility to ensure that all subject data entered in the eCRF are accurate, complete, legible, and supported by the subject's medical records. The investigator attests to this by providing electronic signature within the EDC system.

The CRO will be responsible for entering ranges for local labs (if applicable) and for assigning medical coding utilizing Medical Dictionary for Regulatory Activities and World Health Organization Drug dictionaries. Data quality checks will be applied using manual and electronic verification methods. Original data and any changes in data and reason for change will be recorded in an electronic audit trail in EDC.

After database lock, the investigator will receive a copy of the subject data (e.g., paper, CD-ROM, or other appropriate media) for archiving at the CTS.

12.3 ePRO Data Collection

Sites will assist subjects to download the appropriate application to their device (i.e., smartphone, tablet, etc.) once enrolled in the trial. Subjects without their own device will be provisioned a device for ePRO data collection during the trial.

The ePRO data collection will be used for the following items:

- Memory aid for capturing solicited local and systemic symptoms

- Reminders for capturing the presence of respiratory tract symptoms
- RiiQ questionnaire for subjects with respiratory tract symptoms
- EQ-5D-5L questionnaire at baseline and for subjects with respiratory tract symptom
- 15-dimension health-related quality of life instrument (15D) utility score
- Tilburg Frailty Index part B (TFI) total score at baseline for all participants

Instructions will be provided to the subjects on how to enter data into the ePRO application and subjects will be required to demonstrate understanding prior to entering data on their own. Alerts will be sent to the site if a subject does not complete their diary as directed in Section 4.2.2. Entries will be reviewed by the site staff together with the subject at the next contact (telephone call/onsite visit). During the surveillance period, subjects will also receive ePRO application alerts 3 times per week asking about the presence of new respiratory symptoms and to contact their investigator if so.

12.4 Retention of Records

The investigator/trial staff must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. All essential documents, as listed in ICH-GCP guidelines, will be retained by the investigator for at least 2 years after the date the last marketing application is approved for the drug in the indication being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The investigator must notify and obtain written approval from BN before destroying any clinical trial documents or images (e.g., scan, radiograph, electrocardiogram (ECG) tracing) at any time. The Sponsor will inform the investigator of the date that the trial records may be destroyed or returned to BN.

Should an investigator wish to assign trial records to another party, advance written notice will be given to the Sponsor. BN must also be notified in advance and provide express written approval of any change in the maintenance of clinical trial documents, should the investigator choose to move trial records to another location.

If the investigator cannot guarantee the aforementioned archiving requirements at the clinical trial site, special arrangements must be made between the investigator and BN to store these documents in secure sealed containers away from the clinical trial site. These documents must be able to be returned in their secure sealed containers to the clinical trial site for auditing purposes.

13 Ethical Aspects

13.1 Ethical and Legal Regulations

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

13.2 Approval by IEC/IRB/IBC

IEC/IRB

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

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

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

IBC

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

Confidentiality and Data Protection:

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

Only a subject and site number may identify subjects. Their name or clinic and subject's medical record number may not be used. The PI keeps separate confidential subject logs for trial

recruitment which allows subject numbers to be matched with names and addresses of subjects at any time. Documents not meant to be passed on to third parties have to be stored securely by the PI.

Any information collected in the course of the trial may be made available only to persons directly involved in this trial (PI and his staff members, monitors, statisticians) or to persons authorized by the Sponsor or the PI or to authorities. The Sponsor of the trial will only receive pseudonymized data for analysis.

14 Informed Consent

The informed consent form (ICF) and process must comply with ICH-GCP guidelines, as well as specific national regulations and/or local laws in the countries where the trial is conducted and must be approved by the appropriate IEC/IRB.

The ICF will document the trial-specific information the investigator or his/her designee provides to the subject and the subject's agreement to participate. The investigator, or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the trial; trial procedures; anticipated benefits; potential risks, adverse effects, and discomforts; and any potential future use of blood samples (Section 8.3).

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

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

The consent process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any trial-related (nonstandard of care) activities are performed (such as screening). The initial and any amended signed and dated consent forms must remain in each subject's trial file at the CTS and be available for verification by trial monitor, Sponsor/CRO auditor, or competent regulatory authorities at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

15 Monitoring of the Trial

The CRO (contact information to be found in the "Responsibilities" section in the beginning of this protocol) will be contracted to perform monitoring services according to ICH-GCP. Monitoring will be conducted according to the monitoring plan which must be approved by BN and the CRO. The monitoring plan will outline the monitoring strategy (including rational) and

will specify in detail the items for source data verification and other tasks, to be performed by the CRA.

Monitoring will be conducted through personal visits with the investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the trial is conducted in compliance with the protocol, SOPs, and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. An unblinded monitor/CRA will work with the unblinded site person to ensure appropriate vaccine storage, accountability, and blinding.

To assure the accuracy of data collected in the eCRFs, it is mandatory that the monitor have direct access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical trial. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of BN, its designated agents and authorized employees of the appropriate Regulatory Authority (e.g., FDA) to inspect the facilities used in this clinical trial and, for purposes of verification, allow direct access to the hospital or clinic records of all enrolled subjects. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information. If a subject refuses to consent to this procedure, he/she may not participate in the trial.

