Janssen Vaccines & Prevention B.V.*

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled Phase 1/2a Study for Safety and Immunogenicity Evaluations for Regimen Selection of Ad26.RSV.preF and/or RSV preF Protein Combinations Followed by Expanded Safety Evaluation in Adults Aged 60 Years and Older

Protocol VAC18193RSV1004; Phase 1/2a

Amendment 6

VAC18193 (JNJ-64400141)

* Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study. The sponsor is identified on the Contact Information page that accompanies the protocol

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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Amendment 2	24 September 2018
Amendment 3	28 January 2019
Amendment 4	12 July 2019
Amendment 5	8 June 2020
Amendment 6	06 November 2020

Amendment 6 (Issued date: 06 November 2020)

The overall reason for the amendment: To further examine the immune response to revaccination at different time intervals, this amendment changes the Month 24 vaccination for Group 20, Cohort 3, from placebo to the selected regimen. A 14 day post-third vaccination visit is also added to further examine the kinetics of the immune responses.

The table below gives an overview of each change and all affected sections

Rationale: For Cohort 3, participants in Group 20 will receive the selected regimen at Month 24.

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Rationale: Corrections of errors in footnote numbering have been made.

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Amendment 5 (Issued date: 8 June 2020)

The overall reason for the amendment: This amendment is made to further extend the assessment of durability of the immune response in Groups 14 and 15 in Cohort 2 and to assess the safety and immunogenicity of the selected dose after 2 annual revaccinations in Cohort 3. For Cohort 2, participants in Groups 14 and 15 will continue into a long-term follow-up phase with a final visit 36 months after the first vaccination. For the one-dose regimen in Cohort 3, an additional revaccination at Month 24 (Day 730) with a 1-year post-vaccination follow-up period is added.

The table below gives an overview of each change and all affected sections

Rationale: For Cohort 2, participants in 2 groups (Groups 14 and 15) will continue into a long-term follow-up phase to further extend the assessment of the long-term durability of the immune response in, and to understand the potential effect of a decreased dose level of Ad26.RSV.preF on long-term durability of the immune response. During the long-term follow-up phase, only SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, and all AEs leading to discontinuation will be collected.

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Rationale: To specify that eligibility for revaccination is determined by assessment of signs and symptoms of potential underlying illnesses that should be medically stable in the weeks preceding revaccination.

4.1 Inclusion Criteria

Rationale: For health and safety reasons due to the Coronavirus Disease 2019 (COVID-19), participants may not be able to come to the study site for scheduled procedures. Appendix 1 has been added to provide guidance to the investigator for managing study-related procedures during the COVID-19 pandemic.

Appendix 1

Rationale: Minor textual changes, clarifications and corrections have been made.

Throughout the protocol

Amendment 4 (Issued date: 12 July 2019)

The overall reason for the amendment: This amendment is made to include changes to the dosing regimen to obtain more data on the long-term durability of the immune response. For Cohort 2, study vaccination at the Month 12 visit is removed, and the 7-day and 28-day visits after the Month 12 visit are deleted.

Month 12 re-vaccination of the selected regimen is already included in Cohort 3. The window for the Month 12 re-vaccination for Cohort 3 is amended to –2 months to allow that dose to be administered as early as Month 10, with the intention that the immunogenicity data from the analysis of the 28-day post-dose blood sample would be available in parallel with data from the primary analysis of the proof-of-concept study VAC18193RSV2001 to aid decision making on Month 12 revaccination in that study.

The table below gives an overview of each change and all affected sections

Rationale: For Cohort 2, to remove study vaccination from the procedures at the Month 12 visit, and to delete the 7-day and 28-day visits after the Month 12 visit. Also, to add an analysis at 1 year after the first vaccination for this cohort.

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Rationale: To amend the visit window for the Month 12 vaccination in Cohort 3 from ±2 months to –2 months; and to align the visit windows for Visits 10, 11 and 12 in Cohort 2 to ±1 month.

Synopsis: Schedule of Activities – Cohort 2
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Rationale: Clarification that participants discontinued from study vaccine should be monitored for immunogenicity, if this does not result in safety risks for the participant, as well as safety, and/or for other procedures (eg, RTI follow-up).

10.2 Discontinuation of Study Vaccine/Withdrawal from the Study

Amendment 3 (Issued date: 28 January 2019)

The overall reason for the amendment: To investigate the durability of the immune response both with and without revaccination at Month 12, blood samples for humoral immunogenicity assessments will be collected from all 315 participants in Cohort 3, instead of just the 63 in the subset of Cohort 3 participants. No change is made for the collection of blood for cellular immunogenicity assessments.

The table below gives an overview of the rationale for each change and all affected sections

Rationale: To allow collection of blood samples for humoral immunogenicity assessments from all 315 participants in Cohort 3, instead of just the 63 in the Cohort 3 subset.

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Rationale: To clarify that a participant who misses a vaccination can receive subsequent vaccinations if the investigator determines that the participant is eligible according to the criteria in Section 10.3.

10.2 Discontinuation of Study Vaccine/Withdrawal from the Study

Rationale: Clarification of the data to be used in the primary analysis of Cohort 3.

11.6.3 Expanded Safety Cohort (Cohort 3)

Rationale: Other minor changes, clarifications and corrections made throughout the protocol.

Amendment 2 (Issued date: 24 September 2018)

The overall reason for the amendment: To remove the concomitant seasonal influenza vaccination for Cohort 3, and to increase the sample size in Cohort 3 to generate sufficient safety data to support late stage development. Also, additional blood sample collection for cellular and humoral immunogenicity is included for a subset of 63 participants from Cohort 3 to provide a more in-depth characterization of immune response. Furthermore, to ensure availability of immunogenicity data from Cohort 2 primary analysis in time to support late stage development decisions, assessments of RSV neutralizing antibody levels of the one-dose regimen with separate injections (Group 16) and the two-dose regimen (Group 17) have been moved from primary to secondary endpoints.

The table below gives an overview of the rationale for each change and all affected sections

Rationale: Removal of the seasonal influenza vaccination (or placebo) as timing of Cohort 3 vaccination will no longer coincide with the influenza season.

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Synopsis: Objectives, Endpoints and Hypothesis; Overview of Study Design; Dosage and Administration; Immunogenicity Evaluations; Statistical Methods
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14.1 Physical Description of the Vaccines
15 Study-Specific Materials
16.1 Study-Specific Design Considerations

Rationale: Increase in the sample size for Cohort 3 to 315 participants to provide sufficient safety data on the selected regimen to support late stage development.

Synopsis: Overview of Study Design; Immunogenicity Evaluations
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Rationale: Inclusion of additional blood sample collection (at additional timepoints) for cellular and humoral immunogenicity for a subset of 63 participants from Cohort 3 to provide sufficient timepoints with immunogenicity samples which will be used for immune response modelling in preparation of Phase 3 studies.

Synopsis: Immunogenicity Evaluations
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5 Treatment Allocation and Blinding
9.1.1 Overview
9.1.2 Visit Windows
9.1.6 Post-vaccination Follow-up
9.2.1 Immunogenicity

Rationale: Assessments of RSV neutralizing antibody levels of the one-dose regimen with separate injections (Group 16) and the two-dose regimen (Group 17) were moved from primary to secondary endpoints to ensure availability of immunogenicity data from Cohort 2 primary analysis in time to support late stage development decisions.

Synopsis: Objectives, Endpoints and Hypothesis; Overview of Study Design; Immunogenicity Evaluations; Statistical Methods
2.1 Objectives and Endpoints
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11.6.2 Regimen Selection Cohort (Cohort 2)

Rationale: Other minor changes, clarifications and corrections made throughout the protocol.

Amendment 1 (Issued date: 19 March 2018)

The overall reason for the amendment: The protocol amendment is made to change the timing of the seasonal influenza vaccination for Cohort 3. Changes in project timelines have resulted in the likelihood that some participants in this study would not receive seasonal influenza vaccination until very late in the influenza season. The amended vaccination regimen for Cohort 3 now provides the seasonal influenza vaccination earlier in the season, either at least 14 days prior to Day 1, or at the latest on Day 1 itself. Also, the sample size for Cohort 3 is reduced.

The table below gives an overview of the rationale for each change and all affected sections

Rationale: Retiming of the seasonal influenza vaccination (or placebo)

Synopsis: Objectives and Endpoints; Overview of Study Design; Immunogenicity Evaluations; Statistical Methods
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Rationale: Clarification that participants with a history of allergy to egg protein will be excluded from the study

4.2 Exclusion Criteria

Rationale: Clarification that, for pausing rules 1, 3 and 4, the term "related to study vaccine" excludes seasonal influenza vaccine/placebo for seasonal influenza vaccine

11.9 Study Vaccination Pausing Rules

Rationale: Other clarifications and minor corrections to remove inconsistencies

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SYNOPSIS

A Randomized, Double-blind, Placebo-controlled Phase 1/2a Study for Safety and Immunogenicity Evaluations for Regimen Selection of Ad26.RSV.preF and/or RSV preF Protein Combinations Followed by Expanded Safety Evaluation in Adults Aged 60 Years and Older

A human adenovirus-vectored vaccine candidate and a pre-fusion conformation-stabilized respiratory syncytial virus (RSV) F protein which have shown promise in preclinical animal models of RSV will be assessed in this study:

- Ad26.RSV.preF (JNJ-64400141), a replication-incompetent adenovirus serotype 26 (Ad26) containing a deoxyribonucleic acid (DNA) transgene that encodes the pre-fusion conformation-stabilized F protein (pre-F) derived from the RSV A2 strain.
- RSV preF protein (JNJ-64213175) is a pre-fusion conformation-stabilized F protein derived from the RSV A2 strain.

This will be the first-in-human (FIH) study for RSV preF protein, and for the Ad26.RSV.preF/RSV preF protein combination (administered as separate injections in opposite arms) and Ad26.RSV.preF/RSV preF protein mixture (administered as a single injection).

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives and Endpoints

The current study has an adaptive design to determine a regimen for further clinical development in adults aged ≥60 years based on safety and immunogenicity. The selected regimen should improve humoral immune response with no adverse effect on cellular response compared to Ad26.RSV.preF alone.

SAFETY COHORT OBJECTIVE (COHORT 1): *To determine in small numbers of participants aged 60 years and older the safety of intramuscular homologous two-dose regimens comprising RSV preF protein or Ad26.RSV.preF/RSV preF protein mixture on Days 1 and 57, with a booster at Month 12, or separate administration of Ad26.RSV.preF and RSV preF protein in opposite arms on Day 1 with a booster at Month 12, before progression to regimen selection in a larger number of participants*

Objectives	*Endpoints*
PRIMARY	
• To assess the safety and reactogenicity of the intramuscular one- and two-dose regimens, with a booster at Month 12	• Serious adverse events (SAEs) from first dose administration until the end of the study • Solicited local and systemic adverse events (AEs) for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
SECONDARY	
• To assess the humoral and cellular immune responses elicited by Ad26.RSV.preF, RSV preF protein, and the Ad26.RSV.preF/RSV preF protein combination and mixture	• RSV neutralization assay, F protein binding antibodies (enzyme-linked immunosorbent assay [ELISA]; pre-F and/or post-F), and interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) assay
EXPLORATORY	
• Additional exploratory analyses may be performed to investigate vaccine-elicited immune responses further	• Assays to be used include, but are not limited to, RSV strain cross-neutralization, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization assays, molecular antibody characterization (avidity, Fc cell interaction, antibody isotyping, antibody sequencing for repertoire), and nasal antibodies to RSV, including but not limited to immunoglobulin (Ig)A and IgG; evaluation of the cellular immune response and the functional and memory immune response by intracellular cytokine staining (ICS) and transcriptome analysis

Objectives	*Endpoints*
• To evaluate symptoms of respiratory illness (including respiratory illness due to RSV) via the Respiratory Tract Infection (RTI) Symptoms Form	• During the RSV season: Signs and symptoms of RTI (including RTI due to RSV) from Day 1 until the end of the second RSV season of the study[a]
• Characterization of viral or bacterial infections in the respiratory tract	• Assessment, typing and level of infection by reverse transcriptase polymerase chain reaction (RT-PCR) or response to respiratory infection by serology

REGIMEN SELECTION COHORT OBJECTIVE (COHORT 2): *To select a regimen for progression to evaluation in an expanded safety cohort (Cohort 3; see below) by assessment of the safety and immunogenicity in participants aged 60 years and older of intramuscular one-dose regimens of Ad26.RSV.preF, Ad26.RSV.preF/RSV preF protein mixture, or separate administration of Ad26.RSV.preF and RSV preF protein in opposite arms on Day 1, or a two-dose regimen of Ad26.RSV.preF/ RSV preF protein mixture on Days 1 and 57*

Objectives	*Endpoints*
PRIMARY	
• To assess the safety and reactogenicity of the intramuscular one- and two-dose regimens	• SAEs from first dose administration until the end of the study • Solicited local and systemic AEs for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
• To assess RSV neutralizing antibody levels of the one-dose regimens (Groups 11 to 15) containing RSV preF protein compared to the one-dose Ad26.RSV.preF regimen	• RSV A2 neutralizing antibody levels of the one-dose regimens (Groups 11 to 15) on Day 29[b]
SECONDARY	
• To assess RSV neutralizing antibody levels of the one-dose regimen with separate injections (Group 16) and the two-dose regimen (Group 17) containing RSV preF protein compared to the one-dose Ad26.RSV.preF regimen	• RSV A2 neutralizing antibody levels of: – the one-dose regimen with separate injections (Group 16) on Day 29 – the two-dose regimen (Group 17) on Day 85[b]
• To assess additional humoral immune responses elicited by Ad26.RSV.preF and the Ad26.RSV.preF/RSV preF protein combination and mixture	• F protein binding antibodies (ELISA; pre-F and/or post-F)
• To assess cellular immune responses by IFN-γ ELISpot of all regimens containing RSV preF protein compared to the one-dose Ad26.RSV.preF regimen	• RSV F protein by IFN-γ ELISpot assay - the one-dose regimens on Day 29[b] (Groups 11 to 16) - the two-dose regimen on Day 85[b] (Group 17)
EXPLORATORY	
• Additional exploratory analyses may be performed to investigate vaccine-elicited immune responses further	• Assays to be used include, but are not limited to, RSV strain cross-neutralization, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization assays, molecular antibody characterization (avidity, Fc cell interaction, antibody isotyping, antibody sequencing for repertoire), and nasal antibodies to RSV, including but not limited to IgA and IgG; evaluation of the cellular immune response and the functional and memory immune response by ICS and transcriptome analysis

[a] The second RSV season of the study is defined relative to the enrollment date of the first participant in Cohort 1.

[b] See "STATISTICAL METHODS - Immunogenicity Analyses" for details.

Objectives	*Endpoints*
• To assess the long-term durability of the immune response in selected groups	• Assays to be used include, but are not limited to, RSV neutralizing antibody levels against A and B strain, RSV F protein binding antibodies (ELISA; pre-F and/or post-F), RSV F protein specific functional antibodies, and RSV F protein specific IFN-γ ELISpot in Groups 14 and 15 at Days 912 and 1095
• To evaluate symptoms of respiratory illness (including respiratory illness due to RSV) via the RTI Symptoms Form	• During the RSV season: Signs and symptoms of RTI (including RTI due to RSV) from Day 1 until the end of the second RSV season of the study[a]
• Characterization of viral or bacterial infections in the respiratory tract	• Assessment, typing and level of infection by RT-PCR or response to respiratory infection by serology

EXPANDED SAFETY COHORT OBJECTIVE (COHORT 3): *To determine the safety and immunogenicity of the selected regimen in an expanded cohort of participants aged 60 years and older; and to determine the need for a booster dose at Month 12 and/or Month 24*

Objectives	*Endpoints*
PRIMARY	
• To assess the safety and reactogenicity of the selected regimen and a booster at Month 12 and/or Month 24	• SAEs from first administration until the end of the study • Solicited local and systemic AEs for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
SECONDARY	
• To assess humoral immune responses to the selected regimen in all participants	• RSV neutralization A2 strain
• To assess cellular immune responses to the selected regimen in a subset of participants	• IFN-γ ELISpot assay
EXPLORATORY	
• Additional exploratory analyses may be performed to further investigate vaccine-elicited immune responses	Assays to be used include, but are not limited to: • F protein binding antibodies (ELISA; pre-F and/or post-F) • Flow cytometry • RSV cross-neutralization of B and/or other A strain • F-protein antibody specificity characterization • Cytokines/chemokines in nasal samples (if feasible) • Adenovirus neutralization assays • Functional and molecular antibody characterization • Analysis of nasal antibodies to RSV including, but not limited to IgA and IgG
• To assess the long-term durability of the immune response in groups receiving a booster at different time intervals	• Assays to be used include, but are not limited to, RSV neutralizing antibody levels against A and B strain, RSV F protein binding antibodies (ELISA; pre-F and/or post-F), RSV F protein specific functional antibodies, and RSV F protein specific IFN-γ ELISpot at Days 758, 912 and 1095
• To evaluate symptoms of respiratory illness (including respiratory illness due to RSV) via the RTI Symptoms Form	• During the RSV season: Signs and symptoms of RTI (including RTI due to RSV) from Day 1 until the end of the second RSV season of the study[a]
• Characterization of viral or bacterial infections in the respiratory tract	• Assessment, typing and level of infection by RT-PCR or response to respiratory infection by serology

[a] The second RSV season of the study is defined relative to the enrollment date of the first participant in Cohort 1.

Hypothesis

No formal statistical testing of safety and immunogenicity data is planned. Data will be analyzed descriptively.

OVERVIEW OF STUDY DESIGN

This is a multi-center, randomized, double-blind, placebo-controlled Phase 1/2a study for safety and immunogenicity evaluations for regimen selection of Ad26.RSV.preF and RSV preF protein combinations followed by expanded safety evaluation of the selected regimen in male and female participants aged ≥60 years who are in stable health.

To further extend the assessment of the long-term durability of the immune response to the study vaccine, participants in Groups 14 and 15 (Cohort 2) will continue into a long-term follow-up phase.

The study design includes 3 sequential cohorts: an initial safety cohort (Cohort 1 in a total of 64 participants), a regimen selection cohort (Cohort 2 in a total of 288 participants), and an expanded safety cohort (Cohort 3 in a total of 315 participants).

The overall total number of participants will be approximately 667.

The study duration will be approximately 730 days (2 years) per participant in Cohorts 1 and 2 (Groups 11-13 and Groups 16-18), and approximately 1095 days (3 years) per participant in Cohort 2 (Groups 14-15) and Cohort 3. The study comprises a maximum 28-day screening period for Cohorts 1 and 2 (screening for Cohort 3 will be performed pre-vaccination on Day 1), study vaccination (active or placebo) with a one-dose (on Day 1) or two-dose (on Day 1 and Day 57) regimen and a booster dose (active or placebo) at Month 12 (Cohort 1) or at Month 12 and Month 24 (Cohort 3), a minimum 28-day follow-up period after each vaccination, and a follow-up period until 2 years after the first Ad26.RSV.preF or RSV preF protein vaccination (Cohorts 1 and 2 [Groups 11-13 and Groups 16-18]) or until 3 years after the first Ad26.RSV.preF or RSV preF protein vaccination (Cohort 2 [Groups 14-15] and Cohort 3). The end of the study is defined as the last participant's last visit 24 months after the first vaccination (Cohorts 1 and 2 [Groups 11-13 and Groups 16-18]) or the last participant's last visit approximately 1095 days (3 years) after the first vaccination (Cohort 2 [Groups 14-15] and Cohort 3).

An internal data review committee (DRC) will be established for this study to evaluate safety and reactogenicity data on a regular basis.

If any of the pre-specified study vaccination pausing rules is met, further study vaccination will be paused and a DRC meeting will be convened.

The DRC may also review unblinded immunogenicity data during the course of the study if this is deemed necessary for future vaccine development-related decisions.

Initial Safety Cohort (Cohort 1)

In the initial safety cohort, participants will be randomized progressively in 1 of 4 randomizations (R1a through R1d) with safety checks in place before extending enrollment and progressing from one randomization step to the next as follows (Table 1):

- Cohort R1a. Initially 2 participants will be enrolled, 1 into Group 1 and 1 into Group 2, and will receive a single dose of placebo or 50 µg of RSV preF protein, respectively. Enrollment will be paused to allow for 24-hour safety assessments in these 2 sentinel participants by the principal investigator(s) (PI[s]), the sponsor's study responsible physician/scientist (SRP/S), and the sponsor's medical leader (ML). In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 10 participants will be randomized and dosed. Seven days after the last participant has received his/her

first dose, available safety data will be reviewed by the PI(s), SRP/S, ML, and the sponsor's therapeutic area safety head (TASH) before proceeding to Cohort R1b.

- Cohort R1b. Initially 3 participants will be enrolled, 1 into each of Groups 3 through 5, and will receive a single dose of placebo, 5×10^{10} viral particles (vp) Ad26.RSV.preF/50 μg RSV preF protein, or 150 μg RSV preF protein, respectively. Enrollment will be paused to allow for 24-hour safety assessments in the 3 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 17 participants will be randomized and dosed. Seven days after the last participant has received his/her first dose, available safety data will be reviewed by the PI(s), SRP/S, ML, and TASH before proceeding to Cohort R1c.

- Cohort R1c. Initially 2 participants will be enrolled, 1 into Group 6 and 1 into Group 7, and will receive a single dose of placebo or 5×10^{10} vp Ad26.RSV.preF/150 μg RSV preF protein, respectively. Enrollment will be paused to allow for 24-hour safety assessments in these 2 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 10 participants will be randomized and dosed. Seven days after the last participant has received his/her first dose, available safety data will be reviewed by the PI(s), SRP/S, ML, and TASH before proceeding to Cohort R1d.

- Cohort R1d. Initially 3 participants will be enrolled, 1 into each of Groups 8 through 10, and will receive 2 doses of placebo (1 in each arm), or 1×10^{11} vp Ad26.RSV.preF/150 μg RSV preF protein, with placebo in the opposite arm, or 1×10^{11} vp Ad26.RSV.preF in one arm and 150 μg RSV preF protein in the opposite arm. Enrollment will be paused to allow 24-hour safety assessments in the 3 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 17 participants will be randomized and dosed.

- Seven days after the final participant in Cohort 1 has received his/her first dose, all available safety data at that time for the whole cohort will be reviewed by the DRC before proceeding to Cohort 2.

Sentinel participants will be contacted by telephone 24 hours post-dose to collect safety information.

Progression to the regimen selection cohort will be based on acceptable safety in the initial safety cohort, as determined by DRC review of Day 8 safety data in all participants.

Table 1: Study Design: Initial Safety Cohort (Cohort 1)

Group	R	N	Day 1	Day 57	Month 12
1	R1a	4	Placebo	Placebo	Placebo
2	R1a	8	RSV preF protein 50 µg	RSV preF protein 50 µg	RSV preF protein 50 µg
3	R1b	4	Placebo	Placebo	Placebo
4	R1b	8	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/50 µg	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/50 µg	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/50 µg
5	R1b	8	RSV preF protein 150 µg	RSV preF protein 150 µg	RSV preF protein 150 µg
6	R1c	4	Placebo	Placebo	Placebo
7	R1c	8	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/150 µg	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/150 µg	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/150 µg
8	R1d	4	Placebo + Placebo*	Placebo	Placebo + Placebo*
9	R1d	8	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg + Placebo*	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg + Placebo*
10	R1d	8	*Separate injections*: Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg*	Placebo	*Separate injections*: Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg*
R1 TOTAL:		**64**			

N: number of participants; R: randomization; vp: viral particles
* Each injection to be given in opposite arms

Regimen Selection Cohort (Cohort 2)

In the regimen selection cohort, approximately 288 participants will be randomized in parallel to 1 of 8 groups (Groups 11 through 18; Table 2). No pauses in enrollment for safety assessments are planned.

Based on safety and immunogenicity results available at the time of primary analysis, a sponsor committee will decide which regimen will be used for the expanded safety cohort (Cohort 3). In case none of the groups that are part of the primary objective meet internal criteria, regimen selection may be delayed until additional analyses will be available. Additional factors such as data from other assays, manufacturability, and ease of administration will be taken into account to select the regimen for the expanded safety phase.

Table 2: Study Design: Regimen Selection Cohort (Cohort 2)

Group	R	N	Day 1	Day 57
11	R2	24	Ad26.RSV.preF 1×10^{11} vp + Placebo*	Placebo
12	R2	42	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/50 µg + Placebo*	Placebo
13	R2	42	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/50 µg + Placebo*	Placebo
14	R2	42	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg + Placebo*	Placebo
15	R2	42	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/150 µg + Placebo*	Placebo
16	R2	36	*Separate injections**: Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg	Placebo
17	R2	36	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg + Placebo*	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg
18	R2	24	Placebo + Placebo*	Placebo
R2 TOTAL:		**288**		

N: number of participants (*Note*: Data from Groups 9 and 10 of Cohort 1 will be pooled with those from Groups 16 and 17 of Cohort 2) up to Month 12; R: randomization; vp: viral particles
* Each injection to be given in opposite arms

Expanded Safety Cohort (Cohort 3)

In the expanded safety cohort, approximately 315 participants will be randomized in parallel to 1 of 3 groups (Groups 19 through 21; Table 3 and Table 4). No pauses in enrollment for safety assessments are planned.

Participants will receive the selected one- or two-dose regimen from Cohort 2 or placebo.

If the one-dose regimen is selected (Groups 11 through 16 from Cohort 2), Groups 19 and 20 would receive the selected regimen on Day 1, and a booster at Month 12 (the selected regimen or placebo, respectively) and Month 24 (the selected regimen). Group 21 will receive placebo at all timepoints (Table 3).

If the two-dose regimen is selected (Group 17 of Cohort 2), Groups 19 and 20 would receive the selected regimen on Day 1 and on Day 57, and a booster (the selected regimen or placebo, respectively) at Month 12. Group 21 will receive placebo at all three timepoints (Table 4).

Table 3: Study Design: Expanded Safety Cohort (Cohort 3) with One-dose Regimen and Month 12 and Month 24 Booster

Group	R	N	Day 1	Month 12	Month 24
19	R3	135	Selected Regimen	Selected Regimen	Selected Regimen
20	R3	135	Selected Regimen	Placebo for the Selected Regimen	Selected Regimen
21	R3	45	Placebo for the Selected Regimen	Placebo for the Selected Regimen	Placebo for the Selected Regimen
R3 TOTAL:		**315**			
OVERALL TOTAL:		***667***			

N: number of participants; R: randomization

Table 4: Study Design: Expanded Safety Cohort (Cohort 3) with Two-dose Regimen and Month 12 Booster

Group	R	N	Day 1	Day 57	Month 12
19	R3	135	Selected Regimen	Selected Regimen	Selected Regimen
20	R3	135	Selected Regimen	Selected Regimen	Placebo for the Selected Regimen
21	R3	45	Placebo for the Selected Regimen	Placebo for the Selected Regimen	Placebo for the Selected Regimen
R3 TOTAL:		**315**			
OVERALL TOTAL:		***667***			

N: number of participants; R: randomization

PARTICIPANT POPULATION

Participants will be adult men and women, aged ≥60 years on the day of signing the informed consent form (ICF). Participants will be in good or stable health (on the basis of physical examination, medical history, laboratory safety data[a], 12-lead electrocardiogram,[a] and vital signs measurement performed at screening).

DOSAGE AND ADMINISTRATION

Ad26.RSV.preF and RSV preF protein will be administered as a combination (ie, as separate injections in opposite arms) or as a mixture (ie, as a single injection) into the deltoid muscle according to the schedules shown in Table 1, Table 2, Table 3, and Table 4:

- Ad26.RSV.preF (JNJ-64400141) will be supplied at a concentration of 2×10^{11} vp/1 mL in single-use vials. Dose levels of 5×10^{10} vp and 1×10^{11} vp will be used.
- RSV preF protein (JNJ-64213175) will be supplied at a concentration of 0.3 mg/1 mL in single use vials. Dose levels of 50 µg and 150 µg will be used.
- Placebo for Ad26.RSV.preF and RSV preF protein.

All injections of Ad26.RSV.preF and RSV preF protein (or corresponding placebo) will be 1 mL in volume.

An unblinded pharmacist or other qualified individual will prepare the appropriate vial and/or syringe and provide the syringe in a blinded manner to the vaccine administrator who will perform the injection. The unblinded pharmacist, or other qualified individual, may also perform vaccine administration, but will have no other study function following dosing. Diluent will be used as required.

[a] For participants in Cohorts 1 and 2 only.

All vaccines should be administered in the deltoid muscle:

- When participants receive 2 injections at any given visit, the injections will be given in opposite arms at the same time with no more than 45 minutes between the injections.
- When participants receive a single injection per visit, eg, in Groups 1 through 7 in Cohort 1, alternating injection sites will be used for subsequent injections unless there is a medically justifiable reason in the judgment of the PI(s).

IMMUNOGENICITY EVALUATIONS

All sample collection and processing will be performed by the staff at the clinical sites according to current versions of approved standard operating procedures.

Humoral and cellular immunogenicity assays that may be used in this study (as available and applicable) are summarized in Table 5 and Table 6 below.

Blood for humoral and cellular immune responses will be drawn from all participants in Cohorts 1 and 2. In Cohort 3, blood will be drawn for humoral immune responses from all participants and for cellular immune responses from a subset of 63 participants. Nasal samples will be used for immunogenicity assessments (eg, immunoglobulin or cellular immune component) and identification of the etiology of respiratory infections (if needed). Blood samples for transcriptome analysis will be collected in Cohorts 1 and 2 only.

In addition to RT-PCR performed on nasal samples,[a] any immunogenicity blood sample collected from all participants may be assayed by serology (including but not limited to RSV virus neutralizing antibodies [VNAs] or ELISA specific to RSV protein G [glycoprotein] and/or N [nucleoprotein] as available and applicable) for RSV exposure.

Table 5: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Primary endpoint *(Regimen Selection Cohort [Cohort 2] – Groups 11 to 15 only)*	
RSV neutralization A	Analysis of neutralizing antibodies to an A strain
Secondary endpoints	
RSV neutralization A	Analysis of neutralizing antibodies to an A strain
F protein antibodies (ELISA; pre-F and/or post-F)	Analysis of antibodies binding to RSV F protein in pre-fusion and/or post-fusion form
Exploratory endpoints	
RSV strain cross-neutralization	Analysis of cross-neutralizing antibodies to B and/or a different A strain(s)
F protein antibody specificity characterization	Pre- and post-F specificity by binding or functional assays as ELISA, and/or competition ELISA. Adsorption of serum or plasma with pre-F and post-F protein before any antibody assay, epitope mapping, functional VNAs
G and/or N protein antibodies (ELISA)	Analysis of antibodies binding to RSV G and/or N protein
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to, ADCC, ADCP, avidity, other respiratory viral neutralizing or binding assays, Ig isotype, functional VNAs to other respiratory viruses, and antibody assessments for antibody repertoire

ADCC: antibody-dependent cell-mediated cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; ELISA: enzyme-linked immunosorbent assay; F: fusion; G: glycoprotein; Ig: immunoglobulin; N: nucleoprotein; RSV: respiratory syncytial virus; VNA: virus neutralizing antibody

Note: Antibody analyses might be performed in nasal samples, serum and plasma.

[a] All references to the collection of a "nasal sample" imply a "nasal turbinate sample or its alternative".

Table 6: Summary of Immunogenicity Assays (Cellular)

Assay	Purpose
Secondary endpoints	
IFN-γ ELISpot	T-cell IFN-γ responses to RSV F protein peptides
Exploratory endpoints	
ICS	Analysis of T-cell responses to RSV F protein peptide-stimulated PBMC (including, but not limited to, $CD4^+/CD8^+$, IL-2, IFN-γ, TNF-α, activation markers and memory)
Transcriptome analysis	Regulation of genes (clusters), expression patterns, that predict specific immune responses after vaccination
Chemokine/cytokine analysis	Levels of chemokines and cytokines in nasal samples
Sequencing of B-cells	Including but not limited to sequencing of BCR (B-cell receptor) or VH/VL (heavy/light chain characterization) for specificity

ELISpot: enzyme-linked immunospot; F: fusion; ICS: intracellular cytokine staining; IFN-γ: interferon gamma; IL-2: interleukin-2; PBMC: peripheral blood mononuclear cells; RSV: respiratory syncytial virus; TNF-α: tumor necrosis factor alpha

RTI PROCEDURES

During the first 2 RSV seasons of the study (relative to the enrollment date of the first participant in Cohort 1), participants should record any signs and symptoms of RTI (such as runny nose, fever, severe cough, rapid breathing, or difficulty breathing), including measurement of body temperature, on a daily basis using a specific RTI Symptoms Form, starting on the first day they experience symptoms, including the day on which the symptoms resolve.

If respiratory symptoms develop during the first 2 RSV seasons of the study, the following should take place:

- Participants should contact the site as soon as possible to notify the site of an RTI.
- Participants should record signs and symptoms of the RTI (including measurement of body temperature) daily using the RTI Symptoms Form until the day of symptom resolution.
- If feasible, participants should take a nasal sample at home, preferably between 2 and 3 days after the onset of the RTI symptoms. The sample should be stored refrigerated and brought to the site by the participant within 3 to 4 days.
- Alternatively, participants may go to the site preferably within 2 to 3 days after the onset of the RTI to have a nasal sample taken by the study staff.

During the first 2 RSV seasons of the study, participants will be contacted by telephone every 30±7 days (unless a planned clinic visit has occurred or will occur within 30 days). These calls will remind participants to complete the RTI Symptoms Form in the event of any symptoms of RTI, to contact the site at the time of symptom onset, and to take a nasal sample (or go to the site to have a nasal sample taken by study staff). These calls will also check for any SAEs and concomitant medications associated with SAEs since the previous visit or telephone contact.

The presence of RSV or any other respiratory infection may be assessed by the sponsor by RT-PCR diagnostics on the nasal samples, which may include viral load and RSV subtyping.

Blood from participants with a suspected RTI may be assayed by a serological assay (eg, protein G and/or N ELISA) to confirm RSV infection. (No additional blood sampling is necessary – any serological assay conducted to confirm RSV infection will use blood from the existing samples.)

Every effort should be made to collect data on the clinical course of RTIs including information on oxygenation status, supplemental oxygen requirements and specific drug treatments, as well as other concurrent respiratory illness present at the time of the diagnosis of the event and up to symptom resolution.

Any RTI that is not due to RSV infection will be reported as an AE if it occurs between the time of any vaccination through the next 28 days. Any RTI recorded as an AE in the eCRF will be excluded from any AE analysis if the central laboratory RT-PCR is subsequently found to be positive for RSV. RTIs arising from RSV infection will not be reported as (S)AEs in the Clinical Study Report as they are endpoints of the study and will be tabulated separately.

Any RTI fulfilling the criteria of an SAE will be reported as such during the entire study period if RT-PCR indicates it is not an RSV-RTI. If the RT-PCR is positive for RSV the event should not be reported as an SAE. If the RT-PCR information is not available within 24 hours of knowledge of the event, the event will be reported as an SAE, but will be subsequently downgraded from SAE status if it later turns out to be RT-PCR positive for RSV.

SAFETY EVALUATIONS

On a daily basis, for 7 days after each vaccination, participants will be asked to record the following AEs via the participant diary:

- Solicited local AEs: erythema (measured using the ruler supplied), swelling/induration (measured using the ruler supplied and graded using the functional scale), and pain/tenderness.
- Solicited systemic AEs: fatigue, headache, myalgia, arthralgia, chills, nausea, and fever (ie, body temperature ≥38.0 °C).

Body temperature (oral route preferred) should be measured at approximately the same time each day, preferably in the evening, using the thermometer supplied. All diary assessments, including body temperature, 7 days after each vaccination may be collected earlier in the day to coincide with the clinic visit.

Unsolicited AEs will be collected for 28 days after each vaccination (ie, from the time of each vaccination through the following 28 days).[a] SAEs will be collected from first dose administration to the end of the double-blind phase of the study. During the long-term follow-up phase (Groups 14 and 15 from Cohort 2), only SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, and all AEs leading to discontinuation will be collected. All AEs, including any that are ongoing at 28 days after each dose, will be followed until clinical resolution or stabilization. Concomitant medications will be collected from the time of each vaccination, through 28 days after each vaccination, and additionally outside these periods when associated with any SAE. During the long-term follow-up phase (Groups 14 and 15 from Cohort 2), only medications in conjunction with SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, or in conjunction with AEs leading to discontinuation should be recorded.

All SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up.

[a] AEs that start more than 28 days after a vaccination, but that are still present at the time of the next vaccination will also be recorded.

STATISTICAL METHODS

Sample Size Determination

For Cohort 1, no formal sample size calculations are done.

For Cohort 2, the objective is to compare the RSV A2 neutralizing antibody levels of all regimens containing RSV preF protein (Groups 12 through 17) to the one-dose Ad26.RSV.preF regimen (Group 11). This will be based on the GMT ratios and corresponding 95% confidence intervals (CIs) of the VNA A2 levels of the regimens containing RSV preF protein on Day 29 for the one-dose regimens (Groups 12 through 16) and on Day 85 for the two-dose regimen (Group 17) versus the VNA A2 levels on Day 29 of the one-dose Ad26.RSV.preF regimen (Group 11). The sample size was selected to provide a precision of ~0.53 on the $\log_2$ scale.

Note: Immunogenicity data from Groups 9 and 10 of the initial safety cohort (Cohort 1) will be combined with those from Groups 16 and 17 of the regimen selection cohort (Cohort 2).

The table below presents the resulting 95% CIs for several observed ratios, assuming a standard deviation for VNA of 1 on the $\log_2$ scale and accounting for 5% dropout.

Observed Ratio	Corresponding 95% CI
1	[0.69; 1.44]
1.2	[0.83; 1.73]
1.5	[1.04; 2.17]

In addition to the above, factors such as data from other assays, reactogenicity profiles, manufacturability and ease of administration will be considered when selecting the regimen for the expanded safety phase.

The expanded safety cohort (Cohort 3) should provide sufficient safety data on the selected regimen to support late stage development if the immunogenicity results of Cohort 2 are satisfactory.

Planned Analyses

Note: Depending on the timing, some of the planned analyses might be combined.

Initial Safety Cohort (Cohort 1) – Primary Analysis

Primary analysis: analysis of safety data 28 days post-dose 2. Data collected up to the time of the visit at 28 days after the second dose of study vaccine for the last participant in Cohort 1 will be included in the analysis. This analysis will be performed on unblinded data. The blind will be maintained at the participant/site level.

As immunogenicity data from Groups 9 and 10 of the initial safety cohort (Cohort 1) will be combined with those from Groups 16 and 17 of the regimen selection cohort (Cohort 2), immunogenicity data from the initial safety cohort will be analyzed at the time of the primary analysis of the regimen selection cohort.

Initial Safety Cohort (Cohort 1) – Analysis 28 Days Post-Month 12 Booster

This analysis will include safety and immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 28 days after the Month 12 booster dose of study vaccine for the last participant in this cohort will be included in the analysis. The blind will be maintained at the participant/site level.

Regimen Selection Cohort (Cohort 2) – Primary Analysis

Primary analysis: analysis of safety data 28 days post-dose 2 and immunogenicity data up to at least 28 days post-dose 1.

- This analysis should contain all safety data collected up to the time of the visit at 28 days after the second dose for the last participant in this cohort.
- Immunogenicity data from at least Groups 11 to 15 and part of Group 18 (placebo group), up to at least 28 days post-dose 1 will be included as well.[a]
- This analysis will be performed on unblinded data. The blind will be maintained at the participant/site level.

In this analysis, all available immunogenicity data of the initial safety cohort (Cohort 1) will be analyzed as well.

Regimen Selection Cohort (Cohort 2) – Additional Analysis

Additional analysis: analysis of immunogenicity data 28 days post-dose 1 for all one-dose regimens (including the one-dose regimen with separate injections) and 28 days post-dose 2 for the two-dose regimen. This analysis may include immunogenicity data available from additional timepoints.

This analysis should contain immunogenicity data up to at least day 28 post-dose 1 for one-dose regimens and 28 days post-dose 2 for the two-dose regimen. This analysis will be performed on unblinded data. The blind will be maintained at the participant/site level.

In this analysis, all available immunogenicity data of Groups 9 and 10 from the initial safety cohort (Cohort 1) and immunogenicity data of Cohort 2 included in the primary analysis will be analyzed as well.

The primary analysis of Cohort 1 and Cohort 2 and the additional analysis may be combined into one analysis.

Regimen Selection Cohort (Cohort 2) – Analysis 1 Year Post-first Vaccination

This analysis will include immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 12 months after the first dose of study vaccine for the last participant in this cohort will be included in the analysis. The blind will be maintained at the participant/site level.

Regimen Selection Cohort (Cohort 2-Groups 14 and 15) – Analysis 2 Years Post-first Vaccination

This analysis will include immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 24 months after the first dose of study vaccine for the last participant in these 2 groups will be included in the analysis.

Expanded Safety Cohort (Cohort 3) – Primary Analysis

Primary analysis: analysis of safety and immunogenicity data up to Day 29 if a one-dose regimen is selected or up to Day 85 if a two-dose regimen is selected. This analysis should at least contain safety data collected up to the time of the Day 29 visit for the last participant in this cohort in case a one-dose regimen is selected and up to the time of the Day 85 visit for the last participant in this cohort in case a two-dose regimen is selected.[a] If the corresponding immunogenicity data are not available at the time of database lock, they will be analyzed at a later timepoint. This analysis will be performed on unblinded data. The blind will be maintained at the participant/site level.

[a] An unblinded person who is not part of the study team (or another independent party) will dictate which Day 29 samples should be analyzed by the clinical immunology laboratory. Half of the Day 29 samples of Group 18 (placebo group) will be included to ensure the blind at the level of the clinical immunology laboratory.

Expanded Safety Cohort – Analysis 28 Days Post-Month 12 Booster

This analysis will include safety and immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 28 days after the Month 12 booster dose of study vaccine for the last participant in this cohort will be included in the analysis. The blind will be maintained at the participant/site level.

Expanded Safety Cohort – Analysis 28 Days Post-Month 24 Booster

This analysis will include safety and immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 28 days after the Month 24 booster dose of study vaccine for the last participant in this cohort will be included in the analysis. The blind will be maintained at the participant/site level.

Final Analysis

The final analysis at the end of the study will include safety and immunogenicity data from all cohorts.[a] Data collected up to the time of the last visit for the last participant will be included in the analysis. This analysis will be performed on unblinded data.

Additional Interim Analyses

Additional interim analyses (blinded or, if occurring after the primary analysis of the respective cohort, unblinded) may be performed during the study for the purpose of informing future vaccine development-related decisions in a timely manner, or upon health authority request. If they occur, these unplanned interim analyses may replace planned analyses, depending on the timing. The results will not influence the conduct of the study in terms of early termination or later safety or immunogenicity endpoint assessments, and will only be available to a selected group of sponsor personnel.

Immunogenicity Analyses

No formal hypothesis for immunogenicity will be tested. For the regimen selection cohort (Cohort 2), GMT ratios with corresponding 95% CI of the VNA A2 levels of the combination/mixture regimens on Day 29 for the one-dose regimens (Groups 12 through 16) and Day 85 for the two-dose regimen (Group 17) versus the Day 29 VNA A2 levels of the one-dose Ad26.RSV.preF regimen (Group 11) will be calculated. Therefore, a regression model will be fitted with the respective VNA A2 levels as dependent variable and the respective regimens and baseline levels as covariates, using Satterthwaite's method to calculate the degrees of freedom and allowing different variances for the vaccines. The estimate and CIs obtained as such will be back-transformed (by exponentiation) to a GMT ratio and the corresponding CI. Note that the effect of additional factors, such as age and the interaction with the regimen, might also be explored in this model.

Note: Immunogenicity data from Groups 9 and 10 of the initial safety cohort (Cohort 1) will be combined with those from Groups 16 and 17 of the regimen selection cohort (Cohort 2).

In the expanded safety cohort (Cohort 3), the effect of the Month 12 booster will be assessed. Therefore, the following ratios for VNA A2 will be calculated:

- In the groups with an active vaccination at Month 12, the ratio of the Month 12 booster Day 29 level versus the prime Day 29 level with the corresponding 95% CI will be calculated.
- The groups with an active vaccination at Month 12 will be compared to corresponding groups with placebo vaccination at Month 12 by calculating the ratio with the corresponding 95% CI.

Note that the above might also be repeated for other assays.

[a] Might be done per cohort, depending on the timing.

In addition, for all cohorts, continuous variables will be summarized with descriptive statistics of the actual values and the changes from baseline where appropriate. Graphical representations of immunologic parameters will be made as applicable. For categorical variables, frequency tables will be presented.

Safety Analyses

No formal statistical testing of safety data is planned.

SCHEDULE OF ACTIVITIES – COHORT 1

Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 2 + 7 d	Vac 2 + 28 d	Vac 1 + 26 wk	Vac 1 + 12 mo	Vac 3 + 7 d	Vac 3 + 28 d	Vac 3 + 26 wk	Vac 3 + 12 mo [r]	Early Exit [a]
Visit Day(s)	-28 to 0	1	8 [b c]	15	29	57	64 [d]	85 [d]	183	365	372 [d]	393 [d]	547 [d]	730 [d]	
Visit Window			±2 d	±2 d	±3 d	±3 d	±2 d	-3/+10 d	±14 d	±2 mo	±2 d	±3 d	±14 d	±1 mo	
Visit Type	Screening	STUDY VACCINATION 1	Safety	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 2	Safety	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 3	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Early exit
Written informed consent [e]	●														
Inclusion/exclusion criteria	●														
Demographics	●														
Medical history/pre-study medications	●														
Physical examination [f]	●	❶❼	❼	❼	❼	❶❼	❼	❼	❼	❶	❼	❼	❼	❼	●
Vital signs [g] incl. body temperature	●	❷	●	●	●	❷	●	●	❼	❷	●	●	❼	❼	●
12-lead ECG [h]	●														
Serology (HIV-1/2, hepatitis B/C)	●														
Randomization		❶													
Verification of selected eligibility criteria [i]		❶				❶				❶					
Contraindications to vaccination [j]		❶				❶				❶					
Safety lab blood sample, mL	● 10	❶ 5	● 5												❸ 5
Cellular immunity sample, mL [k]		❶ 50		● 50	● 50	❶ 50		● 50	● 50	❶ 50		● 50	● 50	● 50	❹ 50
Humoral immunity sample, mL		❶ 10		● 10	● 10	❶ 10		● 10	● 10	❶ 10		● 10	● 10	● 10	❹ 10
Transcriptome sample, mL		❶ 2.5	●2.5	● 2.5											
Nasal turbinate sample (or its alternative)		❶		●	●	❶		●		❶		●			
Vaccination		●				●				●					
30 minute post-vaccination observation [l]		●				●				●					
Solicited AE recording		- - Continuous - -				- - Continuous - -				- - Continuous - -					❺
Unsolicited AE recording [m]		- - - - - - - - - - Continuous - - - - - - - - -				- - - - - - Continuous - - - - - -				- - - - - - Continuous - - - - - -					❻
SAE recording [m]		- Continuous - -- -													●
Concomitant medications [n]		- Continuous - -- -													●
Respiratory tract infection (RTI) [o,p]		- During the first 2 RSV seasons of the study - -- -													●
RTI Symptoms Form distribution		- To be distributed before the start of the first 2 RSV seasons of the study- - - - - - - - - - - - - - - - - - - -													
Nasal swab kit distribution		- To be distributed before the start of the first 2 RSV seasons of the study- - - - - - - - - - - - - - - - - - - -													
Participant diary distribution [q]		●				●				●					
Participant diary review by site staff			●				●				●				

Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Visit Timing		**Vac 1**	**Vac 1 + 7 d**	**Vac 1 + 14 d**	**Vac 1 + 28 d**	**Vac 1 + 56 d**	**Vac 2 + 7 d**	**Vac 2 + 28 d**	**Vac 1 + 26 wk**	**Vac 1 + 12 mo**	**Vac 3 + 7 d**	**Vac 3 + 28 d**	**Vac 3 + 26 wk**	**Vac 3 + 12 mo [r]**	**Early Exit [a]**
Visit Day(s)	**-28 to 0**	**1**	**8 [b c]**	**15**	**29**	**57**	**64 [d]**	**85 [d]**	**183**	**365**	**372 [d]**	**393 [d]**	**547 [d]**	**730 [d]**	
Visit Window			**±2 d**	**±2 d**	**±3 d**	**±3 d**	**±2 d**	**-3/+10 d**	**±14 d**	**±2 mo**	**±2 d**	**±3 d**	**±14 d**	**±1 mo**	
Visit Type	Screening	**STUDY VACCINATION 1**	Safety	Safety and Immunogenicity	Safety and Immunogenicity	**STUDY VACCINATION 2**	Safety	Safety and Immunogenicity	Safety and Immunogenicity	**STUDY VACCINATION 3**	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Early exit
Blood draw volumes															
Approximate daily blood draw, mL	10	67.5	7.5	62.5	60	60	--	60	60	60	–	60	60	60	65
Approximate cumulative study blood draw, mL	10	77.5	85	147.5	207.5	267.5	267.5	327.5	387.5	447.5	447.5	507.5	567.5	**627.5**	–

AE: adverse event; d: day; ECG: electrocardiogram; HIV: human immunodeficiency virus; ICF: informed consent form; mo: month; RSV: respiratory syncytial virus; RTI: respiratory tract infection; SAE: serious adverse event; vac: vaccination

❶ pre-dose; ❷ pre- and post-dose; ❸ if the early exit is within 8 days of the first vaccination; ❹ blood samples for immunogenicity will only be taken if the early exit is at least 14 days after the previous immunogenicity blood draw; ❺ if within 7 days of the last vaccination; ❻ if within 28 days of the last vaccination; ❼ at the discretion of the investigator (based on health status of the participant)

Footnotes are presented on page 37.