The site needs to maintain records to identify the nature and location of all source documents as well as essential documents.

15.1 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the trial site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The PI or designee will be responsible for identifying and recording all deviations, which are defined as isolated occurrences involving a procedure that did not follow the protocol or a protocol-specific procedure. All deviations from the protocol and actions taken will be recorded in the source data and placed in the trial-specific regulatory file. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/trial staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in a trial-specific procedure.

16 Audits and Inspections

Site audits may be carried out by the BN quality assurance department or designee at any time during or after completion of this trial. All documents pertinent to the trial must be made

available to the designated auditor. Subject privacy must, however, be respected. The investigator and clinical staff are to be present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or designee.

In addition, representatives from local, state, or federal regulatory authorities may choose to inspect a trial site at any time before, during, or after completion of the clinical trial. The investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection. In the event of such an inspection, BN will be available to assist in the preparation. All pertinent trial data should be made available as requested by the Regulatory Authority for verification, audit, or inspection purposes.

17 Responsibility of the Investigator

The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor, the IRB/IEC, or the regulatory authority(ies).

The PI agrees to carry out the trial in accordance with the guidelines and procedures outlined in this clinical trial protocol. The PI especially consents to strictly adhere to the ethical aspects (see Section 13 of this protocol).

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

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

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

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

Each investigator will maintain appropriate medical and research records for this trial, in compliance with the ICH E6 Guideline for GCP and regulatory and institutional requirements for

the protection of confidentiality of subjects. He/she will permit authorized representatives of the Sponsor and regulatory authorities to review (and, when required by applicable law, to copy) clinical records for the purposes of quality reviews, audits/inspections, and evaluation of the trial safety and progress.

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

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

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19 Appendices

Appendix 1: Toxicity Scale for Laboratory Values

This protocol does not schedule any safety labs. Therefore, the provision of toxicity scales for laboratory values is not applicable. However, for the purpose of reporting adverse events based on ad-hoc findings from local laboratories, the local reference ranges should be considered, and an investigator assessment of clinical significance should be performed. Only clinically significant laboratory abnormalities should be reported as adverse events.

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

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

Serious or life-threatening AEs

ANY clinical event deemed by the Investigator clinician to be serious (hospitalization, life-threatening, disability, important medical event) should be considered a grade 4 event. Clinical events considered to be serious include, but are not limited to: Seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

Table 13 Toxicity Scale for Serum Chemistry

Lab Value, Serum[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)[b]
Sodium – Hyponatremia mmoL/L	132 < 136	130-131	125-129	<125
Sodium – Hypernatremia mmoL/L	>145-146	147	148-150	>150
Potassium – Hyperkalemia mmoL/L	>5.1-5.2	5.3-5.4	5.5-5.6	>5.6
Potassium – Hypokalemia mmoL/L	3.4 < 3.5	3.3	3.1-3.2	<3.1
Calcium – Hypercalcaemia mg/dL	>10.2-11.0	11.1-11.5	11.6-12.0	>12.0
Calcium- Hypocalcaemia mg/dL	8.0 < 8.6	7.5-7.9	7.0-7.4	<7.0
Creatinine mg/dL	1.5-1.7	1.8-2.0	2.1-2.5	>2.5 or requires dialysis
Alkaline Phosphatase increase by factor	1.1-2.0 × ULN	2.1-3.0 × ULN	3.1-10 × ULN	>10 × ULN
ALT (SGPT) and AST (SGOT) increase by factor	1.1-2.5 × ULN	2.6-5.0 × ULN	5.1-10 × ULN	>10 × ULN
Bilirubin – when accompanied by any increase in Liver Function Test; increase by factor	1.10-1.25 × ULN	1.26-1.50 × ULN	1.51-1.75 × ULN	>1.75 × ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1-1.5 × ULN	1.6-2.0 × ULN	2.1-3.0 × ULN	>3.0 × ULN

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

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

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

Table 14 Toxicity Scale for Hematology

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

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

Table 15 Grading for Troponin I

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

Appendix 2: Signature Pages

Investigator Signature Page

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

A Randomized, Double-blind, Phase 3 Trial to Assess Clinical Efficacy, Safety, and Reactogenicity of the Recombinant MVA-BN®-RSV Vaccine in Adults ≥60 Years of Age

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

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

Function [redacted]

Coordinating Investigator Signature Page

A Randomized, Double-blind, Phase 3 Trial to Assess Clinical Efficacy, Safety, and Reactogenicity of the Recombinant MVA-BN®-RSV Vaccine in Adults ≥60 Years of Age

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

Function [redacted]

Sponsor Signature Page

By signing the protocol:

A Randomized, Double-blind, Phase 3 Trial to Assess Clinical Efficacy, Safety, and Reactogenicity of the Recombinant MVA-BN®-RSV Vaccine in Adults ≥60 Years of Age

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