SCHEDULE OF ACTIVITIES – COHORT 2

Phase	Screening	Vac	Post-vac FU			Vac	Post-vac FU				Second Year FU [s]		
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 2 + 7 d	Vac 2 + 28 d	Vac 1 + 26 wk	Vac 1 + 12 mo	Vac 1 + 18 mo	Vac 1 + 24 mo	Early Exit [a]
Visit Day(s)	-28 to 0	1	8 [c]	15	29	57	64 [d]	85 [d]	183	365	547	730	
Visit Window			±2 d	±2 d	±3 d	±3 d	±2 d	-3/+10 d	±14 d	±1 mo	±1 mo	±1 mo	
Visit Type	Screening	STUDY VACCINATION 1	Safety	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 2	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Early exit
Written informed consent [e]	●											●	
Inclusion/exclusion criteria	●												
Demographics	●												
Medical history/pre-study medications	●												
Physical examination [f]	●	❶❼	❼	❼	❼	❶❼	❼	❼	❼	❼	❼	❼	●
Vital signs [g] incl. body temperature	●	❷	●	●	●	❷	●	●	❼	❼	❼	❼	●
12-lead ECG [h]	●												
Serology (HIV-1/2, hepatitis B/C)	●												
Randomization		❶											
Verification of selected eligibility criteria		❶				❶							
Contraindications to vaccination [j]		❶				❶							
Safety lab blood sample, mL	● 10	❶ 5	● 5										❸ 5
Cellular immunity sample, mL [k]		❶ 50		● 50	● 50	❶ 50		● 50	● 50	● 50	● 50	● 50	❹ 50
Humoral immunity sample, mL		❶ 10		● 10	● 10	❶ 10		● 10	● 10	● 10	● 10	● 10	❹ 10
Transcriptome sample, mL		❶ 2.5	●2.5	● 2.5									
Nasal turbinate sample (or its alternative)		❶		●	●	❶		●		●			
Vaccination		●				●							
30 minute post-vaccination observation [l]		●				●							
Solicited AE recording		*- - Continuous - -*				*- - Continuous - -*							❺
Unsolicited AE recording [m]		*- - - - - - - - - - Continuous - - - - - - - - -*				*- - - - - - Continuous - - - - - -*							❻
SAE recording [m]		*- Continuous -*											●
Concomitant medications [n]		*- Continuous -*											●
Respiratory tract infection (RTI) [o,p]		*- During the first 2 RSV seasons of the study -*											●
RTI Symptoms Form distribution		*- - - - - - - - - - - - - - - - - To be distributed before the start of the first 2 RSV seasons of the study- - - - - - - - - - - - - - - - - - - -*											
Nasal swab kit distribution		*- - - - - - - - - - - - - - - - - To be distributed before the start of the first 2 RSV seasons of the study- - - - - - - - - - - - - - - - - - - -*											
Participant diary distribution [q]		●				●							
Participant diary review by site staff			●				●						

Phase	Screening	Vac	Post-vac FU			Vac	Post-vac FU				Second Year FU [s]		
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 2 + 7 d	Vac 2 + 28 d	Vac 1 + 26 wk	Vac 1 + 12 mo	Vac 1 + 18 mo	Vac 1 + 24 mo	Early Exit [a]
Visit Day(s)	-28 to 0	1	8 [c]	15	29	57	64 [d]	85 [d]	183	365	547	730	
Visit Window			±2 d	±2 d	±3 d	±3 d	±2 d	-3/+10 d	±14 d	±1 mo	±1 mo	±1 mo	
Visit Type	Screening	STUDY VACCINATION 1	Safety	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 2	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Early exit
Blood draw volumes													
Approximate daily blood draw, mL	10	67.5	7.5	62.5	60	60	--	60	60	60	60	60	65
Approximate cumulative study blood draw, mL	10	77.5	85	147.5	207.5	267.5	267.5	327.5	387.5	447.5	507.5	**567.5**	–

AE: adverse event; d: day; ECG: electrocardiogram; HIV: human immunodeficiency virus; ICF: informed consent form; mo: month; RSV: respiratory syncytial virus; RTI: respiratory tract infection; SAE: serious adverse event; vac: vaccination

❶ pre-dose; ❷ pre- and post-dose; ❸ if the early exit is within 8 days of the first vaccination; ❹ blood samples for immunogenicity will only be taken if the early exit is at least 14 days after the previous immunogenicity blood draw; ❺ if within 7 days of the last vaccination; ❻ if within 28 days of the last vaccination; ❼ at the discretion of the investigator (based on health status of the participant)

Footnotes are presented on page 37.

SCHEDULE OF ACTIVITIES – COHORT 2 (GROUPS 14-15) LONG-TERM FOLLOW-UP PHASE

Study Phase	Long-term Safety and Immunogenicity Follow-up	
Clinic Visit #	**13**	**14**
Visit Timing	**Vac 1 + 911 d (30 mo)**	**Vac 1 + 1094 d (36 mo)**
Visit Day(s)	**912**	**1095**
Visit Window	**±30 d**	**±30 d**
Cellular immunity sample, mL [k]	● 50	● 50
Humoral immunity sample, mL	● 10	● 10
SAE recording [t]	●	●
Concomitant medication [u]	●	●
Blood draw volumes		
Approximate daily blood draw, mL	60	60
Approximate cumulative study blood draw, mL	627.5	**687.5**

Footnotes are presented on page 37.

SCHEDULE OF ACTIVITIES – COHORT 3 WITH ONE-DOSE REGIMEN AND MONTH 12 AND MONTH 24 BOOSTER

Phase	Vac	Post-vac FU						Vac	Post-vac FU			Vac	Post-vac FU					
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Visit Timing	Vac 1	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 1 + 12 wk	Vac 1 + 26 wk	Vac 1 + 12 mo	Vac 2 + 7 d	Vac 2 + 28 d	Vac 2 + 26 wk	Vac 1 + 729 d (24 mo)	Vac 3 + 7 d	Vac 3 + 14 d	Vac 3 + 28 d	Vac 3 + 182 d (26 wk)	Vac 1 + 1094 d (36 mo)	Early Exit [a]
Visit Day(s)	1	8 [c]	15	29	57	85	183	365	372 [d]	393 [d]	547 [d]	730 [d]	737 [d,v]	744 [d]	758 [d]	912 [d]	1095 [d]	
Visit Window		±2 d	±2 d	±3 d	±3 d	-3/+10 d	±14 d	–2 mo	±2 d	±3 d	±14 d	±30 d	±2 d	±2 d	±3 d	±14 d	±30 d	
Visit Type	Screening and STUDY VACCINATION 1	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 2	Safety	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 3	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Early exit
Written informed consent [e]	❶											●						
Inclusion/exclusion criteria	❶																	
Demographics	❶																	
Medical history/pre-study medications	❶																	
Physical examination [f]	❶	❻	❻	❻	❻	❻	❻	❶	❻	❻	❻	❶	❻	❻	❻	❻	❻	●
Vital signs [g] incl. body temperature	❷	●	●	●	❻	❻	❻	❷	●	●	❻	❷	●	●	●	❻	❻	●
Randomization	❶																	
Verification of selected eligibility criteria [i]								❶				❶						
Contraindications to vaccination [j]	❶							❶				❶						
Cellular immunity sample, mL (in subset of Cohort 3 participants) [k]	❶ 50		● 50	● 50	● 50	● 50	● 50	❶ 50		● 50	● 50	❶ 50		● 50	● 50	● 50	● 50	❸ 50
Humoral immunity sample, mL [k]	❶ 10		● 10	● 10	● 10	● 10	● 10	❶ 10		● 10	● 10	❶ 10		● 10	● 10	● 10	● 10	❸ 10
Nasal turbinate sample (or its alternative)	❶		●	●	●	●		❶		●		❶			●			
Vaccination	●							●				●						
30 minute post-vaccination observation [l]	●							●				●						
Solicited AE recording	*Continuous*							*Continuous*				*Continuous*						❹
Unsolicited AE recording [m]	*Continuous*							*Continuous*				*Continuous*						❺
SAE recording [m]	*Continuous*																	●
Concomitant medications [n]	*Continuous*																	●
Respiratory tract infection (RTI) [o,p]	*During the first 2 RSV seasons of the study*																	●
RTI Symptoms Form distribution	*To be distributed before the start of the first 2 RSV seasons of the study*																	
Nasal swab kit distribution	*To be distributed before the start of the first 2 RSV seasons of the study*																	
Participant diary distribution [q]	●							●				●						

Phase	Vac	Post-vac FU						Vac	Post-vac FU			Vac	Post-vac FU					
Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Visit Timing	Vac 1	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 1 + 12 wk	Vac 1 + 26 wk	Vac 1 + 12 mo	Vac 2 + 7 d	Vac 2 + 28 d	Vac 2 + 26 wk	Vac 1 + 729 d (24 mo)	Vac 3 + 7 d	Vac 3 + 14 d	Vac 3 + 28 d	Vac 3 + 182 d (26 wk)	Vac 1 + 1094 d (36 mo)	Early Exit [a]
Visit Day(s)	1	8 [c]	15	29	57	85	183	365	372 [d]	393 [d]	547 [d]	730 [d]	737 [d,v]	744 [d]	758 [d]	912 [d]	1095 [d]	
Visit Window		±2 d	±2 d	±3 d	±3 d	-3/+10 d	±14 d	–2 mo	±2 d	±3 d	±14 d	±30 d	±2 d	±2 d	±3 d	±14 d	±30 d	
Visit Type	Screening and STUDY VACCINATION 1	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 2	Safety	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 3	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Early exit
Participant diary review by site staff		●							●				●					
Blood draw volumes: Participants with blood draws for humoral responses only (N=252)																		
Approximate daily blood draw, mL	10	–	10	10	10	10	10	10	–	10	10	10	10	10	10	10		10
Approximate cumulative study blood draw, mL	10	10	20	30	40	50	60	70	70	80	90	100	110	120	130	**140**		–
Blood draw volumes: Participants with blood draws for both humoral and cellular responses (N=63)																		
Approximate daily blood draw, mL	60	–	60	60	60	60	60	60	–	60	60	60	60	60	60	60		60
Approximate cumulative study blood draw, mL	60	–	120	180	240	300	360	420	420	480	540	600	660	720	780	**840**		–

AE: adverse event; d: day; eCRF: electronic case report form; ICF: informed consent form; mo: month; RSV: respiratory syncytial virus; RTI: respiratory tract infection; SAE: serious adverse event; vac: vaccination

❶ pre-dose; ❷ pre- and post-dose; ❸ blood samples for immunogenicity will only be taken if the early exit is at least 14 days after the previous immunogenicity blood draw; ❹ if within 7 days of the last vaccination; ❺ if within 28 days of the last vaccination; ❻ at the discretion of the investigator (based on health status of the participant)

Footnotes are presented on page 37.

SCHEDULE OF ACTIVITIES – COHORT 3 WITH TWO-DOSE REGIMEN AND MONTH 12 BOOSTER

Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	
Visit Timing	Vac 1	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 1 + 56 d	Vac 2 + 7 d	Vac 2 + 28 d	Vac 1 + 26 wk	Vac 1 + 12 mo	Vac 3 + 7 d	Vac 3 + 28 d	Vac 3 + 26 wk	Vac 3 + 12 mo [r]	Early Exit [a]
Visit Day(s)	1	8 [c]	15	29	57	64 [d]	85 [d]	183	365	372 [d]	393 [d]	547 [d]	730 [d]	
Visit Window		±2 d	±2 d	±3 d	±3 d	±2 d	-3/+10 d	±14 d	–2 mo	±2 d	±3 d	±14 d	±1 mo	
Visit Type	Screening and STUDY VACCINATION 1	Safety	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 2	Safety	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 3	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Early exit
Written informed consent [e]	❶													
Inclusion/exclusion criteria	❶													
Demographics	❶													
Medical history/pre-study medications	❶													
Physical examination [f]	❶	❻	❻	❻	❶❻	❻	❻	❻	❶	❻	❻	❻	❻	●
Vital signs [g] incl. body temperature	❷	●	●	●	❷	●	●	❻	❷	●	●	❻	❻	●
Randomization	❶													
Verification of selected eligibility criteria [i]					❶				❶					
Contraindications to vaccination [j]	❶				❶				❶					
Cellular immunity sample, mL (in subset of Cohort 3 participants) [k]	❶ 50		● 50	● 50	❶ 50		● 50	● 50	❶ 50		● 50	● 50	● 50	❸ 50
Humoral immunity sample, mL [k]	❶ 10		● 10	● 10	❶ 10		● 10	● 10	❶ 10		● 10	● 10	● 10	❸ 10
Nasal turbinate sample (or its alternative)	❶		●	●	❶		●		❶		●			
Vaccination	●				●				●					
30 minute post-vaccination observation [l]	●				●				●					
Solicited AE recording	- - Continuous - -				- - Continuous - -				- - Continuous - -					❹
Unsolicited AE recording [m]	- - - - - - - - Continuous - - - - - - - - -				- - - - - - Continuous - - - - -				- - - - - - Continuous - - - - -					❺
SAE recording [m]	- Continuous- -													●
Concomitant medications [n]	- Continuous- -													●
Respiratory tract infection (RTI) [o,p]	- During the first 2 RSV seasons of the study -													●
RTI Symptoms Form distribution	- To be distributed before the start of the first 2 RSV seasons of the study -													
Nasal swab kit distribution	- To be distributed before the start of the first 2 RSV seasons of the study -													
Participant diary distribution [q]	●				●				●					
Participant diary review by site staff		●				●				●				
Blood draw volumes: Participants with blood draws for humoral responses only (N=252)														
Approximate daily blood draw, mL	10	–	10	10	10	–	10	10	10	–	10	10	10	10
Approximate cumulative study blood draw, mL	10	10	20	30	40	40	50	60	70	70	80	90	100	–

Clinic Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	
Visit Timing	**Vac 1**	**Vac 1 + 7 d**	**Vac 1 + 14 d**	**Vac 1 + 28 d**	**Vac 1 + 56 d**	**Vac 2 + 7 d**	**Vac 2 + 28 d**	**Vac 1 + 26 wk**	**Vac 1 + 12 mo**	**Vac 3 + 7 d**	**Vac 3 + 28 d**	**Vac 3 + 26 wk**	**Vac 3 + 12 mo [r]**	**Early Exit [a]**
Visit Day(s)	**1**	**8 [c]**	**15**	**29**	**57**	**64 [d]**	**85 [d]**	**183**	**365**	**372 [d]**	**393 [d]**	**547 [d]**	**730 [d]**	
Visit Window		**±2 d**	**±2 d**	**±3 d**	**±3 d**	**±2 d**	**-3/+10 d**	**±14 d**	**–2 mo**	**±2 d**	**±3 d**	**±14 d**	**±1 mo**	
Visit Type	**Screening and STUDY VACCINATION 1**	Safety	Safety and Immunogenicity	Safety and Immunogenicity	**STUDY VACCINATION 2**	Safety	Safety and Immunogenicity	Safety and Immunogenicity	**STUDY VACCINATION 3**	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Early exit
Blood draw volumes: ***Participants with blood draws for both humoral and cellular responses (N=63)***														
Approximate daily blood draw, mL	60	–	60	60	60	–	60	60	60	–	60	60	60	60
Approximate cumulative study blood draw, mL	60	60	120	180	240	240	300	360	420	420	480	540	**600**	–

AE: adverse event; d: day; ICF: informed consent form; mo: month; RSV: respiratory syncytial virus; RTI: respiratory tract infection; SAE: serious adverse event; vac: vaccination

❶ pre-dose; ❷ pre- and post-dose; ❸ blood samples for immunogenicity will only be taken if the early exit is at least 14 days after the previous immunogenicity blood draw; ❹ if within 7 days of the last vaccination; ❺ if within 28 days of the last vaccination; ❻ at the discretion of the investigator (based on health status of the participant)

Footnotes are presented on page 37.

Table footnotes for all cohorts:

a. For those participants who are unable to continue participation in the study, but for whom consent is not withdrawn, an exit visit will be conducted as soon as possible.
b. In addition, sentinel participants will be contacted by telephone 24 hours post-dose to collect safety information.
c. If any of the participants for 7-day post-first study vaccine dose safety review come in earlier than Day 8 for Visit 3 in Cohorts 1 and 2, and Visit 2 in Cohort 3 (allowed window is ±2 days), a subsequent phone call will be made at the end of the diary period to collect diary card information recorded between the actual visit and the end of the diary period on Day 8.
d. The timings of the post-vaccination visits will be determined relative to the actual day of that vaccination.
e. Signing of the Informed Consent Form (ICF) should be done before any study-related activity. Additional written informed consent for participants in Groups 14 and 15 (Cohort 2) progressing into the long-term follow-up phase and participants in Cohort 3 who will receive an additional vaccination at Day 730 (Month 24 booster) will be required.
f. A full physical examination, including height and body weight, will be carried out at screening and before the Month 12 booster (Cohorts 1 and 3) and before the Month 24 booster (Day 730) (Cohort 3 only). At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.
g. Body temperature (oral route preferred), supine systolic and diastolic blood pressure, heart rate and respiratory rate after at least 5 minutes rest. Vital signs are to be measured before blood draws and nasal samples.
h. Supine electrocardiogram (ECG) after at least 5 minutes rest.
i. To include inclusion criteria 4 and 5, and exclusion criteria 1, 4, 12, 13, and 14.
j. Investigator must check for acute illness or body temperature ≥38.0 °C at the time of vaccination. In such cases, the participant may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn from vaccination at the discretion of the investigator.
k. Blood for cellular and humoral immune responses will be drawn from all participants in Cohorts 1 and 2. In Cohort 3, blood will be drawn for humoral immune responses from all participants and for cellular immune responses from a subset of 63 participants.
l. Participants will be closely observed for a minimum of 30 minutes post-vaccination. Any unsolicited, solicited local and solicited systemic AEs, and vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) will be documented by study-site personnel following this observation period.
m. All adverse events (AEs) and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards. All other AEs (unsolicited) and special reporting situations will be reported from each vaccination through the following 28 days. All serious adverse events (SAEs) related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards. All other SAEs will be reported from the first vaccination onwards.
n. Concomitant medications will be collected from the time of each vaccination, through 28 days after each vaccination, and additionally outside of these periods when associated with any SAE. Pre-study therapies administered up to 30 days before first dose of study vaccine will be recorded during screening.
o. Signs and symptoms of RTI will be recorded during the first 2 RSV seasons of the study (relative to the enrollment date of the first participant in Cohort 1) using the specific RTI Symptoms Form. Participants will be notified of the RSV season. During the first 2 RSV seasons, they will be contacted by telephone every 30±7 days (unless a prescheduled clinic visit has occurred or will occur within 30 days). Calls will remind participants to complete the RTI Symptoms Form in the event of any symptoms of RTI, to contact the site at the time of symptom onset, and to take a nasal sample at home preferably between 2 and 3 days after the onset of the RTI symptoms (or go to the site preferably within 2 to 3 days after the onset of the RTI to have a nasal sample taken by study staff). Calls will also check for any SAEs and associated concomitant medications since the previous visit or telephone contact. Details of the RTI procedures are provided in Section 9.2.2.
p. During the first 2 RSV seasons of the study (relative to the enrollment date of the first participant in Cohort 1), every effort should be made to collect data on the clinical course of RTIs including information on oxygenation status, supplemental oxygen requirements and specific drug treatments, as well as other concurrent respiratory illness present at the time of the diagnosis of the event and up to symptom resolution.
q. Rulers and thermometers will also be distributed at these visits.
r. Vac 3+12 mo is the same as Vac 1+24 mo.
s. Participants in Groups 14 and 15 will continue into the long-term follow-up phase (see Cohort 2 long-term follow-up phase Time and Events Schedule).
t. During the long-term follow-up phase, only SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, and all AEs leading to discontinuation will be collected during the long-term follow-up phase
u. During the long-term follow-up phase, only medications in conjunction with SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, or in conjunction with AEs leading to discontinuation should be recorded.
v. Visit 13 (7 days post-third vaccination) is not required for any Cohort 3 participant who misses the third vaccination.

ABBREVIATIONS

Ad26	adenovirus serotype 26
Ad35	adenovirus serotype 35
AE	adverse event
CDC	Clinical Development Committee
CI	confidence interval
CS	circumsporozoite
DNA	deoxyribonucleic acid
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot (assay)
ERD	enhanced respiratory disease
F protein	fusion protein
FA	full analysis (set)
FA2	fusion protein of the RSV A2 strain
FDA	United States Food and Drug Administration
FI	formalin-inactivated
FIH	first-in-human
G protein	glycoprotein
GCP	Good Clinical Practice
GMT	geometric mean titer
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	intracellular cytokine staining
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IL	interleukin
IRB	Institutional Review Board
IWRS	interactive web response system
ML	medical leader
N protein	nucleoprotein
NSAID	non-steroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cells
PI	principal investigator
PPI	per-protocol RSV immunogenicity (set)
pre-F	pre-fusion
post-F	post-fusion
PQC	Product Quality Complaint
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SRP/S	study responsible physician/scientist
SUSAR	suspected unexpected serious adverse reaction
TASH	therapeutic area safety head
Th	T-helper (cell)
TNF-α	tumor necrosis factor alpha
VNA	virus neutralizing antibody
vp	viral particles

1. INTRODUCTION

A human adenovirus-vectored vaccine candidate and a pre-fusion conformation-stabilized respiratory syncytial virus (RSV) F protein which have shown promise in preclinical animal models of RSV will be assessed in this study:

- Ad26.RSV.preF (JNJ-64400141), a replication-incompetent adenovirus serotype 26 (Ad26) containing a deoxyribonucleic acid (DNA) transgene that encodes the pre-fusion conformation-stabilized F protein (pre-F) derived from the RSV A2 strain.
- RSV preF protein (JNJ-64213175), a pre-fusion conformation-stabilized F protein derived from the RSV A2 strain.

Different naming conventions are being used for clinical studies. The first part of the study identifier is one of the following, depending on the vaccine and study population:

- VAC18192 (used for studies to test the Ad26.RSV.FA2 vaccine in the adult population)
- VAC18193 (used for studies to test the Ad26.RSV.preF vaccine in the adult and elderly populations)
- VAC18194 (used for studies to test the Ad26.RSV.preF vaccine in the pediatric population)

Studies are given a suffix of a 4-digit number preceded by the letters RSV (for 'Respiratory Syncytial Virus').

The following sponsor RSV vaccine studies are referenced in this protocol:

Study Identifier	Clinical Phase	Vaccine	Study Population
VAC18192RSV1001	1	Ad26.RSV.FA2	Adults aged 18 to 50 years
VAC18192RSV1003	1	Ad26.RSV.FA2	Adults aged 18 to 50 years
VAC18193RSV1003	1	Ad26.RSV.preF vaccine	Adults aged 60 years and older
Current study: VAC18193RSV1004	1/2a	Ad26.RSV.preF vaccine	Adults aged 60 years and older
VAC18193RSV2002	2a	Ad26.RSV.preF vaccine	Adults aged 18 to 50 years
VAC18193RSV2003	2a	Ad26.RSV.preF vaccine	Adults aged 60 years and older
VAC18194RSV2001	1/2a	Ad26.RSV.preF vaccine	Adults aged 18 to 50 years and RSV-seropositive toddlers aged 12 to 24 months

This will be the first-in-human (FIH) study for RSV preF protein, and for the Ad26.RSV.preF/ RSV preF protein combination (administered as separate injections in opposite arms) and the Ad26.RSV.preF/RSV preF protein mixture (administered as a single injection).

For the most comprehensive nonclinical information regarding Ad26.RSV.preF, refer to the latest version of the Investigator's Brochure for Ad26.RSV.preF.[17]

For the most comprehensive nonclinical information regarding RSV preF protein, refer to the latest version of the Investigator's Brochure for RSV preF protein.[18]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Background

RSV is an important cause of serious respiratory infections in the elderly, immunocompromised, and those with underlying chronic cardiopulmonary conditions.[8] Although most adults mount a long-lasting fully protective immune response, waning immune responses in the elderly might contribute to increased susceptibility to severe disease after RSV infection causing significant morbidity and mortality. In long-term care facilities, RSV is estimated to infect 5% to 10% of the residents per year with significant rates of pneumonia (10% to 20%) and death (2% to 5%).[9] In an epidemiology study of RSV burden, it was estimated that 11,000 elderly persons die annually of RSV in the United States.[35] These data support the importance of developing an effective vaccine for certain adult populations, such as the elderly.

RSV is also considered to be the most important cause of serious acute respiratory illness in infants and children under 5 years of age: worldwide in 2005, RSV caused an estimated 33.8 million new episodes of acute lower respiratory tract infections in this age range, with 3.4 million cases requiring hospitalization due to severe illness.[13,32,33]

Despite the high RSV disease burden, no licensed vaccine is available for RSV. The first vaccine candidate for use in young children, which consisted of formalin-inactivated RSV (FI-RSV), was associated with enhanced respiratory disease (ERD) upon infection with RSV.[21] Although the mechanisms for ERD are not fully understood, it is thought that FI-RSV failed to induce adequate neutralizing antibody titers and $CD8^+$ priming, and induced a T-helper (Th)2 skewed response.[28]

As all adults have been exposed to RSV, and therefore previously primed by a live virus infection, ERD is not expected to be a concern in this study.[6]

Adenoviral-vectored Vaccines

It is thought that an efficacious RSV vaccine should induce high levels of neutralizing antibodies, antigen-specific $CD8^+$ T-cell responses, and Th1-type $CD4^+$ T-cells.[2] The Ad26.RSV.preF candidate RSV vaccine being evaluated in this protocol is based on the AdVac® platform which has been shown to promote a strong antibody response as well as $CD8^+$ T-cell and Th1-type $CD4^+$ T-cell responses.

The immunogenicity profile of adenoviral vectors, with particular emphasis on Th1 responses, is illustrated by data obtained following the immunization of adults with an Ad26-vectored human immunodeficiency virus (HIV) vaccine (Ad26.ENVA.01), and immunization of adults and infants with an adenovirus serotype 35 (Ad35)-vectored tuberculosis (TB) vaccine (Ad35.TB-S). These

data demonstrate predominantly interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) production in $CD4^+$ and $CD8^+$ T-cells.[1,5,31]

Ad26.RSV.FA2 Clinical Data

Ad26 encoding for a wild-type RSV F protein of the RSV A2 strain (FA2) has been evaluated in studies VAC18192RSV1001 and VAC18192RSV1003 (N=48 and N=32, respectively, of which 35 and 24 participants, respectively, received Ad26.RSV.FA2) in healthy adults at doses of 5×10^{10} viral particles (vp). Both studies have been completed.

The results indicate that there have been no safety concerns following vaccination in either study. After vaccination with Ad26.RSV.FA2, local reactogenicity comprised almost exclusively mild to moderate pain of median duration 1 to 3 days. The most commonly experienced solicited systemic adverse events (AEs) (headache, fatigue, chills, and myalgia) were also mostly mild to moderate in severity, with a median duration of 1 to 3 days; most unsolicited AEs and most laboratory toxicities were mild to moderate in severity. No serious adverse events (SAEs) were reported and no AEs led to withdrawal from study vaccine.[19,20]

Single vaccination with 5×10^{10} vp of Ad26.RSV.FA2 raised both humoral and cellular immunity. An increase in RSV neutralizing antibody titers was observed; RSV-specific T-cell responses were also increased.

FA2 and preF RSV Vaccines

The clinical studies VAC18192RSV1001 (FIH for Ad35.RSV.FA2) and VAC18192RSV1003 (FIH for Ad26.RSV.FA2) have been completed with Ad26.RSV.FA2 and Ad35.RSV.FA2 (a similar recombinant, replication-incompetent vaccine using an Ad35 vector), in which Ad26 and Ad35, respectively, encode for a wild-type RSV F protein of the RSV A2 strain.

The adenoviral vectors Ad26 and Ad35 are derived from Group B and D serotype adenoviruses and have been similarly modified to be replication-incompetent; expression of the antigen is controlled by the same promotor. An Ad26-based RSV vaccine was chosen for further clinical development over the Ad35-based counterpart based on a better immunogenicity profile from nonclinical data, a similar safety and immunogenicity profile but at half the Ad35 dose from clinical data, and a better manufacturing profile.

The F protein of RSV undergoes a conformational transition from a metastable pre-fusion conformation to a stable post-fusion conformation. Neutralizing sensitive epitopes reside on both proteins, but recent evidence indicates that those epitopes specific to the pre-F protein seem to be more potent than those previously identified and present on the post-F protein.[11,12] This evidence resulted in the design of the candidate RSV vaccine (Ad26.RSV.preF) in which the adenoviral vector encodes a full length RSV F protein stabilized in the pre-F protein conformation. The full length membrane-bound RSV F protein in a pre-F configuration encoded by this vector differs by only 5 amino acids from the wild-type used in the FA2 construct.[24] This change in the transgene confers more stability to the pre-fusion form of the molecule before it undergoes its natural transition to the post-fusion form.[24] This change also induces higher immune responses against

pre-fusion epitopes because the majority of neutralizing antibodies target the pre-fusion protein conformation.[25,29] For these reasons, it is anticipated that the Ad26.RSV.preF vaccine candidate will generate more neutralizing antibodies relative to the Ad26.RSV.FA2 vaccine.[16]

Ad26.RSV.preF and RSV preF Protein Preclinical Data

Preclinical studies were performed in naïve and RSV pre-exposed animals. Ad26.RSV.preF is immunogenic in mice and cotton rats, with humoral responses that include the induction of RSV neutralizing antibodies. In addition, in mice it was shown that Ad26.RSV.preF elicits cellular responses, characterized by the induction of RSV F-specific $CD8^+$ IFN-γ^+ T-cells. The immune response following Ad26.RSV.preF immunization was Th1-biased.

RSV preF protein induced virus neutralizing antibody (VNA) titers in mice, cotton rats, and non-human primates. Furthermore, prime-boost immunization with non-adjuvanted RSV preF protein gave partial protection from RSV infection in the lung in cotton rats. In RSV pre-exposed mice, high neutralizing antibody titers were boosted by a single administration of RSV preF protein; RSV preF protein induced low RSV F-specific cellular responses in pre-exposed mice, in contrast to Ad26.RSV.preF which induced high cellular responses.

The mixture of Ad26.RSV.preF and RSV preF protein induced both high VNA titers and a cellular response in mice, maintaining the advantage of each vaccine component. RSV preF protein boost-immunization, after Ad26.RSV.preF prime, induced high virus neutralizing titers, and the cellular responses induced by the adenoviral vector were also maintained. In RSV pre-exposed non-human primates, the mixture of Ad26.RSV.preF and RSV preF protein induced both cellular responses and high VNA titers by single administration.[16]

The RSV preF protein has been evaluated in a single dose pilot toxicology study in the rabbit up to 250 µg. No clinically significant toxicological changes were noted. In a follow-up good laboratory practice (GLP) toxicology study in the rabbit, RSV preF protein was evaluated at 250 µg per injection, either alone in a prime-boost regimen with Ad26.RSV.preF (1×10^{11} vp) or in a single injection mixture with Ad26.RSV.preF for 3 dosing days with 2-week intervals. Test article-related mortality was not observed, and no effects were noted on clinical observations, dermal scores, body weight, hematology, ophthalmology, and body temperature. All vaccine regimens were well tolerated and without adverse effects.

Ad26.RSV.preF and RSV preF Protein Clinical Data

Ad26.RSV.preF:

Ad26.RSV.preF is currently under evaluation in four other ongoing studies: one Phase 1 study (VAC18193RSV1003), two Phase 2a studies (VAC18193RSV2002 and VAC18193RSV2003) and one Phase 1/2a study (VAC18194RSV2001) (Table 7).

Table 7: Other Ongoing Clinical Studies with Ad26.RSV.preF

Study Identifier	Clinical Phase	Vaccine	N Planned	Study Population
VAC18193RSV1003	1	Ad26.RSV.preF	72	Adult participants aged 60 years and older
VAC18193RSV2002	2a	Ad26.RSV.preF	44-70	Adult participants aged 18 to 50 years
VAC18193RSV2003	2a	Ad26.RSV.preF	180	Adult participants aged 60 years and older
VAC18194RSV2001	1/2a	Ad26.RSV.preF	12 adults 48 toddlers	Adult participants aged 18 to 50 years and RSV-seropositive toddlers aged 12 to 24 months

In one of these studies, interim safety and immunogenicity data are available, as follows:

VAC18193RSV1003: This is an ongoing single-center, randomized, placebo-controlled, double-blind, FIH, Phase 1 study to evaluate the safety, tolerability and immunogenicity of 2 Ad26.RSV.preF vaccinations, administered 1 year apart, in 72 male and female subjects aged 60 years and older in stable health. Participants were randomized to 1 of 5 groups and have received 2 intramuscular injections as follows:

- Group 1: 5×10^{10} vp Ad26.RSV.preF on Day 1 and 1 year* later
- Group 2: 5×10^{10} vp Ad26.RSV.preF on Day 1 and placebo 1 year later
- Group 3: 1×10^{11} vp Ad26.RSV.preF on Day 1 and 1 year later
- Group 4: 1×10^{11} vp Ad26.RSV.preF on Day 1 and placebo 1 year later
- Group 5: placebo on Day 1 and 1 year later.

** Window of -2 months to +1 month*

Safety and immunogenicity data from the unblinded (at the study group level) analysis 28 days post-Dose 1 from all 72 participants who received Ad26.RSV.preF (5×10^{10} vp or 1×10^{11} vp) or placebo confirmed that the 1×10^{11} vp dose of Ad26.RSV.preF was more immunogenic compared with the 5×10^{10} vp dose. Data from this ongoing study, which is still blinded, show that the Ad26.RSV.preF vaccine is immunogenic and that there is a favorable Th1/Th2 profile. No safety concerns were revealed; the reactogenicity of both doses was comparable.

In study VAC18194RSV2001, first 12 male and female adults, and then 48 male and female RSV-seropositive toddlers, are randomized to receive 2 intramuscular injections as follows:

Adults (aged ≥18 to ≤50 years):

- Group 1: 1×10^{11} vp Ad26.RSV.preF on Day 1 and Day 29
- Group 2: placebo on Day 1 and Day 29

RSV-seropositive toddlers (aged 12 to 24 months):

- Group 3: 5×10^{10} vp Ad26.RSV.preF on Day 1 and Day 29
- Group 4: placebo on Day 1 and Day 29

All participants are planned to have been dosed prior to the start of the current study.

In study VAC18193RSV2002, more than 44 (and up to 70) healthy male and female participants aged 18 to 50 years who have been prescreened for susceptibility to RSV infection receive a single intramuscular injection with Ad26.RSV.preF 1×10^{11} vp or placebo, followed by intranasal challenge with the RSV-A Memphis 37b virus within 24 to 90 days following vaccination. All participants are planned to have been dosed prior to the start of the current study.

In study VAC18193RSV2003, 180 male and female participants aged ≥60 years in stable health are randomized to 1 of 2 groups. Participants in Group 1 receive Ad26.RSV.preF 1×10^{11} vp on Day 1 administered at the same time as a commercially available seasonal influenza vaccine (Fluarix® Quadrivalent), and placebo on Day 29. Participants in Group 2 receive placebo on Day 1, administered at the same time as a commercially available seasonal influenza vaccine (Fluarix Quadrivalent), and Ad26.RSV.preF 1×10^{11} vp on Day 29. All vaccines are given by intramuscular injection. The primary analysis for safety and immunogenicity at 28 days after the second dose is expected to have been completed prior to the start of the current study.

In study VAC18193RSV1003, Ad26.RSV.preF was provided in a different formulation buffer (Formulation Buffer 1[a]) from the one used in the current study and studies VAC18194RSV2001, VAC18193RSV2002 and VAC18193RSV2003 (Formulation Buffer 2[b]).

RSV preF Protein:

To date, RSV preF protein has not been tested in humans. This is the FIH study for RSV preF protein, and for the Ad26.RSV.preF/RSV preF protein combination (administered as separate injections in opposite arms) and Ad26.RSV.preF/RSV preF protein mixture (administered as a single injection).

Safety Data Supporting the Ad26.RSV.preF Dose Selection

The dose levels for Ad26.RSV.preF used in the current study are supported by experience in adults with other Ad26-based vaccines encoding for different antigens (including EnvA [in Ad26.ENVA.01 against HIV];[4,5] circumsporozoite (CS) protein [in Ad26.CS.01 against malaria];[34] and Ebola glycoprotein [in Ad26.ZEBOV against Ebola virus][27]).

In completed clinical studies, the safety of Ad26.ENVA.01, Ad26.CS.01, and Ad26.RSV.FA2 has been evaluated in 584 adults, of whom 519 (88.9%) received Ad26 at a dose level of 5×10^{10} vp and 25 (4.3%) were vaccinated with Ad26 at the highest dose level tested (1×10^{11} vp).

CCI [redacted]

In addition, 17 clinical studies with Ad26 vaccines (Ad26.RSV.preF, Ad26.Mos[4].HIV, and Ad26.ZEBOV) are ongoing. At least 4,579 participants have been enrolled in these ongoing studies, of whom approximately 456 received at least one vaccination with an Ad26-based vaccine (mainly 5×10^{10} vp) up to 31 August 2017. For the remainder of participants, study vaccine assignment is not yet known. To date, all Ad26-based vaccines were found to be well-tolerated, no safety concerns have been identified. Note that, in general, at a given dose level, no significant differences in safety profiles of Ad26-based vaccines have been observed based upon the transgene used.[14,15]

Overall, these clinical data are supportive of dosing Ad26.RSV.preF at 5×10^{10} vp and 1×10^{11} vp in the current study.

1.2. Overall Rationale for the Study

Despite the high RSV disease burden, no licensed vaccine is available for RSV.

The current study has an adaptive design to determine a regimen for further clinical development in adults aged ≥60 years based on safety and immunogenicity. The selected regimen should improve humoral immune responses with no adverse effect on cellular responses compared with Ad26.RSV.preF alone.

The potential use of RSV preF protein as a component of an RSV vaccine will be assessed by evaluation of the safety and reactogenicity of intramuscular regimens of Ad26.RSV.preF, RSV preF protein, the combination or mixture of Ad26.RSV.preF and RSV preF protein, or placebo. Approximately 667 male and female participants aged ≥60 years will be randomized in 3 cohorts as outlined in Table 8, Table 9, Table 10, and Table 11, respectively.

The current study will be the FIH study for the RSV preF protein, and for the Ad26.RSV.preF/ RSV preF protein combination and mixture.

The initial safety cohort (Cohort 1) is designed to assess the safety and immunogenicity of 2 dose levels of RSV preF protein (50 µg and 150 µg). The safety of RSV preF protein at each dose will be checked before administration of the combination or mixture of Ad26.RSV.preF and RSV preF protein.

The dose selection rationale is provided in Section 3.2.

An internal data review committee (DRC) will be established for this study to evaluate safety and reactogenicity data on a regular basis.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

SAFETY COHORT OBJECTIVE (COHORT 1):

To determine in small numbers of participants aged 60 years and older the safety of intramuscular homologous two-dose regimens comprising RSV preF protein or Ad26.RSV.preF/RSV preF protein mixture on Days 1 and 57, with a booster at Month 12, or separate administration of Ad26.RSV.preF and RSV preF protein in opposite arms on Day 1 with a booster at Month 12, before progression to regimen selection in a larger number of participants

Objectives	***Endpoints***
PRIMARY	
• To assess the safety and reactogenicity of the intramuscular one- and two-dose regimens, with a booster at Month 12	• SAEs from first dose administration until the end of the study • Solicited local and systemic AEs for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
SECONDARY	
• To assess the humoral and cellular immune responses elicited by Ad26.RSV.preF, RSV preF protein, and the Ad26.RSV.preF/RSV preF protein combination and mixture	• RSV neutralization assay, F protein binding antibodies (enzyme-linked immunosorbent assay [ELISA]; pre-F and/or post-F), and IFN-γ enzyme-linked immunospot (ELISpot) assay
EXPLORATORY	
• Additional exploratory analyses may be performed to investigate vaccine-elicited immune responses further	• Assays to be used include, but are not limited to, RSV strain cross-neutralization, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization assays, molecular antibody characterization (avidity, Fc cell interaction, antibody isotyping, antibody sequencing for repertoire), and nasal antibodies to RSV, including but not limited to immunoglobulin (Ig)A and IgG; evaluation of the cellular immune response and the functional and memory immune response by intracellular cytokine staining (ICS) and transcriptome analysis
• To evaluate symptoms of respiratory illness (including respiratory illness due to RSV) via the Respiratory Tract Infection (RTI) Symptoms Form	• During the RSV season: Signs and symptoms of RTI (including RTI due to RSV) from Day 1 until the end of the second RSV season of the study[a]
• Characterization of viral or bacterial infections in the respiratory tract	• Assessment, typing and level of infection by reverse transcriptase polymerase chain reaction (RT-PCR) or response to respiratory infection by serology

[a] The second RSV season of the study is defined relative to the enrollment date of the first participant in Cohort 1.

REGIMEN SELECTION COHORT OBJECTIVE (COHORT 2):

To select a regimen for progression to evaluation in an expanded safety cohort (Cohort 3; see below) by assessment of the safety and immunogenicity in participants aged 60 years and older of intramuscular one-dose regimens of Ad26.RSV.preF, Ad26.RSV.preF/RSV preF protein mixture, or separate administration of Ad26.RSV.preF and RSV preF protein in opposite arms on Day 1, or a two-dose regimen of Ad26.RSV.preF/RSV preF protein mixture on Days 1 and 57

Objectives	***Endpoints***
PRIMARY	
• To assess the safety and reactogenicity of the intramuscular one- and two-dose regimens	• SAEs from first dose administration until the end of the study • Solicited local and systemic AEs for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
• To assess RSV neutralizing antibody levels of the one-dose regimens (Groups 11 to 15) containing RSV preF protein compared to the one-dose Ad26.RSV.preF regimen	• RSV A2 neutralizing antibody levels of the one-dose regimens (Groups 11 to 15) on Day 29[a]
SECONDARY	
• To assess RSV neutralizing antibody levels of the one-dose regimen with separate injections (Group 16) and the two-dose regimen (Group 17) containing RSV preF protein compared to the one-dose Ad26.RSV.preF regimen	• RSV A2 neutralizing antibody levels of: – the one-dose regimen with separate injections (Group 16) on Day 29 – the two-dose regimen (Group 17) on Day 85[a]
• To assess additional humoral immune responses elicited by Ad26.RSV.preF and the Ad26.RSV.preF/RSV preF protein combination and mixture	• F protein binding antibodies (ELISA; pre-F and/or post-F)
• To assess cellular immune responses by IFN-γ ELISpot of all regimens containing RSV preF protein compared to the one-dose Ad26.RSV.preF regimen	• RSV F protein by IFN-γ ELISpot assay - the one-dose regimens on Day 29[a] (Groups 11 to 16) - the two-dose regimen on Day 85[a] (Group 17)
EXPLORATORY	
• Additional exploratory analyses may be performed to investigate vaccine-elicited immune responses further	• Assays to be used include, but are not limited to, RSV strain cross-neutralization, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization assays, molecular antibody characterization (avidity, Fc cell interaction, antibody isotyping, antibody sequencing for repertoire), and nasal antibodies to RSV, including but not limited to IgA and IgG; evaluation of the cellular immune response and the functional and memory immune response by ICS and transcriptome analysis

[a] See "STATISTICAL METHODS - Immunogenicity Analyses" for details.

Objectives	*Endpoints*
• To assess the long-term durability of the immune response in selected groups	• Assays to be used include, but are not limited to, RSV neutralizing antibody levels against A and B strain, RSV F protein binding antibodies (ELISA; pre-F and/or post-F), RSV F protein specific functional antibodies, and RSV F protein specific IFN-γ ELISpot in Groups 14 and 15 at Days 912 and 1095
• To evaluate symptoms of respiratory illness (including respiratory illness due to RSV) via the RTI Symptoms Form	• During the RSV season: Signs and symptoms of RTI (including RTI due to RSV) from Day 1 until the end of the second RSV season of the study[a]
• Characterization of viral or bacterial infections in the respiratory tract	• Assessment, typing and level of infection by RT-PCR or response to respiratory infection by serology

EXPANDED SAFETY COHORT OBJECTIVE (COHORT 3):

To determine the safety and immunogenicity of the selected regimen in an expanded cohort of participants aged 60 years and older; and to determine the need for a booster dose at Month 12 and/or Month 24

Objectives	*Endpoints*
PRIMARY	
• To assess the safety and reactogenicity of the selected regimen and a booster at Month 12 and/or Month 24	• SAEs from first administration until the end of the study • Solicited local and systemic AEs for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
SECONDARY	
• To assess humoral immune responses to the selected regimen in all participants	• RSV neutralization A2 strain
• To assess cellular immune responses to the selected regimen in a subset of participants	• IFN-γ ELISpot assay
EXPLORATORY	
• Additional exploratory analyses may be performed to further investigate vaccine-elicited immune responses	Assays to be used include, but are not limited to: • F protein binding antibodies (ELISA; pre-F and/or post-F) • Flow cytometry • RSV cross-neutralization of B and/or other A strain • F-protein antibody specificity characterization • Cytokines/chemokines in nasal samples (if feasible) • Adenovirus neutralization assays

[a] The second RSV season of the study is defined relative to the enrollment date of the first participant in Cohort 1.

Objectives	*Endpoints*
	• Functional and molecular antibody characterization • Analysis of nasal antibodies to RSV including, but not limited to IgA and IgG
• To assess the long-term durability of the immune response in groups receiving a booster at different time intervals	• Assays to be used include, but are not limited to, RSV neutralizing antibody levels against A and B strain, RSV F protein binding antibodies (ELISA; pre-F and/or post-F), RSV F protein specific functional antibodies, and RSV F protein specific IFN-γ ELISpot at Days 758, 912 and 1095
• To evaluate symptoms of respiratory illness (including respiratory illness due to RSV) via the RTI Symptoms Form	• During the RSV season: Signs and symptoms of RTI (including RTI due to RSV) from Day 1 until the end of the second RSV season of the study[a]
• Characterization of viral or bacterial infections in the respiratory tract	• Assessment, typing and level of infection by RT-PCR or response to respiratory infection by serology

See Section 9.2 for evaluations related to endpoints.

2.2. Hypothesis

No formal statistical testing of safety and immunogenicity data is planned.

Data will be analyzed descriptively.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study

3.1.1. Study Design

This is a multi-center, randomized, double-blind, placebo-controlled Phase 1/2a study for safety and immunogenicity evaluations for regimen selection of Ad26.RSV.preF and RSV preF protein combinations followed by expanded safety evaluation of the selected regimen in male and female participants aged ≥60 years who are in stable health.

To further extend the assessment of the long-term durability of the immune response to the study vaccine, participants in Groups 14 and 15 in Cohort 2 will continue into a long-term follow-up phase.

The study design includes 3 sequential cohorts: an initial safety cohort (Cohort 1 in a total of 64 participants), a regimen selection cohort (Cohort 2 in a total of 288 participants), and an expanded safety cohort (Cohort 3 in a total of 315 participants).

[a] The second RSV season of the study is defined relative to the enrollment date of the first participant in Cohort 1.

The overall total number of participants will be approximately 667.

This study will be the FIH study for RSV preF protein, and for the Ad26.RSV.preF/RSV preF protein combination (administered as separate injections in opposite arms) and Ad26.RSV.preF/ RSV preF protein mixture (administered as a single injection).

The study duration will be approximately 730 days (2 years) per participant in Cohorts 1 and 2 (Groups 11-13 and Groups 16-18), and approximately 1095 days (3 years) per participant in Cohort 2 (Groups 14-15) and Cohort 3. The study comprises a maximum 28-day screening period for Cohorts 1 and 2 (screening for Cohort 3 will be done pre-vaccination on Day 1), study vaccination (active or placebo) with a one-dose (on Day 1) or two-dose (on Day 1 and Day 57) regimen and a booster dose (active or placebo) at Month 12 (Cohort 1) or at Month 12 and Month 24 (Cohort 3), a minimum 28-day follow-up period after each vaccination, and a follow-up period until 2 years after the first Ad26.RSV.preF or RSV preF protein vaccination (Cohorts 1 and 2 [Groups 11-13 and Groups 16-18]) or until 3 years after the first Ad26.RSV.preF or RSV preF protein vaccination (Cohort 2 [Groups 14-15] and Cohort 3). The end of the study is defined as the last participant's last visit 24 months after the first vaccination (Cohorts 1 and 2 [Groups 11-13 and Groups 16-18]) or the last participant's last visit approximately 1095 days (3 years) after the first vaccination (Cohort 2 [Groups 14-15] and Cohort 3).

If any of the pre-specified study vaccination pausing rules is met, further study vaccination will be paused and a DRC meeting will be convened. For details on the pausing rules, see Section 11.9.

Initial Safety Cohort (Cohort 1)

In the initial safety cohort, participants will be randomized progressively in 1 of 4 randomizations (R1a through R1d) with safety checks in place before extending enrollment and progressing from one randomization step to the next as follows (see also Table 8):

- Cohort R1a. Initially 2 participants will be enrolled, 1 into Group 1 and 1 into Group 2, and will receive a single dose of placebo or 50 μg of RSV preF protein, respectively. Enrollment will be paused to allow for 24-hour safety assessments in these 2 sentinel participants by the principal investigator(s) (PI[s]), the sponsor's study responsible physician/scientist (SRP/S), and the sponsor's medical leader (ML). In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 10 participants will be randomized and dosed. Seven days after the last participant has received his/her first dose, available safety data will be reviewed by the PI(s), SRP/S, ML, and the sponsor's therapeutic area safety head (TASH) before proceeding to Cohort R1b.
- Cohort R1b. Initially 3 participants will be enrolled, 1 into each of Groups 3 through 5, and will receive a single dose of placebo, 5×10^{10} vp Ad26.RSV.preF/50 μg RSV preF protein, or 150 μg RSV preF protein, respectively. Enrollment will be paused to allow for 24-hour safety assessments in the 3 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 17 participants will be randomized and dosed. Seven days after the last participant has received his/her first dose,

available safety data will be reviewed by the PI(s), SRP/S, ML, and TASH before proceeding to Cohort R1c.

- Cohort R1c. Initially 2 participants will be enrolled, 1 into Group 6 and 1 into Group 7, and will receive a single dose of placebo or 5×10^{10} vp Ad26.RSV.preF/150 μg RSV preF protein, respectively. Enrollment will be paused to allow for 24-hour safety assessments in these 2 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 10 participants will be randomized and dosed. Seven days after the last participant has received his/her first dose, available safety data will be reviewed by the PI(s), SRP/S, ML, and TASH before proceeding to Cohort R1d.
- Cohort R1d. Initially 3 participants will be enrolled, 1 into each of Groups 8 through 10, and will receive 2 doses of placebo (1 in each arm), or 1×10^{11} vp Ad26.RSV.preF/150 μg RSV preF protein, with placebo in the opposite arm, or 1×10^{11} vp Ad26.RSV.preF in one arm and 150 μg RSV preF protein in the opposite arm. Enrollment will be paused to allow 24-hour safety assessments in the 3 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 17 participants will be randomized and dosed.
- Seven days after the final participant in Cohort 1 has received his/her first dose, all available safety data at that time for the whole cohort will be reviewed by the DRC before proceeding to Cohort 2.

Sentinel participants will be contacted by telephone 24 hours post-vaccination to collect safety information.

Progression to the regimen selection cohort will be based on acceptable safety in the initial safety cohort, as determined by DRC review of Day 8 safety data in all participants.

Table 8: Study Design: Initial Safety Cohort (Cohort 1)

Group	R	N	Day 1	Day 57	Month 12
1	R1a	4	Placebo	Placebo	Placebo
2	R1a	8	RSV preF protein 50 µg	RSV preF protein 50 µg	RSV preF protein 50 µg
3	R1b	4	Placebo	Placebo	Placebo
4	R1b	8	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/50 µg	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/50 µg	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/50 µg
5	R1b	8	RSV preF protein 150 µg	RSV preF protein 150 µg	RSV preF protein 150 µg
6	R1c	4	Placebo	Placebo	Placebo
7	R1c	8	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/150 µg	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/150 µg	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/150 µg
8	R1d	4	Placebo + Placebo*	Placebo	Placebo + Placebo*
9	R1d	8	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg + Placebo*	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg + Placebo*
10	R1d	8	*Separate injections*: Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg*	Placebo	*Separate injections*: Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg*
R1 TOTAL:		**64**			

N: number of participants; R: randomization; vp: viral particles
* Each injection to be given in opposite arms

Regimen Selection Cohort (Cohort 2)

In the regimen selection cohort, approximately 288 participants will be randomized in parallel to 1 of 8 groups (Groups 11 through 18; Table 9). No pauses in enrollment for safety assessments are planned.

Based on safety and immunogenicity results available at the time of primary analysis, a sponsor committee will decide which regimen will be used for the expanded safety cohort (Cohort 3). In case none of the groups that are part of the primary objective meet internal criteria, regimen selection may be delayed until additional analyses will be available.

The sponsor committee will consist of the Clinical Development Committee (CDC), Head of Clinical Development, Senior Advisors on Clinical Development, Head of Regulatory Affairs, Senior Statistician, Head of Biomarkers, Representative of Chemistry, Manufacturing Control, Head of Early Development and Translational Medicine, Head of Late Development, and other Senior Functions from the CDC. Additional factors such as data from other assays, manufacturability, and ease of administration will be taken into account to select the regimen for the expanded safety phase. More details will be described in the Statistical Analysis Plan.

Table 9: Study Design: Regimen Selection Cohort (Cohort 2)

Group	R	N	Day 1	Day 57
11	R2	24	Ad26.RSV.preF 1×10^{11} vp + Placebo*	Placebo
12	R2	42	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/50 µg + Placebo*	Placebo
13	R2	42	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/50 µg + Placebo*	Placebo
14	R2	42	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg + Placebo*	Placebo
15	R2	42	Ad26.RSV.preF/ RSV preF protein mixture: 5×10^{10} vp/150 µg + Placebo*	Placebo
16	R2	36	*Separate injections**: Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg	Placebo
17	R2	36	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg + Placebo*	Ad26.RSV.preF/ RSV preF protein mixture: 1×10^{11} vp/150 µg
18	R2	24	Placebo + Placebo*	Placebo
R2 TOTAL:		**288**		

N: number of participants (*Note*: Data from Groups 9 and 10 of Cohort 1 will be pooled with those from Groups 16 and 17 of Cohort 2 up to Month 12); R: randomization; vp: viral particles
* Each injection to be given in opposite arms

Expanded Safety Cohort (Cohort 3)

In the expanded safety cohort, approximately 315 participants will be randomized in parallel to 1 of 3 groups (Groups 19 through 21; Table 10 and Table 11). No pauses in enrollment for safety assessments are planned.

Participants will receive the selected one- or two-dose regimen from Cohort 2 or placebo.

If the one-dose regimen is selected (Groups 11 through 16 from Cohort 2), Groups 19 and 20 would receive the selected regimen on Day 1, and a booster at Month 12 (the selected regimen or placebo, respectively) and Month 24 (the selected regimen). Group 21 will receive placebo at all timepoints (Table 10).

If the two-dose regimen is selected (Group 17 of Cohort 2), Groups 19 and 20 would receive the selected regimen on Day 1 and Day 57, and a booster (the selected regimen or placebo, respectively) at Month 12. Group 21 will receive placebo at all three timepoints (Table 11).

Table 10: Study Design: Expanded Safety Cohort (Cohort 3) with One-dose Regimen and Month 12 and Month 24 Booster

Group	R	N	Day 1	Month 12	Month 24
19	R3	135	Selected Regimen	Selected Regimen	Selected Regimen
20	R3	135	Selected Regimen	Placebo for the Selected Regimen	Selected Regimen
21	R3	45	Placebo for the Selected Regimen	Placebo for the Selected Regimen	Placebo for the Selected Regimen
R3 TOTAL:		**315**			
OVERALL TOTAL:		***667***			

N: number of participants; R: randomization

Table 11: Study Design: Expanded Safety Cohort (Cohort 3) with Two-dose Regimen and Month 12 Booster

Group	R	N	Day 1	Day 57	Month 12
19	R3	135	Selected Regimen	Selected Regimen	Selected Regimen
20	R3	135	Selected Regimen	Selected Regimen	Placebo for the Selected Regimen
21	R3	45	Placebo for the Selected Regimen	Placebo for the Selected Regimen	Placebo for the Selected Regimen
R3 TOTAL:		**315**			
OVERALL TOTAL:		***667***			

N: number of participants; R: randomization

3.1.2. Study Procedures

After each vaccination, participants will be closely observed for a minimum of 30 minutes post-vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or solicited systemic AEs will be documented by study personnel following this observation period. Participants will be given a thermometer, ruler and daily assessment (participant) diary with instructions for the proper recording of events. Each participant will record solicited local (at injection site) and solicited systemic AEs and body temperatures, beginning on the evening of each vaccine dosing day and on a daily basis for the following 7 days. Body temperatures (oral route preferred) should be taken at approximately the same time each day.[a] Study-site personnel will collect and review participant diary information and confirm the entries at subsequent site visits.

[a] Temperature 7 days after each vaccination may be collected earlier in the day to coincide with the clinic visit.

Unsolicited AEs will be collected from the time of each vaccine administration through the following 28 days.[a] SAEs will be collected from first dose administration until the end of the double-blind phase of the study. During the long-term follow-up phase (Groups 14 and 15 from Cohort 2), only SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, and all AEs leading to discontinuation will be collected. All AEs, including any that are ongoing at 28 days after each dose, will be followed until clinical resolution or stabilization. Concomitant therapies will be collected and recorded in the electronic case report form (eCRF) from time of each vaccine administration through 28 days after each vaccination, and additionally outside of these periods when associated with an SAE. During the long-term follow-up phase (Groups 14 and 15 from Cohort 2), only medications in conjunction with SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, or in conjunction with AEs leading to discontinuation should be recorded.

All SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up.

For participants in Cohorts 1 and 2, blood will be collected for serology and for laboratory safety assessments at the screening visit. Additionally, for participants in Cohorts 1 and 2, blood will be collected for laboratory safety assessments on Day 1 (pre-vaccination) and Day 8 (or at the exit visit if early exit is within 8 days of the first vaccination and the participant terminates without withdrawing consent).

Blood for humoral and cellular immune responses will be drawn from all participants in Cohorts 1 and 2. In Cohort 3, blood will be drawn for humoral immune responses from all participants and for cellular immune responses from a subset of 63 participants, as specified in the Schedule of Activities.

Transcriptome analysis will be performed on samples collected on Day 1 (prior to vaccination), Day 8, and Day 15 in Cohorts 1 and 2 only.

Nasal samples will be collected for immunogenicity assessments as specified in the Schedule of Activities.

Note: All references throughout the protocol to the collection of a "nasal sample" imply a "nasal turbinate sample or its alternative".

During the first 2 RSV seasons of the study (relative to the enrollment date of the first participant in Cohort 1), participants should record any signs and symptoms of RTI (eg, runny nose, fever, severe cough, rapid breathing, or difficulty breathing) on a daily basis using a study-specific RTI

[a] AEs that start more than 28 days after a vaccination, but that are still present at the time of the next vaccination will also be recorded.

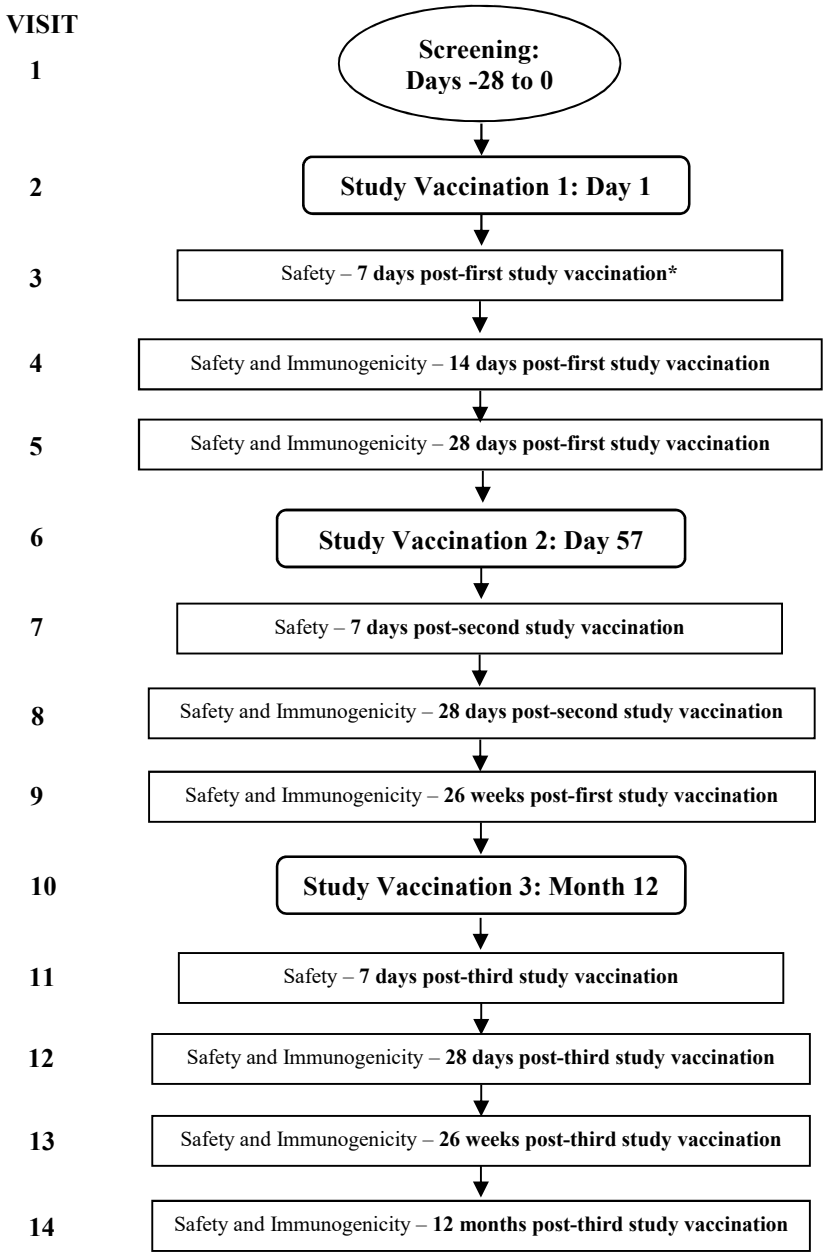
Symptoms Form, starting on the first day they experience symptoms, including the day on which the symptoms resolve. For details of RTI procedures, including nasal sampling, see Section 9.2.2.

During the first 2 RSV seasons of the study, participants will be contacted by telephone every 30±7 days (unless a planned clinic visit has occurred or will occur within 30 days). Calls will remind the participants to complete the RTI Symptoms Form in the event of any symptoms of RTI, to contact the site at the time of symptom onset, and to take a nasal sample at home preferably between 2 and 3 days after the onset of the RTI symptoms (or go to the site preferably within 2 to 3 days after the onset of the RTI to have a nasal sample taken by study staff). Calls will also check for any SAEs and associated concomitant medications since the previous visit or telephone contact.

Unscheduled visits may be performed based on investigator's clinical judgment and may include further evaluations, as needed.

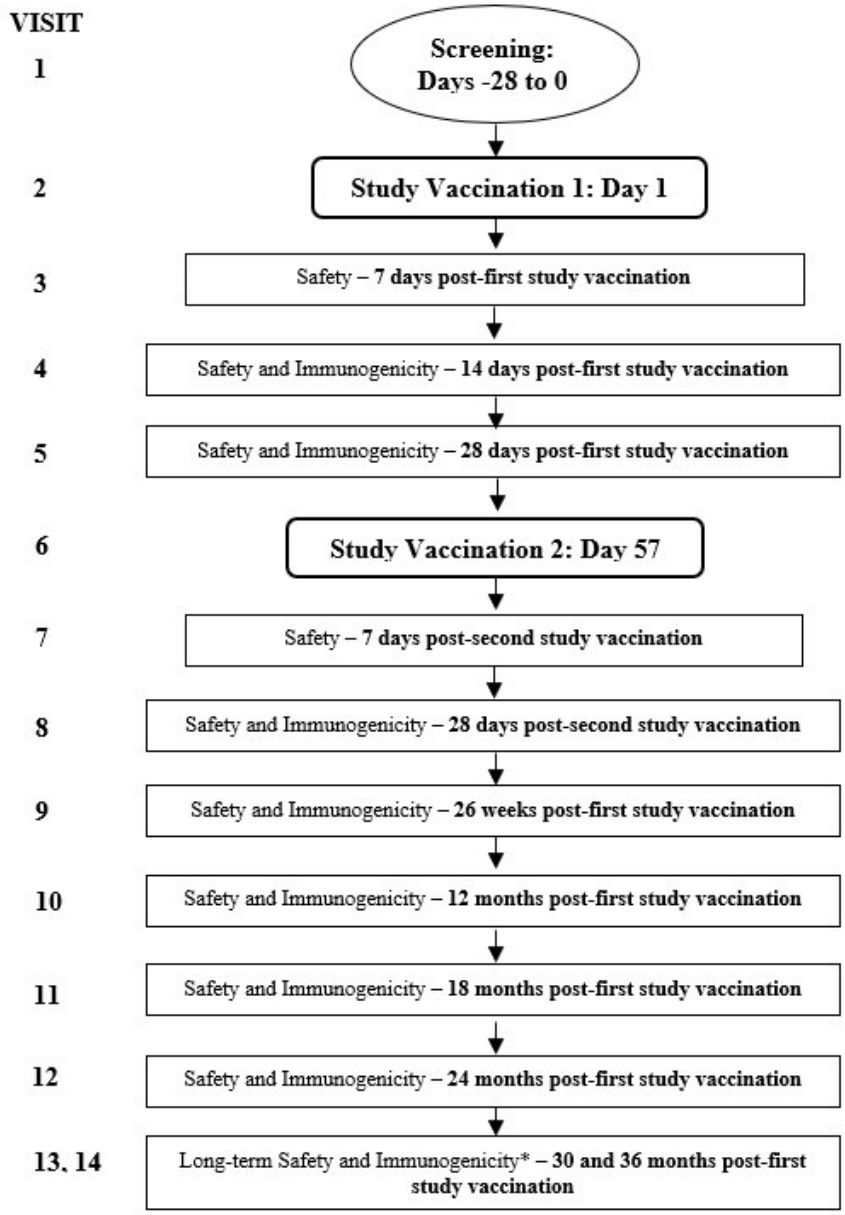
A diagram of the study design is provided in Figure 1, Figure 2, Figure 3, and Figure 4.

Figure 1: Schematic Overview of the Study for Cohort 1



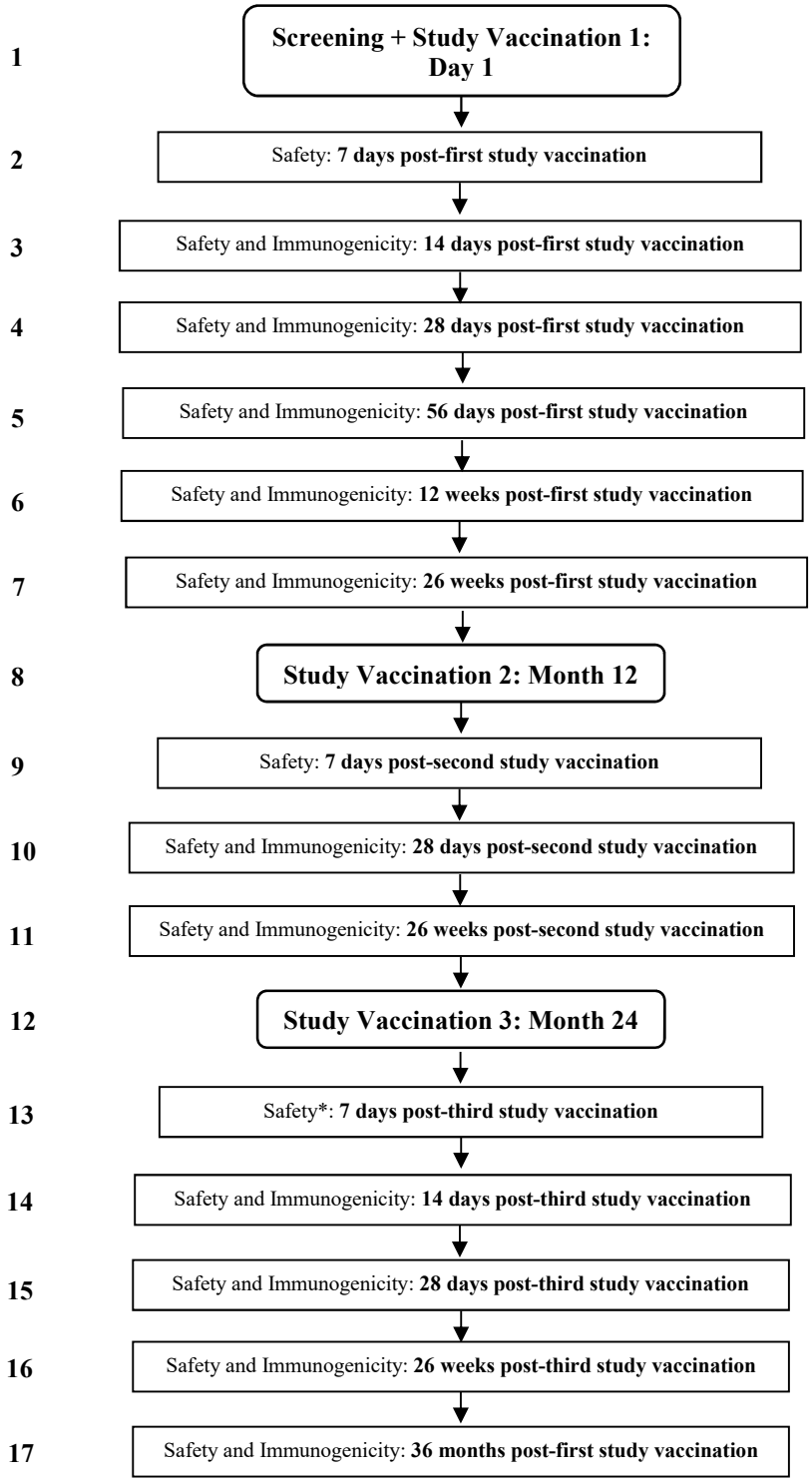
* In addition, sentinel participants in Cohort 1 will be contacted by telephone 24 hours post-dose to collect safety information.

Figure 2: Schematic Overview of the Study for Cohort 2



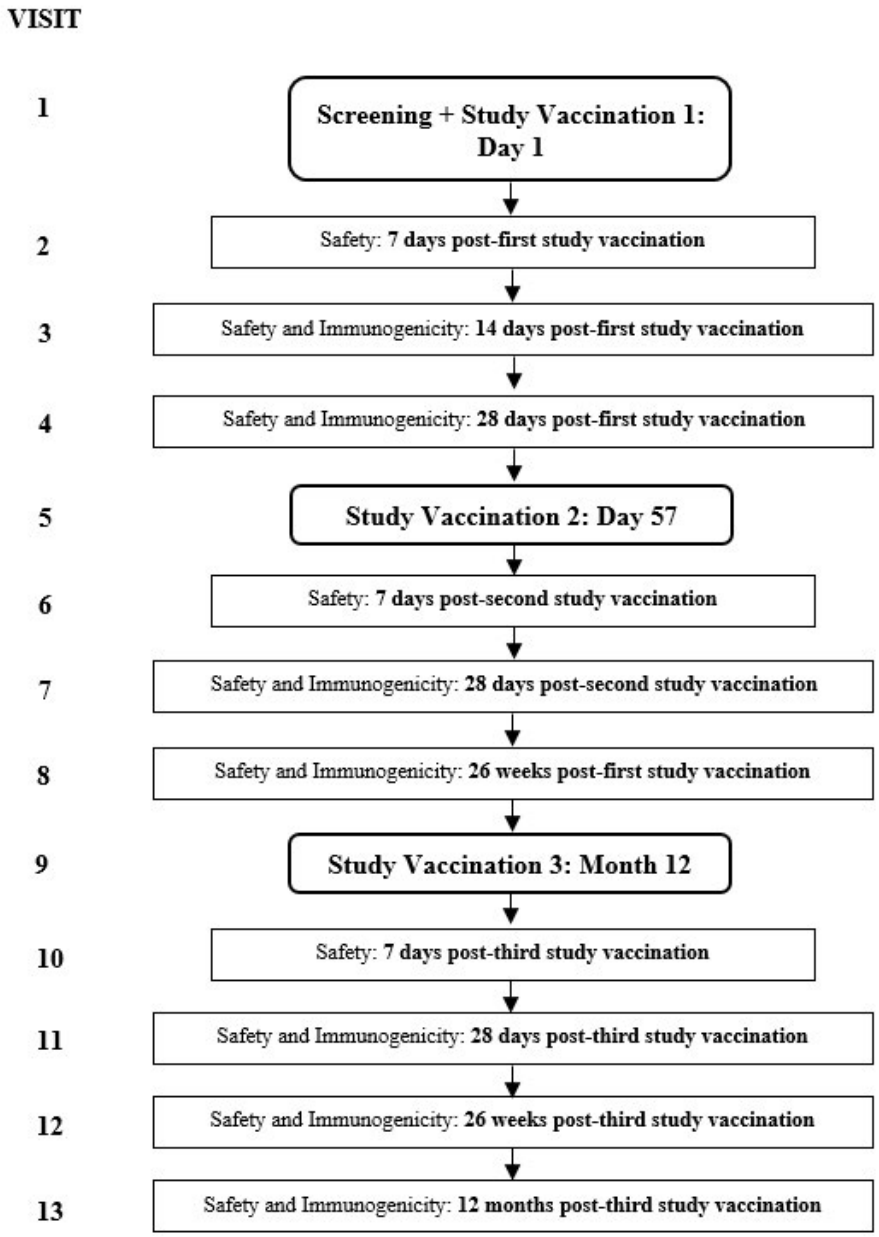
* Participants in Groups 14 and 15 will continue into the long-term follow-up phase.

Figure 3: Schematic Overview of the Study for Cohort 3 One-dose Regimen and Month 12 and Month 24 Booster



* Visit 13 (7 days post-third vaccination) is not required for any Cohort 3 participant who misses the third vaccination.

Figure 4: Schematic Overview of the Study for Cohort 3 Two-dose Regimen and Month 12 Booster



3.2. Study Design Rationale

Vector Selection

The rationale behind the selection of the Ad26 vector is described in Section 1.1.

Dose Selection

The 5×10^{10} vp dose is the most commonly used dose in previous RSV vaccine studies and other programs, and has good safety and immunogenicity profiles. Moreover, in study VAC18193RSV1003, the 1×10^{11} vp dose of Ad26.RSV.preF was well-tolerated in adults aged ≥60 years and was found to induce higher humoral immune responses than the 5×10^{10} vp dose

whilst maintaining good cellular responses. As the current study is FIH for the Ad26.RSV.preF/ RSV preF protein combination (separate injections in opposite arms) and Ad26.RSV.preF/RSV preF protein mixture (single injection), both the 5×10^{10} vp and 1×10^{11} vp Ad26.RSV.preF doses will be assessed.

The dose levels of 50 µg and 150 µg of RSV preF protein to be used were chosen based on the supposition that half log intervals in dose response are biologically meaningful for vaccines. Dose levels of 15 µg, 50 µg, 150 µg, and 500 µg would correspond to such a series. It was decided that the 15 µg dose would be too low, while the 500 µg dose did not appear to be feasible at this time. Therefore, the 50 µg and 150 µg were chosen for initial exploration. These doses are comparable to doses utilized by other investigators studying RSV protein vaccines in humans.[3,7,30]

Regimen Selection

In the initial safety cohort (Cohort 1), RSV preF protein dosing is increased from 50 µg to 150 µg for initial safety assessment. Safety of protein at each dose is assessed before dosing of the Ad26.RSV.preF/RSV preF protein combination or mixture. The dose of the mixture will also be increased from a protein/adeno dose of 50 µg/5×10^{10} vp to a protein/adeno dose of 150 µg/1×10^{11} vp for initial safety assessment.

In Group 10 of Cohort 1 (Ad26.RSV.preF/RSV preF protein 1×10^{11} vp/150 µg combination given as separate injections in opposite arms on Day 1 and at Month 12), no active boost vaccination will be administered on Day 57 as the combination will not be investigated further for immunogenicity in the regimen selection (Cohort 2).

In the regimen selection cohort (Cohort 2), regimens under consideration include dose ranging with all dose combinations of the mixture, including high dose Ad26.RSV.preF with high dose RSV preF protein; a 2-month prime-boost regimen with a mixture of high dose Ad26.RSV.preF with high dose RSV preF protein; and separate administration (in opposite arms) of high dose Ad26.RSV.preF and high dose RSV preF protein.

In Cohort 2, only Group 17 (Ad26.RSV.preF/RSV preF protein mixture 1×10^{11} vp/150 µg given as a single injection on Day 1 and Day 57) will include an active boost vaccination on Day 57, because it is anticipated that if a Day 57 boost is required it would be the highest dose combination of Ad26.RSV.preF and RSV preF protein.

All Cohort 1 and 3 regimens include a Month 12 booster dose to assess the need for a yearly revaccination. Additionally, the Cohort 3 one-dose regimen includes a Month 24 booster dose to assess the long-term durability of the immune response to the selected dose.

Screening Period

The study includes a maximum 28-day screening period for Cohorts 1 and 2, including but not limited to safety laboratory testing and a 12-lead ECG. As the screening period of participants for Cohorts 1 and 2 will generate sufficient safety data before the start of Cohort 3, screening of

participants for Cohort 3 will be performed on Day 1 without safety laboratory testing and a 12-lead ECG.

Blinding, Control, Study Phase/Periods, Vaccine Groups

Placebo controls will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of active vaccine. Randomization will be used to minimize bias in the assignment of participants to vaccine groups, to increase the likelihood that known and unknown participant attributes (eg, demographics, baseline characteristics) are evenly balanced across vaccine groups, and to enhance the validity of statistical comparisons across vaccine groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

4. PARTICIPANT POPULATION

Screening for eligible participants in Cohorts 1 and 2 will be performed within 28 days before administration of the first dose of study vaccine. Screening for eligible participants in Cohort 3 will be performed on Day 1.

The inclusion and exclusion criteria for enrolling participants in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

Note: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study vaccine is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Each participant must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study, is willing to participate in the study and attend all scheduled visits, and is willing and able to comply with all study procedures and adhere to the prohibitions and restrictions specified in this protocol.
2. Participant must be a man or woman, ≥60 years old on the day of signing the ICF and available for the duration of the study.
3. Criterion amended per Amendment 2

   3.1. Before randomization, a woman must be:

   - postmenopausal (postmenopausal state is defined as no menses for 12 months without an alternative medical cause); and

- not intending to conceive by any methods.

Note: Hysterectomized women are also eligible for the study.

4. Criterion amended per Amendment 5

   4.1 In the investigator's clinical judgment, participant must be either in good or stable health. Participants may have underlying illnesses such as hypertension, type 2 diabetes mellitus, hyperlipoproteinemia, or hypothyroidism, as long as their symptoms and signs are medically controlled. If they are on medication for a condition, the medication dose must have been stable for at least 12 weeks preceding vaccination and expected to remain stable for the duration of the study. Participants will be included on the basis of physical examination, medical history, vital signs[a], and 12-lead electrocardiogram (ECG)[b] performed at screening.

   Note: To determine eligibility for revaccination, signs and symptoms of potential underlying illnesses should be medically stable in the weeks preceding revaccination. Participants with changes in medication 12 weeks preceding revaccination may be revaccinated if the change is considered minor and judged by the investigator not to impact signs or symptoms of the underlying illness.

5. For participants in Cohorts 1 and 2 only: Participant must be healthy on the basis of clinical laboratory tests performed at screening. If the results of the laboratory screening tests are outside the central laboratory normal reference ranges and additionally within the limits of toxicity Grade 2 according to the US Food and Drug Administration (FDA) toxicity tables (ie, for tests in the FDA table[c]), the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant and appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.

   Note: If laboratory screening tests are out of central laboratory normal ranges and deemed clinically significant, repeat of screening tests is permitted once, using an unscheduled visit during the screening period to assess eligibility. Screening laboratory tests are to be done within 28 days of randomization.

6. From the time of each vaccination through 3 months after each vaccination, participant agrees not to donate blood.

7. Participant must be willing to provide verifiable identification, have means to be contacted and to contact the investigator during the study.

[a] Participants can be enrolled with Grade 1 or Grade 2 values for vital signs measurements.

[b] For participants in Cohorts 1 and 2 only.

[c] For the FDA toxicity grading tables, see Attachment 1: FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).

4.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Participant has acute illness (this does not include minor illnesses such as diarrhea) or body temperature ≥38.0 ºC within 24 hours prior to the first dose of study vaccine. In such a situation, the participant may be vaccinated up to, and no later than 10 days after the scheduled vaccination.

   Note: For participants in Cohorts 1 and 2, safety laboratory tests should be repeated if vaccination is postponed and the time between the safety laboratory tests and vaccination exceeds 28 days.

2. Participant has a serious chronic disorder, including severe chronic obstructive pulmonary disease or clinically significant congestive heart failure, requirement for supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, Alzheimer's disease, or has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise well-being) or that could prevent, limit, or confound the protocol-specified assessments.
3. Participant has history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).
4. Participant has had major surgery (per the investigator's judgment), within 4 weeks before dosing, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study or within 6 months after the last dose of study vaccine.

   Note: Participants with planned surgical procedures to be conducted under local or locoregional anesthesia and not judged as major by the investigator may participate.

5. Per serology testing in Cohorts 1 and 2 and per medical history in Cohort 3: Participant has chronic active hepatitis B or hepatitis C infection, documented by hepatitis B surface antigen and hepatitis C antibody, respectively.
6. Per serology testing in Cohorts 1 and 2 and per medical history in Cohort 3: Participant has HIV type 1 or type 2 infection.
7. Participant has had major psychiatric illness and/or drug or alcohol abuse which in the investigator's opinion would compromise the participant's safety and/or compliance with the study procedures.
8. Participant has a known allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine components (including any of the constituents of the study vaccine).
9. Participant has a history of chronic urticaria (recurrent hives), eczema and/or atopic dermatitis.
10. Participant has a history of acute polyneuropathy (eg, Guillain-Barré syndrome).

11. Criterion amended per Amendment 2:

    11.1 Participant has abnormal function of the immune system resulting from:

    - Clinical conditions (eg, autoimmune disease or immunodeficiency)
    - Chronic (longer than 10 days) or recurrent use of systemic corticosteroids during the study and within 6 months before first administration of study vaccine (*Note:* Ocular, topical or inhaled steroids are allowed; intra-articular steroid injections are not allowed.)
    - Administration of antineoplastic and immunomodulating agents or radiotherapy during the study and within 6 months before the first administration of study vaccine.

12. Participant has received treatment with immunoglobulins in the 2 months, immunoglobulins specific to RSV, human metapneumovirus or parainfluenza viruses in the last 12 months, or blood products in the 4 months before the planned administration of the first dose of study vaccine or has any plans to receive such treatment during the study.

13. Criterion amended per Amendment 2:

    13.1 Participant is in receipt of, or planning to receive, licensed live attenuated vaccine within 28 days of each study vaccination (ie, before and after); other licensed vaccines (ie, not live: eg, influenza, tetanus, hepatitis A or B, rabies) should be given at least 14 days before or 14 days after each study vaccination.

14. Criterion amended per Amendment 5:

    14.1 Participant has received an investigational drug or used an invasive investigational medical device within 30 days or received an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine or is currently enrolled or plans to participate in another investigational study during the course of the double-blind phase of this study.

    Note: Participation in an observational clinical study (ie, with no intervention) is allowed upon approval of the sponsor.

    Note: During the long-term follow-up period (Groups 14 and 15 from Cohort 2 only), participation in another investigational study is allowed only upon approval of the sponsor.

15. Participant has a contraindication to intramuscular injections and blood draws, eg, bleeding disorders.

16. Criterion deleted per Amendment 2.

17. Participant has received RSV vaccine in a previous RSV vaccine study at any time prior to randomization.

18. Participant who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or is unlikely to complete the full course of vaccination and observation.

19. Participant cannot communicate reliably with the investigator.

20. Participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.
21. Criterion deleted per Amendment 2.

4.3. Prohibitions and Restrictions

Potential participants must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. See Section 8 regarding prohibited and restricted therapies and vaccines during the study.
2. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (Section 4.1 and Section 4.2, respectively).

5. TREATMENT ALLOCATION AND BLINDING

Study Vaccine Allocation

Central randomization will be implemented in this study. Participants will be randomly assigned to a vaccination group based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks.

In the initial safety cohort (Cohort 1), the randomization ratio in Cohorts R1a and R1c is 1:2, in Cohorts R1b and R1d the ratio is 1:2:2. In each of those cohorts, 1 sentinel participant from each group (each active group and the placebo group to maintain the blind) will initially be enrolled to monitor for any unexpected severe adverse reaction. Therefore, the randomization will be phased to accommodate this and to end up with the overall randomization ratios specified above. No stratification will be applied.

In the regimen selection cohort (Cohort 2), the randomization ratio is 4:7:7:7:7:6:6:4. No stratification will be applied.

In the expanded safety cohort (Cohort 3), stratification will be applied: participants will be assigned to 1 of 2 strata prior to randomization, depending on the blood mononuclear cell (PBMC) sampling capability and capacity of the site. One stratum will contain a maximum of 63 participants from whom blood samples to assess humoral and cellular (PBMC samples) immunogenicity will be collected. The other stratum will contain the remaining participants, from whom blood samples will be collected only for humoral immunogenicity assessments, to reach the target of a total of 315 participants in Cohort 3. Within each stratum, participants will be randomized 3:3:1 ratio to one of the respective groups.

The interactive web response system (IWRS) will assign a unique code, which will dictate the group assignment for the participant. The requestor must use his or her own user identification and

personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

If randomized participants are withdrawn from vaccination before the first dose of study vaccine is administered, additional participants may be recruited to replace these participants at the discretion of the sponsor. Any replacement participant will be assigned to the same group as the original (discontinued) participant. The replacement participant's randomization number will equal the randomization number of the discontinued participant +1000 (eg, participant 0001 would be replaced by participant 1001). These additional participants should also be randomized through IWRS.

In the initial safety cohort (Cohort 1), any randomized participant who is withdrawn from the study for reasons other than due to an AE after the first dose but before the second dose might be replaced at the discretion of the sponsor. Any replacement participant will be randomized through IWRS. The replacement participant's randomization number will equal the randomization number of the discontinued participant +2000.

In the regimen selection cohort (Cohort 2), no replacements or additional randomizations will be done for withdrawals after the first dose.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

At the sponsor level, unblinding (at the participant level) will occur at the time of the primary analysis for each cohort. After the primary analysis, group level results may be shared as needed; however, efforts will be made to preserve the blinding to the individual participant allocation until the timepoints specified below.

While the responsibility to break the study vaccine allocation code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or sponsor designee to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or the sponsor designee will be available 24 hours per day, 7 days per week. In such cases, the investigator may in an emergency determine the identity of the study vaccine by contacting the IWRS. If the blind is broken, the sponsor must be informed as soon as possible. Date, time and reason for the unblinding must be documented by the IWRS, in the appropriate section of the eCRF, and in the source document. Documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

For Cohorts 1 and 3, the participants, study-site personnel and investigator will be blinded to study vaccine allocation throughout the main study until after the database lock of the final analysis at Day 730 for Cohort 1 and at Day 1095 for Cohort 3, except for the pharmacist or qualified staff member with primary responsibility for study vaccine preparation and dispensing.

For Cohort 2, the participants, study-site personnel and investigator will be blinded to study vaccine allocation throughout the double-blind phase of the main study until after the database lock of the analysis at Day 730, except for the pharmacist or qualified staff member with primary responsibility for study vaccine preparation and dispensing. By participating in the long-term follow-up phase of the study, clinical staff, the investigator and eligible participants from Groups 14 and 15 (Cohort 2), will be partially unblinded to their treatment received (ie, will be informed that they were randomized to either Group 14 or 15) prior to full unblinding after the database lock of the final analysis at the end of the long-term follow-up phase (Day 1095). The pharmacy and the preparation of study vaccines will be monitored by an independent vaccine monitor (see also Section 17.8).

Note: The unblinded pharmacist, or other qualified individual, may also perform administration of the vaccine, but will have no other study function following dosing.

If the randomization code is broken by the investigator or the study-site personnel, the participant must discontinue further study vaccine administration and must be followed as appropriate (see Section 10.2 for details). If the randomization code is broken by the sponsor for safety reporting purposes, the participant should not discontinue further vaccine administration and may remain in the study (if the randomization code is still blinded to the study-site personnel and the participant).

6. DOSAGE AND ADMINISTRATION

Ad26.RSV.preF and RSV preF protein will be administered either as a combination (as separate injections in opposite arms) or as a mixture (a single injection) into the deltoid muscle according to the schedules shown in Table 8, Table 9, Table 10 and Table 11:

- Ad26.RSV.preF (JNJ-64400141): will be supplied at a concentration of 2×10^{11} vp/1 mL in single-use vials. Dose levels of 5×10^{10} vp and 1×10^{11} vp will be used.
- RSV preF protein (JNJ-64213175): will be supplied at a concentration of 0.3 mg/1 mL in single use vials. Dose levels of 50 µg and 150 µg will be used.
- Placebo for Ad26.RSV.preF and RSV preF protein.

All injections of Ad26.RSV.preF and RSV preF protein (or corresponding placebo) will be 1 mL in volume.

An unblinded pharmacist, or other qualified individual, will prepare the appropriate vial and/or syringe and provide the syringe in a blinded manner to the vaccine administrator who will perform the injection. The unblinded pharmacist, or other qualified individual, may also perform vaccine administration, but will have no other study function following dosing. Diluent will be used as required.

Full details of vaccine preparation, including mixing of Ad26.RSV.preF and RSV preF protein, are provided in the Investigational Product Preparation Instructions.

All vaccines should be administered in the deltoid muscle:

- When participants receive 2 injections at any given visit, these injections will be given in opposite arms at the same time with no more than 45 minutes between the injections.
- When participants receive a single injection per visit, eg, in Groups 1 through 7 in Cohort 1, alternating injection sites will be used for subsequent injections unless there is a medically justifiable reason in the judgment of the PI(s).

No local or topical anesthetic should be used prior to the injection.

For each injection, a record should be made in the eCRF of which arm was injected.

7. VACCINE COMPLIANCE

Study vaccine (active or placebo) will be administered intramuscularly by a blinded vaccine administrator (a trained and qualified study nurse, medical doctor, or otherwise qualified healthcare professional). The unblinded pharmacist, or other qualified individual, may also perform vaccine administration, but will have no other study function following dosing. The date and time of each study vaccine administration will be recorded in the eCRF.

8. PRE-STUDY AND CONCOMITANT THERAPY

Pre-study therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs (NSAIDs) used up to 30 days before the first dose of study vaccine must be recorded in the eCRF during screening.

Concomitant therapies will be collected and recorded in the eCRF from the time of each vaccine administration through 28 days after each vaccination, and additionally outside of these periods when associated with any SAE that meets the criteria outlined in Section 12.3.2. During the long-term follow-up phase (Groups 14 and 15 from Cohort 2), only concomitant therapies in conjunction with SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, or in conjunction with AEs leading to discontinuation should be recorded.

Information on concomitant use of herbal supplements or vitamins will not be collected.

Use of experimental medications (including experimental vaccines other than the study vaccine) during the study is not allowed. *Note: During the long-term follow-up period (Groups 14 and 15 from Cohort 2 only), use of experimental medications during participation in another investigational study is allowed only upon approval of the sponsor.*

Analgesic/antipyretic medications and NSAIDs may be used post-vaccination only in case of medical need (eg, fever or pain) and their use must be documented. Use of these medications as routine prophylaxis prior to study vaccine administration is discouraged.

Chronic (longer than 10 days) or recurrent use of systemic corticosteroids is prohibited during the study and within 6 months before first administration of study vaccine (ocular, topical or inhaled steroids are allowed; intra-articular steroid injections are not allowed). Antineoplastic and

immunomodulating agents or radiotherapy are prohibited in the 6 months before the first administration of study vaccine and during the study.

If chronic use of prohibited therapies becomes medically indicated during the study for any participant, the sponsor should be contacted.

Vaccination with live attenuated vaccines within 28 days of a vaccination in this study (ie, before and after) is prohibited. Other licensed vaccines (ie, not live: eg, influenza, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before or 14 days after each study vaccination to avoid potential confusion of adverse reactions and potential immune interference. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the vaccines in this study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY PROCEDURES AND EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

Evaluation of the safety and reactogenicity will include laboratory assessments (Cohorts 1 and 2 only), measurements of vital signs, physical examination by study-site personnel, and participant reports on signs and symptoms post-vaccination. Additional study visits may be required if, in the investigator's opinion, further clinical or laboratory evaluation is needed.

All participants will be provided with a thermometer, a ruler and a participant diary to measure and record body temperature, solicited local AEs (at the injection site), and solicited systemic AEs.

The diary includes instructions on how to capture data and grading scales to assess the severity of the symptoms. Study staff are responsible for providing appropriate training to the participant to avoid any missing or incorrect data. The diary card will be reviewed by the study-site personnel at visits indicated in the Schedule of Activities. If the diary card review is missed, the diary card will be reviewed at the next visit. If a participant misses a vaccination, the diary card covering the period after the missed vaccination does not have to be completed.

During the first 2 RSV seasons of the study (relative to the enrollment date of the first participant in Cohort 1), participants will be contacted by telephone every 30±7 days (unless a planned visit has occurred or will occur within 30 days). These calls will remind participants to complete the RTI Symptoms Form in the event of any symptoms of RTI, to contact the site at the time of symptom onset, and to take a nasal sample at home preferably between 2 and 3 days after the onset of the RTI symptoms (or go to the site preferably within 2 to 3 days after the onset of the RTI to have a nasal sample taken by study staff). These calls will also check for any SAEs and associated concomitant medications since the previous visit or telephone contact.

The Schedule of Activities summarizes the frequency and timing of safety and immunogenicity assessments applicable to this study. The total blood volume to be collected over the entire study from each participant will be:

- In Cohort 1: approximately 627.5 mL. The maximum volume of blood to be drawn at any given visit will be 67.5 mL.
- In Cohort 2 (Groups 11-13 and Groups 16-18): approximately 567.5 mL. The maximum volume of blood to be drawn at any given visit will be 67.5 mL.
- In Cohort 2 participants in Groups 14 and 15 who continue into the long-term follow-up phase: approximately 687.5 mL. The maximum volume of blood to be drawn at any given visit will be 67.5 mL.
- In the randomly selected subset of 63 participants in Cohort 3 with blood draws for humoral as well as cellular responses: approximately 840 mL. The maximum volume of blood to be drawn at any given visit will be 60 mL.
- In the remaining 252 participants in Cohort 3, blood samples will be taken for humoral responses only, with a total blood draw of approximately 140 mL. The maximum volume of blood to be drawn at any given visit will be 10 mL.

9.1.2. Visit Windows

Visit windows will be allowed as indicated in Table 12, Table 13, Table 14, and Table 15.

The timings of the post-vaccination visits will be determined relative to the actual day of the corresponding vaccination. If a participant misses a vaccination, the post-vaccination visits will be calculated from the imputative vaccination date according to protocol.

Table 12: Visit Windows: Initial Safety Cohort (Cohort 1)

VISIT	Visit Day	Window	Primary Purpose
Visit 2	Day 1	--	FIRST STUDY VACCINATION
Visit 3	Day 8	±2 days	7-day post-first study vaccination safety only visit
Visit 4	Day 15	±2 days	14-day post-first study vaccination safety and immunogenicity visit
Visit 5	Day 29	±3 days	28-day post-first study vaccination safety and immunogenicity visit
Visit 6	Day 57	±3 days	SECOND STUDY VACCINATION
Visit 7	Day 64 (Vac 2 +7 days)	±2 days	7-day post-second study vaccination safety only visit
Visit 8	Day 85 (Vac 2 +28 days)	–3 days/+10 days	28-day post-second study vaccination safety and immunogenicity visit
Visit 9	Day 183 (Vac 1 +26 weeks)	±14 days	26-week post-first study vaccination safety and immunogenicity visit
Visit 10	Day 365	±2 months	THIRD STUDY VACCINATION (MONTH 12 BOOSTER)
Visit 11	Day 372 (Vac 3 +7 days)	±2 days	7-day post-third study vaccination safety only visit
Visit 12	Day 393 (Vac 3 +28 days)	±3 days	28-day post-third study vaccination safety and immunogenicity visit
Visit 13	Day 547 (Vac 3 +26 weeks)	±14 days	26-week post-third study vaccination safety and immunogenicity visit
Visit 14	Day 730 (Vac 3 +12 months)	±1 month	FINAL VISIT: 12-month post-third study vaccination safety and immunogenicity visit

Table 13: Visit Windows: Regimen Selection Cohort (Cohort 2)

VISIT	Visit Day	Window	Primary Purpose
Visit 2	Day 1	--	FIRST STUDY VACCINATION
Visit 3	Day 8	±2 days	7-day post-first study vaccination safety only visit
Visit 4	Day 15	±2 days	14-day post-first study vaccination safety and immunogenicity visit
Visit 5	Day 29	±3 days	28-day post-first study vaccination safety and immunogenicity visit
Visit 6	Day 57	±3 days	SECOND STUDY VACCINATION
Visit 7	Day 64 (Vac 2 +7 days)	±2 days	7-day post-second study vaccination safety only visit
Visit 8	Day 85 (Vac 2 +28 days)	–3 days/+10 days	28-day post-second study vaccination safety and immunogenicity visit
Visit 9	Day 183 (Vac 1 +26 weeks)	±14 days	26-week post-first study vaccination safety and immunogenicity visit
Visit 10	Day 365 (Vac 1 +12 months)	±1 month	12-month post-first study vaccination safety and immunogenicity visit
Visit 11	Day 547 (Vac 1 +18 months)	±1 month	18-month post-first study vaccination safety and immunogenicity visit
Visit 12	Day 730 (Vac 1 +24 months)	±1 month	FINAL VISIT for Groups 11-13 and Groups 16-18: 24-month post-first study vaccination safety and immunogenicity visit
Visit 13*	Day 912 (Vac 1 + 911 days)	±30 days	30-month post-first study vaccination immunogenicity visit
Visit 14*	Day 1095 (Vac 1 +1094 days)	±30 days	FINAL VISIT: 36-month post-first study vaccination immunogenicity visit

*Visits during long-term follow-up phase for participants in Groups 14 and 15 only.

Table 14: Visit Windows: Expanded Safety Cohort (Cohort 3) - One-dose Regimen and Month 12 and Month 24 Booster

VISIT	Visit Day	Window	Primary Purpose
Visit 1	Day 1	–	FIRST STUDY VACCINATION
Visit 2	Day 8	±2 days	7-day post-first study vaccination safety only visit
Visit 3	Day 15	±2 days	14-day post-first study vaccination safety and immunogenicity visit
Visit 4	Day 29	±3 days	28-day post-first study vaccination safety and immunogenicity visit
Visit 5	Day 57	±3 days	56-day post-first study vaccination safety and immunogenicity visit
Visit 6	Day 85 (Vac 1 +12 weeks)	-3/+10 days	12-week post-first study vaccination safety and immunogenicity visit
Visit 7	Day 183 (Vac 1 +26 weeks)	±14 days	26-week post-first study vaccination safety and immunogenicity visit
Visit 8	Day 365	–2 months	SECOND STUDY VACCINATION (MONTH 12 BOOSTER)
Visit 9	Day 372 (Vac 2 +7 days)	±2 days	7-day post-second study vaccination safety only visit
Visit 10	Day 393 (Vac 2 +28 days)	±3 days	28-day post-second study vaccination safety and immunogenicity visit
Visit 11	Day 547 (Vac 2 +26 weeks)	±14 days	26-week post-second study vaccination safety and immunogenicity visit
Visit 12	Day 730 (Vac 1 +729 days)	±30 days	THIRD STUDY VACCINATION (MONTH 24 BOOSTER)
Visit 13	Day 737 (Vac 3 +7 days)	±2 days	7-day post-third study vaccination safety only visit
Visit 14	Day 744 (Vac 3 +14 days)	±2 days	14-day post-third study vaccination safety and immunogenicity visit
Visit 15	Day 758 (Vac 3 +28 days)	±3 days	28-day post-third study vaccination safety and immunogenicity visit
Visit 16	Day 912 (Vac 3 +182 days)	±14 days	26-week post-third study vaccination safety and immunogenicity visit
Visit 17	Day 1095 (Vac 1 +1094 days)	±30 days	FINAL VISIT: 12-month post-third study vaccination safety and immunogenicity visit

Table 15: Visit Windows: Expanded Safety Cohort (Cohort 3) - Two-dose Regimen and Month 12 Booster

VISIT	Visit Day	Window	Primary Purpose
Visit 1	Day 1	–	FIRST STUDY VACCINATION
Visit 2	Day 8	±2 days	7-day post-first study vaccination safety only visit
Visit 3	Day 15	±2 days	14-day post-first study vaccination safety and immunogenicity visit
Visit 4	Day 29	±3 days	28-day post-first study vaccination safety and immunogenicity visit
Visit 5	Day 57	±3 days	SECOND STUDY VACCINATION
Visit 6	Day 64 (Vac 2 +7 days)	±2 days	7-day post-second study vaccination safety only visit
Visit 7	Day 85 (Vac 2 +28 days)	-3/+10 days	28-day post-second study vaccination safety and immunogenicity visit
Visit 8	Day 183 (Vac 1 +26 weeks)	±14 days	26-week post-first study vaccination safety and immunogenicity visit
Visit 9	Day 365	–2 months	THIRD STUDY VACCINATION (MONTH 12 BOOSTER)
Visit 10	Day 372 (Vac 3 +7 days)	±2 days	7-day post-third study vaccination safety only visit
Visit 11	Day 393 (Vac 3 +28 days)	±3 days	28-day post-third study vaccination safety and immunogenicity visit
Visit 12	Day 547 (Vac 3 +26 weeks)	±14 days	26-week post-third study vaccination safety and immunogenicity visit
Visit 13	Day 730 (Vac 3 +12 months)	±1 month	FINAL VISIT: 12-month post-third study vaccination safety and immunogenicity visit

9.1.3. Screening Phase (Days -28 to 0 for Cohorts 1 and 2; Before Randomization on Day 1 for Cohort 3)

Only participants in good or stable health without acute illness or fever and complying with the inclusion and exclusion criteria as specified in Sections 4.1 and 4.2 will be included in the study. The investigator will provide detailed information on the study to the participants and will obtain written informed consent prior to each participant's participation in the study. All the procedures described in the Schedule of Activities will only take place after the written informed consent has been obtained.

The following evaluations will be performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Demographic information
- Medical history
- Review of pre-study medications

- Review of inclusion/exclusion criteria
- Full physical examination including vital signs measurement (respiratory rate, heart rate, supine systolic and diastolic blood pressure, and body temperature) and height and weight

The following evaluations will additionally be performed for participants in Cohorts 1 and 2:

- 12-lead ECG
- Serology testing (HIV type 1 or type 2, hepatitis B, hepatitis C)
- Blood sampling for laboratory safety testing (hematology and biochemistry)

Study participants who qualify for inclusion in Cohorts 1 and 2 will be contacted and scheduled for enrollment and first vaccination (Visit 2) within 28 days. If necessary, the screening visit may be split into several visits.

Participants in Cohorts 1 and 2 with laboratory values or vital signs (eg, elevated blood pressure) not meeting eligibility criteria at the screening visit may have 1 repeat testing at the discretion of the investigator if the abnormality is not clinically significant and may be a testing aberrancy. Enrollment of a participant with laboratory values representing toxicity Grade 2 is allowed if the investigator considers the values not to be clinically significant and reasonable for the population under study. Details on toxicity grade assessment are provided in Section 12.1.3.

After all data have been reviewed for completeness and adherence to the inclusion and exclusion criteria, the participant can be deemed eligible for the study.

SAEs (and any concomitant medications associated with SAEs) will be collected from first dose administration until the end of the study. Unsolicited AEs will be recorded on the Adverse Event page of the eCRF from the time of each vaccination through the following 28 days, together with information on any concomitant medications.[a] Additionally, (S)AEs that are related to the study procedures or to non-investigational (concomitant) Janssen products will be collected from ICF signature onwards.

9.1.4. Randomization (Day 1)

Cohorts 1 and 2: After verification of selected inclusion and exclusion criteria,[b] abbreviated physical examination (at the discretion of the investigator), and measurement of vital signs, eligible participants will be randomized as described in Section 5. If the medical status and/or physical examination suggest that significant changes have occurred since screening, the safety laboratory

[a] AEs that start more than 28 days after a vaccination, but that are still present at the time of the next vaccination will also be recorded.

[b] Inclusion criteria 4 and 5, and exclusion criteria 1, 4, 12, 13, and 14.

tests will be repeated and the randomization visit re-scheduled, or the participant excluded from the study if he or she fails to meet the inclusion and exclusion criteria.

Cohort 3: After verification of all inclusion and exclusion criteria, physical examination, and measurement of vital signs, eligible participants will be randomized as described in Section 5.

All eligible participants will receive their first vaccination following the procedures as described in Section 9.1.5.

9.1.5. Vaccination

On each vaccination day according to the schedules presented in Table 8, Table 9, Table 10 and Table 11, the following procedures will apply pre- and post-vaccination:

- Pre-vaccination, verification of selected inclusion/exclusion criteria, [a] physical examination,[b] and measurement of vital signs will be performed for all participants.
- Pre-vaccination, blood and nasal samples will be collected for immunogenicity assessments. In Cohorts 1 and 2, pre-dose blood samples will be taken on Day 1 for transcriptome analysis and safety laboratory tests (hematology and biochemistry).
- Pre-vaccination, the investigator must check for any symptoms of acute illness or fever (body temperature ≥38.0 °C). In such a situation, the participant may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or withdrawn from further vaccination at the discretion of the investigator.
- Post-vaccination, participants will be closely observed for at least 30 minutes to monitor for development of any acute reactions, or longer if deemed necessary by the investigator. Vital signs measurement will be performed. Any unsolicited or solicited AEs and vital signs will be documented in the eCRF by study-site personnel following this observation period.
- All participants will be provided with a participant diary, thermometer, and ruler to measure and record body temperature, and solicited local and solicited systemic AEs for 7 days post-vaccination.
- Nasal swab kits and RTI Symptoms Forms will be distributed to all participants before the start of the first 2 RSV seasons of the study (relative to the enrollment date of the first participant in Cohort 1); during these RSV seasons, participants should record signs and symptoms of RTI using the RTI Symptoms Form.

[a] To include receipt of any routine immunizations.

[b] A full physical examination, including height and body weight, will be carried out at screening, and before final vaccination. At other vaccination visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.

9.1.6. Post-Vaccination Follow-up

At 24 hours after vaccination on Day 1, a telephone call will be made to each sentinel participant in Cohort 1 to collect safety information (solicited and unsolicited AEs, SAEs, and concomitant medications).

The **7-day post-vaccination visits** include an abbreviated physical examination (at the discretion of the investigator), measurement of vital signs, and recording of any AEs/SAEs, concomitant medications and RTIs.[a,b] The participant diary will be reviewed and collected. If the visit occurs before the end of the diary period after the vaccination, review of the diary will still take place, but the diary will be returned by the participant at the next study visit. In Cohorts 1 and 2, blood samples for transcriptome analysis and for safety laboratory tests (hematology and biochemistry) will be collected (after the first dose only, not applicable to subsequent doses).

The **14-day post-vaccination visit** (post-dose 1 and post-dose 3) includes an abbreviated physical examination (at the discretion of the investigator), measurement of vital signs, and recording of unsolicited AEs/SAEs, concomitant medications and RTIs.[a] Blood and nasal samples for immunogenicity assessments will be collected. Blood samples for transcriptome analysis will also be taken (in Cohorts 1 and 2 only).

The **28-day post-vaccination visits** include an abbreviated physical examination (at the discretion of the investigator), measurement of vital signs, and recording of unsolicited AEs/SAEs, concomitant medications, and RTIs.[a] Blood and nasal samples for immunogenicity assessments will be collected.

The **56-day post-vaccination visit** (post-dose 1 in Cohort 3 with one-dose regimen only) includes an abbreviated physical examination and vital signs measurement (both at the discretion of the investigator), and recording of any SAEs and concomitant medications, and RTIs.[a] Blood and nasal samples for immunogenicity assessments will be collected.

The **12-week post-vaccination visit** (post-dose 1 in Cohort 3 with one-dose regimen only) includes an abbreviated physical examination and vital signs measurement (both at the discretion of the investigator), and recording of any SAEs and concomitant medications, and RTIs.[a] Blood and nasal samples for immunogenicity assessments will be collected.

The **26-week post-vaccination visits** include an abbreviated physical examination and vital signs measurement (both at the discretion of the investigator) and recording of any SAEs and associated concomitant medications, and RTIs.[a] Blood samples for immunogenicity assessments will be collected.

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[a] RTIs will only be recorded during the first 2 RSV seasons of the study (relative to the enrollment date of the first participant in Cohort 1).

[b] Visit 13 (7 days post-third vaccination) is not required for any Cohort 3 participant who misses the third vaccination.

The **12-month post-first vaccination visit** includes an abbreviated physical examination and vital signs measurement (both at the discretion of the investigator) and recording of any SAEs and associated concomitant medications, and RTIs.[a] Blood and nasal samples for immunogenicity assessments will be collected.

The **18-month post-first vaccination visit** (Cohort 2 only) includes an abbreviated physical examination and vital signs measurement (both at the discretion of the investigator) and recording of any SAEs and associated concomitant medications, and RTIs.[a] Blood samples for immunogenicity assessments will be collected.

9.1.7. Final Visit

For Cohorts 1 and 2 (Groups 11-13 and Groups 16-18), the visit at 24 months after the first vaccination will be the final visit and include an abbreviated physical examination and vital signs measurement (both at the discretion of the investigator), and recording of any SAEs and associated concomitant medications, and RTIs.[a] Blood samples for immunogenicity assessments will be collected. Participants in Groups 14 and 15 (Cohort 2) will continue into a long-term follow-up phase. Their final visit will be the visit at 36 months after the first vaccination.

For Cohort 3, the visit at 36 months after the first vaccination will be the final visit and include an abbreviated physical examination and vital signs measurement (both at the discretion of the investigator), and recording of any SAEs and associated concomitant medications. Blood samples for immunogenicity assessments will be collected.

9.1.8. Early Withdrawal: Early Exit Visit

For participants who are unable to continue participation in the study, but who do not withdraw consent, an early exit visit will be conducted as soon as possible. In the event of early withdrawal from the study, all procedures as required at the final visit (see Section 9.1.7) will be performed. Blood samples for safety laboratory assessments (hematology and biochemistry; Cohorts 1 and 2 only) will be collected if the early exit is within 8 days of the first vaccination. Blood samples for immunogenicity assessments will only be collected if the early exit is at least 14 days after the previous immunogenicity blood draw.

If the early exit visit takes place within 7 days of the previous vaccination, solicited AEs will be recorded; if the early exit visit takes place within 28 days of the previous vaccination, unsolicited AEs will be recorded.

9.1.9. Long-term Follow-up (Groups 14 and 15 from Cohort 2)

Participants in Groups 14 and 15 will continue into the long-term follow-up phase.

[a] RTIs will only be recorded during the first 2 RSV seasons of the study (relative to the enrollment date of the first participant in Cohort 1).

Participants will make follow-up visits at the clinic every 6 months (26 weeks) until the final visit at Day 1095. Each visit includes recording of any SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, recording of any AEs leading to discontinuation; recording of concomitant medications in conjunction with SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, or in conjunction with AEs leading to discontinuation; and collection of samples for cellular and humoral immunogenicity assays.

9.2. Study Evaluations

9.2.1. Immunogenicity

Venous blood samples of approximately 10 mL and 50 mL will be collected for determination of humoral and cellular immune responses, respectively, at the timepoints shown in the Schedule of Activities, or at the early exit visit if the participant prematurely terminates without withdrawing consent (if the early exit is at least 14 days after the previous immunogenicity blood draw).

Venous blood samples (2.5 mL) for transcriptome analysis will be collected on Day 1 (pre-dose), Day 8, and Day 15 in Cohorts 1 and 2.

All sample collection and processing will be performed by the staff at the clinical sites according to current approved standard operating procedures.

It is assumed that all participants will have a pre-existing immune response due to previous RSV exposure.

The humoral and cellular immunogenicity assays that may be used in this study (as available and applicable) are summarized in Table 16 and Table 17 below.

Blood for humoral and cellular immune responses will be drawn from all participants in Cohorts 1 and 2. In Cohort 3, blood will be drawn for humoral immune responses from all participants and for cellular immune responses from a subset of 63 participants.

Immunogenicity samples will be prioritized as outlined in the Laboratory Manual.

Table 16: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Primary endpoint (Regimen Selection Cohort [Cohort 2] – Groups 11 to 15 only)	
RSV neutralization A	Analysis of neutralizing antibodies to an A strain
Secondary endpoints	
RSV neutralization A	Analysis of neutralizing antibodies to an A strain
F protein antibodies (ELISA; pre-F and/or post-F)	Analysis of antibodies binding to RSV F protein in pre-fusion and/or post-fusion form
Exploratory endpoints	
RSV strain cross-neutralization	Analysis of cross-neutralizing antibodies to B and/or a different A strain(s)
F protein antibody specificity characterization	Pre- and post-F specificity by binding or functional assays as ELISA, and/or competition ELISA. Adsorption of serum or plasma with pre-F and post-F protein before any antibody assay, epitope mapping, functional VNAs
G and/or N protein antibodies (ELISA)	Analysis of antibodies binding to RSV G and/or N protein
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to, ADCC, ADCP, avidity, other respiratory viral neutralizing or binding assays, Ig isotype, functional VNAs to other respiratory viruses, and antibody assessments for antibody repertoire

ADCC: antibody-dependent cell-mediated cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; ELISA: enzyme-linked immunosorbent assay; F: fusion; G: glycoprotein; Ig: immunoglobulin; N: nucleoprotein; RSV: respiratory syncytial virus; VNA: virus neutralizing antibody

Note: Antibody analyses might be performed in nasal samples, serum and plasma.

Table 17: Summary of Immunogenicity Assays (Cellular)

Assay	Purpose
Secondary endpoints	
IFN-γ ELISpot	T-cell IFN-γ responses to RSV F protein peptides
Exploratory endpoints	
ICS	Analysis of T-cell responses to RSV F protein peptide-stimulated PBMC (including, but not limited to, $CD4^+/CD8^+$, IL-2, IFN-γ, TNF-α, activation markers and memory)
Transcriptome analysis	Regulation of genes (clusters), expression patterns, that predict specific immune responses after vaccination
Chemokine/cytokine analysis	Levels of chemokines and cytokines in nasal samples
Sequencing of B-cells	Including but not limited to sequencing of BCR (B-cell receptor) or VH/VL (heavy/light chain characterization) for specificity

ELISpot: enzyme-linked immunospot; F: fusion; ICS: intracellular cytokine staining; IFN-γ: interferon gamma; IL-2: interleukin-2; PBMC: peripheral blood mononuclear cells; RSV: respiratory syncytial virus; TNF-α: tumor necrosis factor alpha

Nasal samples, collected at the timepoints indicated in the Schedule of Activities, will be used for immunogenicity assessments (for example, immunoglobulin or cellular immune component) and identification of the etiology of respiratory infections (if needed).

In addition to RT-PCR performed on nasal samples, any immunogenicity blood sample collected from all participants may also be assayed by serology (including but not limited to RSV VNA or ELISA specific to RSV protein G [glycoprotein] and/or N [nucleoprotein] as available and applicable) for RSV exposure.

Instructions for the collection, handling, storage, and shipment of blood and nasal samples for the immunogenicity assays can be found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples to the central laboratory must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

9.2.2. RTI Procedures

Participants will be informed of the timing of the start and end of the RSV season in accordance with the country/region-specific RSV local surveillance system.

During the first 2 RSV seasons of the study (relative to the enrollment date of the first participant in Cohort 1), participants should record any signs and symptoms of RTI (such as runny nose, fever, severe cough, rapid breathing, difficulty breathing), including measurement of body temperature, on a daily basis until symptoms have resolved using a specific RTI Symptoms Form. Signs and symptoms of RTI recorded on the RTI Symptoms Form will be transferred onto the RTI Symptoms page in the eCRF. RTI Symptoms Forms will be the primary source for RTI monitoring. Participants should complete a new form on each day they experience symptoms, including the day on which the symptoms resolve. Completed RTI forms can either be mailed to the site or brought to the site at the next visit.

If respiratory symptoms develop during the first 2 RSV seasons of the study, the following should take place:

- Participants should contact the site as soon as possible to notify the site of an RTI.
- Participants should record signs and symptoms of the RTI (including measurement of body temperature) daily using the RTI Symptoms Form until the day of symptom resolution.
- If feasible, participants should take a nasal sample at home, preferably between 2 and 3 days after the onset of the RTI symptoms. The sample should be stored refrigerated and brought to the site by the participant within 3 to 4 days.
- Alternatively, participants may go to the site preferably within 2 to 3 days after the onset of the RTI to have a nasal sample taken by the study staff.

The RTI Symptoms Forms and nasal swab kits for use at home will be distributed before the start of the RSV seasons.

During the first 2 RSV seasons of the study, participants will be contacted by telephone every 30±7 days (unless a planned visit has occurred or will occur within 30 days). These calls will remind participants to complete the RTI Symptoms Form in the event of any symptoms of RTI, to contact the site at the time of symptom onset, and to take a nasal sample (or go to the site to have a nasal sample taken by study staff). These calls will also check for any SAEs and associated concomitant medications since the previous visit or telephone contact.

The presence of RSV or any other respiratory infection may be assessed by the sponsor by RT-PCR diagnostics on the nasal samples, which may include viral load and RSV subtyping.

Blood from participants with a suspected RTI may be assayed by a serological assay (eg, protein G and/or N ELISA) to confirm RSV infection. (No additional blood sampling is necessary – any serological assay conducted to confirm RSV infection will use blood from the existing samples.)

Every effort should be made to collect data on the clinical course of RTIs including information on oxygenation status, supplemental oxygen requirements and specific drug treatments, as well as other concurrent respiratory illness present at the time of the diagnosis of the event and up to symptom resolution.

Any RTI that is not due to RSV infection will be reported as an AE if it occurs between the time of any vaccination through the following 28 days. Any RTI recorded as an AE in the eCRF will be excluded from any AE analysis if the central laboratory RT-PCR is subsequently found to be positive for RSV. RTIs arising from RSV infection will not be reported as (S)AEs in the Clinical Study Report as they are endpoints of the study and will be tabulated separately.

Any RTI fulfilling the criteria of an SAE will be reported as such during the entire study period if RT-PCR indicates it is not an RSV-RTI. If the RT-PCR is positive for RSV the event should not be reported as an SAE. If RT-PCR information is not available within 24 hours of knowledge of the event, the event will be reported as an SAE, but will be subsequently downgraded from SAE status if it later turns out to be RT-PCR positive for RSV.

9.2.3. Safety Evaluations

Any clinically relevant changes must be recorded in the eCRF.

Any clinically significant abnormalities, including abnormalities persisting at the end of the study or at early withdrawal, will be followed by the investigator until resolution or a clinically stable endpoint is reached.

The study includes the following evaluations of safety and reactogenicity on timepoints provided in the Schedule of Activities.

9.2.3.1. Adverse Events

All AEs will be reported as specified in Section 12, Adverse Event Reporting. All SAEs will be collected until the end of the double-blind phase; only SAEs related to study vaccine, study procedures, or non-investigational (concomitant) Janssen products, and all AEs leading to discontinuation will be collected during the long-term follow-up phase (Groups 14-15 in Cohort 2).

Unsolicited AEs

Unsolicited AEs will be reported by the participant from the time of each vaccination through the following 28 days, or early discontinuation.[a] Relatedness of the AEs should be determined by the investigator. Additionally, AEs that are related to the study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards.

Solicited AEs

Information related to solicited AEs defined below, will be recorded by participants in a diary for 7 days after each vaccination. Each participant will be provided with a diary and instructions on how to complete the diary (Section 9.1.1). There will be a minimum 30-minute post-vaccination assessment of solicited events at the site. Diary information will be transcribed by the study-site personnel in the appropriate diary pages of the eCRF. Once a solicited symptom from a diary is considered to be of severity Grade 1 or above, it will be referred to as a solicited AE.

Injection Site (Local) Adverse Events

Participants will be asked to note in the diary occurrences of pain/tenderness, induration/swelling and erythema at the vaccine injection site daily for 7 days post-vaccination. The extent (ie, largest diameter) of any erythema and induration/swelling should be measured (using the ruler supplied), graded (using the functional scale) and recorded daily.

- **Injection Site Pain/Tenderness**

  Injection site pain (eg, stinging, burning) is an unpleasant sensory and emotional experience associated with actual or potential tissue damage and occurring at the immunization site (with or without involvement of surrounding tissue). Injection site tenderness is a painful sensation localized at the injection site upon palpation or movement of the limb. Due to the subjective nature of the reaction, the severity assessment of pain/tenderness is self-reported (if a participant is unable to provide self-report, other reporters include a healthcare provider or caregiver).[10]

- **Injection Site Erythema**

  Injection site erythema is a redness of the skin caused by dilatation and congestion of the capillaries localized at the injection site. It can best be described by looking and measuring.

- **Injection Site Swelling/Induration**

  Injection site swelling is a visible enlargement of an injected limb. It may be soft (typically) or firm (less typical). Injection site induration is a palpable thickening, firmness, or hardening of soft tissue, usually has well-demarcated palpable borders, can be visible (raised or sunken compared to surrounding skin), is often 'woody' to touch, and has a flat shape. As differentiation between swelling and induration may be difficult without a healthcare

[a] AEs that start more than 28 days after a vaccination, but that are still present at the time of the next vaccination will also be recorded.

professional's assessment, both symptoms have been combined to allow self-assessment by the participants. Swelling and induration can best be described by looking and measuring.

Note: Any other injection site events not meeting the above case definitions should be reported separately as unsolicited AEs.[22,23]

Systemic Adverse Events

Participants will be instructed on how to record daily body temperature using the thermometer provided for home use. Participants should record the temperature in the diary in the evening of each day of vaccination, and then daily for the next 7 days approximately at the same time each day.[a] If more than 1 measurement is made on any given day, the highest temperature of that day will be used in the eCRF.

Fever is defined as an endogenous elevation of body temperature ≥38.0 °C, as recorded in at least one measurement.[26]

In addition to fever, participants will be instructed on how to record daily in the diary for 7 days after each vaccination symptoms of the following events: fatigue, headache, myalgia, arthralgia, chills, and nausea. Severity of these event will be graded by the investigator according to the criteria presented in Section 12.1.3.

If a solicited local or solicited systemic AE is not resolved by 7 days after the vaccination, the follow-up will be captured on the diary. The participant will be instructed to record the date of last symptoms and maximum severity in the diary after resolution.

9.2.3.2. Clinical Laboratory Tests

In Cohorts 1 and 2, blood samples for biochemistry and hematology will be collected at screening, on Day 1, and at 7 days after the first vaccination (or at the exit visit if early exit is within 8 days of the vaccination and the participant terminates from the study without withdrawing consent).

The following tests will be performed by a central laboratory (*parameters will only be measured at screening):

- **Hematology Panel**

  hemoglobin
  white blood cell (WBC) count with differential
  platelet count
  prothrombin time*
  activated partial thromboplastin time*

[a] All diary assessments, including body temperature, 7 days after each vaccination may be collected earlier in the day to coincide with the clinic visit.

- **Biochemistry Panel**

  sodium
  potassium
  creatinine
  blood urea nitrogen
  aspartate aminotransferase (AST)
  alanine aminotransferase (ALT)

Review and Grading of Laboratory Data

The investigator must review each laboratory result, document this review, and systematically assess any clinical significance. The laboratory reports must be filed with the source documents.

Laboratory values will be initially evaluated by the investigator according to central laboratory criteria. Abnormal values outside the central laboratory range of normal will be graded according to the FDA Guidance document "Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Attachment 1). Laboratory values within central laboratory normal limits will not be FDA graded and will be considered as normal.

Reporting Laboratory Abnormalities as Adverse Events

Any clinically significant abnormal laboratory value within 28 days post-vaccination that falls outside of the central laboratory normal range and that requires follow-up will be captured as an AE. Laboratory values outside normal ranges that are not clinically significant in the judgment of the investigator, should not be recorded as an AE. Any laboratory value falling within the central laboratory normal range will not be severity graded or recorded as an AE, regardless of whether the value falls within FDA ranges for Grade 1 or higher.

Values for parameters falling within the central laboratory normal range should not be reported as an AE.

Repeat of Clinically Significant Laboratory Tests

For any clinically significant abnormal laboratory value that has increased in grade over baseline, the test must be repeated at the next scheduled visit or sooner based on investigator's judgment, however Grade 3 and above abnormalities should be retested within 48 hours. Any clinically significant abnormalities (including those persisting at the end of the study or early withdrawal) will be followed by the investigator until resolution or a clinically stable endpoint is reached.

Screening Procedures (Cohorts 1 and 2 Only)

For entry into the study, each participant must be healthy on the basis of clinical laboratory tests performed at screening. Enrollment of a participant with clinical laboratory values outside of the central laboratory normal range representing FDA toxicity Grade 2 is allowed if the investigator considers the values reasonable for the population under study and not clinically significant.

Additional clinical laboratory assessments to be performed at screening include serology testing (HIV type 1 or type 2, hepatitis B, hepatitis C).

9.2.3.3. Electrocardiogram

In Cohorts 1 and 2, supine 12-lead ECGs will be performed at screening and interpreted locally; ECGs will only be performed thereafter during the study if clinically indicated based on signs and symptoms.

For 30 minutes prior to the ECG, participants should refrain from meals, hot or cold beverages and strenuous exercise, and should remain in a room with a comfortable temperature. Each ECG should be obtained after the participant has been at rest for at least 5 minutes.

Enrollment of a participant is allowed even with abnormal ECG results as long as the investigator feels that these are not clinically significant and appropriate for the population.

9.2.3.4. Vital Signs

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Vital signs are to be measured before blood draws and nasal samples.

The following measurements will be performed:

- Heart rate (beats per minutes), respiratory rate (breaths per minute), supine systolic blood pressure (mmHg) and supine diastolic blood pressure (mmHg)
- Body temperature (oral route preferred, or in accordance with the local standard of care)

Confirmatory vital signs measurement can be done if inconsistent with a prior measurement. If any clinically significant changes in vital signs are observed, they will be reported as an AE and followed to resolution, or until reaching a clinically stable endpoint.

9.2.3.5. Physical Examination

A full physical examination, including height and body weight, will be carried out at screening and before the Month 12 booster (Cohorts 1 and 3) and before the Month 24 booster (Cohort 3 only). At all other visits, an abbreviated, symptom-directed examination will be performed by the investigator based on clinically relevant issues, clinically relevant symptoms and medical history. Symptom-directed physical examination may be repeated if deemed necessary by the investigator.

Physical examinations will be performed by the investigator or an appropriately trained delegate. Any clinically relevant abnormalities or changes in severity observed during the review of body systems should be documented in the eCRF as an AE.

10. PARTICIPANT COMPLETION/DISCONTINUATION OF STUDY VACCINE/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A participant will be considered to have completed study vaccination if he or she has received all vaccinations. A participant will be considered to have completed the study if he or she completed assessments at the final visit 24 months (Cohort 1 and Cohort 2 [Groups 11-13 and Groups 16-18]) or 36 months (Cohort 2 [Groups 14 and 15] and Cohort 3) after the first vaccination.

10.2. Discontinuation of Study Vaccine/Withdrawal from the Study

Discontinuation of Any Study Vaccine

A participant will not be automatically withdrawn from the study if he or she has to discontinue from study vaccination before the end of the study vaccine regimen.

Participants will be discontinued from vaccination for the reasons listed below. These participants must not receive any additional dose of any study vaccine but should continue to be monitored for safety and, if this does not result in safety risks for the participant, for immunogenicity (if the reason for discontinuation is not because of impaired functioning of the immune system) and/or other study procedures (eg, RTI follow-up). Additional unscheduled visits may be performed for safety/reactogenicity reasons, if needed.

In the event of questions, the investigator is encouraged to contact the sponsor:

- Anaphylactic reaction post vaccination, not attributable to causes other than vaccination
- An SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Any related AE, worsening of health status or intercurrent illness that, in the opinion of the investigator, requires study vaccine discontinuation
- Chronic or recurrent use of immunosuppressants (after discussion with the sponsor)
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data

Participants who miss a vaccination, not due to the reasons above, can receive subsequent vaccinations if, at the time of administration, the investigator determines that they are eligible to receive the vaccination according to the criteria in Section 10.3. In the event of questions, the investigator is encouraged to contact the sponsor.

Withdrawal from the Study

Each participant has the right to withdraw from the study at any time for any reason without affecting the right to treatment by the investigator. The investigator should make an attempt to contact participants who did not return for scheduled visits or follow-up. Although participants are

not obliged to give a reason for withdrawing prematurely, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the participant's rights.

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Repeated failure to comply with protocol requirements
- Decision by sponsor, investigator, or local regulatory authorities and Institutional Review Board/Independent Ethics Committee (IRB/IEC)

If a participant is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study vaccine assigned to the withdrawn participant may not be assigned to another participant. In general, participants who withdraw will not be replaced, unless the participant was randomized but did not receive any study vaccine.

In Cohort 1, any randomized participant withdrawn from the study for reasons other than (an) AE(s) after the first dose but before the second dose might be replaced at the discretion of the sponsor. In Cohort 2, no replacements or additional randomizations will be done for withdrawals after the first dose. In Cohort 3, if randomized participants are withdrawn from vaccination before the first dose of the selected regimen is administered, additional participants may be recruited to replace these participants at the discretion of the sponsor.

If a participant withdraws prematurely from the study, assessments for early withdrawal should be obtained (see also Section 9.1.8). Participants who wish to withdraw consent from participation in the study will be offered a single exit visit for safety follow-up (prior to formal withdrawal of consent). They have the right to refuse.

Withdrawal from the Use of Samples in Future Research

The participant may withdraw consent for use of samples for future research (see Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

10.3. Contraindications to Vaccination

The following events constitute a contraindication to vaccination at that point in time. If any of these events occur at the scheduled time for vaccination, the participant may be vaccinated up to

10 days beyond the scheduled vaccination, or be withdrawn from vaccination at the discretion of the investigator and after consultation with the sponsor:

- Severe acute illness at the time of vaccination. This does not include minor illnesses such as diarrhea.
- Fever (body temperature ≥38.0 °C) at the planned time of vaccination.
- Medically-indicated vaccines should be given at least 14 days before or 14 days after study vaccine administration (see Section 8).

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the immunogenicity and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

Planned analyses are described in Section 11.6.

11.1. Analysis Sets

Vaccine assignment will follow the as-treated principle.

The Full Analysis (FA) Set will include all participants who were randomized and received at least one dose of vaccine (active or placebo), regardless of the occurrence of protocol deviations or the type of vaccine (ie, Ad26.RSV.preF, RSV preF protein, Ad26.RSV.preF/RSV preF protein combination or mixture). All safety and participant information analyses will be based on the FA set.

The Per-protocol RSV Immunogenicity (PPI) Set will include all participants who were randomized and received the complete first dose, and for whom immunogenicity data are available, excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes.

In addition, the following samples will not be included in the PPI set:

- For participants who experience a natural RSV infection (based on RT-PCR, or other sources), samples collected after the natural infection will not be taken into account in the assessment of the immunogenicity of the selected regimen.
- If a participant misses one or more active dose(s) of the selected regimen but continues the planned visit schedule, samples after the missed active dose(s) will not be taken into account.

The analysis of all secondary and exploratory immunogenicity endpoints related to RSV will be based on the PPI set. Depending on the number of samples excluded, a post-hoc exploratory analysis might be performed, including the excluded samples. To visualize excluded samples, participant profiles from several assays might be repeated, indicating the excluded samples.

11.2. Sample Size Determination

11.2.1. Initial Safety Cohort (Cohort 1)

The number of participants chosen for the initial safety cohort will provide a preliminary safety assessment. Placebo recipients are included for blinding and safety purposes and will provide additional control specimens for immunogenicity assays.

While mild to moderate vaccine reactions (local injection site, systemic responses) are expected, AEs that preclude further vaccine administration or more serious ones that would limit product development are not anticipated.

Table 18 shows the probabilities of observing at least one AE in the initial safety cohort at given true AE rates. In the analysis of the initial safety cohort (Cohort 1), placebo recipients will be shown pooled.

Table 18: Probability of Observing at Least One Adverse Event in the Initial Safety Cohort (Cohort 1) at a Given True Adverse Event Rate

True Adverse Event Rate	Probability of Observing at Least One Adverse Event in N Participants		
	N=4	N=8	N=16
0.5%	2%	4%	8%
1%	4%	8%	15%
2.5%	10%	18%	33%
5%	19%	34%	56%
10%	34%	57%	81%
25%	68%	90%	99%
50%	94%	100%	100%

11.2.2. Regimen Selection Cohort (Cohort 2)

The objective is to compare the RSV A2 neutralizing antibody levels of all regimens containing RSV preF protein (Groups 12 through 17) to the one-dose Ad26.RSV.preF regimen (Group 11). This will be based on the estimation of GMT ratios and corresponding 95% confidence intervals (CIs) of the VNA A2 levels of the regimens containing RSV preF protein on Day 29 for the one-dose regimens (Groups 12 through 16) and on Day 85 for the two-dose regimen (Group 17) versus the VNA A2 levels on Day 29 of the one-dose Ad26.RSV.preF regimen (Group 11). The sample size was selected to provide a precision of ~0.53 on the $\log_2$ scale.

Note: Immunogenicity data from Groups 9 and 10 of the initial safety cohort (Cohort 1) will be combined with those from Groups 16 and 17 of the regimen selection cohort (Cohort 2).

The table below presents the resulting 95% CIs for several observed ratios, assuming a standard deviation for VNA of 1 on the $\log_2$ scale and accounting for 5% dropout.

Observed Ratio	Corresponding 95% CI
1	[0.69; 1.44]
1.2	[0.83; 1.73]
1.5	[1.04; 2.17]

In addition to the above, factors such as data from other assays, reactogenicity profiles, manufacturability and ease of administration will be considered when selecting the regimen for the expanded safety phase. A more detailed rule will be described in the Statistical Analysis Plan.

11.2.3. Expanded Safety Cohort (Cohort 3)

The expanded safety cohort (Cohort 3) should provide sufficient safety data on the selected regimen to support late stage development if the immunogenicity results of Cohort 2 are satisfactory.

Table 19 shows the probabilities of observing at least one AE in the expanded safety cohort at given true AE rates. This table shows that the current numbers give a reasonable probability to also observe less frequent events in the active groups in this cohort.

Table 19: Probability of Observing at Least One Adverse Event in the Expanded Safety Cohort (Cohort 3) at a Given True Adverse Event Rate

True Adverse Event Rate	Probability of Observing at Least One Adverse Event in N Participants		
	N=45	N=135	N=270
0.5%	20%	49%	74%
1%	36%	74%	93%
2.5%	68%	97%	100%
5%	90%	100%	100%
10%	99%	100%	100%
25%	100%	100%	100%

11.3. Participant Information

For all participants, demographic characteristics (eg, age, height, weight, body mass index, race, and gender), and other baseline characteristics (eg, physical examination, medical history, and concomitant diseases) will be tabulated and summarized with descriptive statistics. This will be done per cohort.

11.4. Immunogenicity Analyses

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% CI for ELISA and RSV neutralization assay; median and quartiles for IFN-γ ELISpot and ICS) will be calculated for continuous immunologic parameters at all timepoints. For the humoral assays, geometric mean fold rises from baseline and corresponding 95% CIs might additionally be calculated. Baseline is considered as the last available assessment before the first vaccination. Graphical representations of immunologic parameters will be made as applicable.

For categorical variables, frequency tables will be presented.

In addition, for the regimen selection cohort (Cohort 2), GMT ratios with corresponding 95% CI of the VNA A2 levels of the combination/mixture regimens on Day 29 for the one-dose regimens (Groups 12 through 16) and Day 85 for the two-dose regimen (Group 17) versus the Day 29 VNA A2 levels of the one-dose Ad26.RSV.preF regimen (Group 11) will be calculated. Therefore, a regression model will be fitted with the respective VNA A2 levels as dependent variable and the respective regimens and baseline levels as covariates, using Satterthwaite's method to calculate

the degrees of freedom and allowing different variances for the vaccines. The estimate and CIs obtained as such will be back-transformed (by exponentiation) to a GMT ratio and the corresponding CI. Note that the effect of additional factors, such as age and the interaction with the regimen, might also be explored in this model.

Note: Immunogenicity data from Groups 9 and 10 of the initial safety cohort (Cohort 1) will be combined with those from Groups 16 and 17 of the regimen selection cohort (Cohort 2).

The same model might be repeated for other assays.

In the expanded safety cohort (Cohort 3), the effect of the Month 12 and Month 24 booster will be assessed. Therefore, the following ratios for VNA A2 will be calculated:

- In the groups with an active vaccination at Month 12/Month 24, the ratio of the Month 12/Month 24 booster Day 29 level versus the prime Day 29 level with the corresponding 95% CI will be calculated.
- The groups with an active vaccination at Month 12/Month 24 will be compared to corresponding groups with placebo vaccination at Month 12/Month 24 by calculating the ratio with the corresponding 95% CI.

Note that the above might also be repeated for other assays.

The primary analysis set for the above is the PPI set. As a sensitivity analysis, key tables may also be based on the FA set. Depending on their occurrence, the effect of natural infections might be further explored.

11.5. Safety Analyses

No formal statistical testing of safety data is planned. Per cohort, all safety data will be analyzed descriptively by regimen.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the active phase (ie, AEs occurring after vaccination up to 28 days post-vaccination), and all SAEs will be included in the analysis. For each AE, the number and percentage of participants who experience at least one occurrence of the given event will be summarized by group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study vaccine due to an AE, or who experience a severe AE or an SAE.

Summaries and/or listings may be provided separately for AEs with onset outside the above defined timeframe (ie, beyond 28 days post-vaccination) and that were reported pre-dose at the time of subsequent vaccinations for studies using multiple doses.

Solicited local (at injection sites) and solicited systemic AEs will be summarized descriptively. The overall frequencies per vaccine group as well as frequencies according to severity and duration will be calculated for solicited AEs. In addition, the number and percentages of participants with at least one solicited local (at the injection site) or solicited systemic AE will be presented. Frequencies of unsolicited AEs, separately for all and vaccine-related only, will be presented by System Organ Class and Preferred Term.

Any RTI recorded as an AE in the eCRF that is subsequently determined to be RSV-positive by central laboratory RT-PCR will be excluded from the safety analysis and tabulated separately.

Clinical Laboratory Tests

For participants in Cohorts 1 and 2, laboratory abnormalities will be determined according to the FDA toxicity grading tables (see Attachment 1), or in accordance with the normal ranges for the clinical laboratory parameter if no grades are available. Any laboratory value shown as a "graded" value in the FDA table that is within central laboratory normal ranges will not be graded for severity.

Vital Signs

A tabulation of the distribution of body temperatures per half degree intervals will be provided. For systolic and diastolic blood pressures, pulse rate and respiratory rate, the percentage of participants with values beyond clinically relevant limits will be summarized.

Electrocardiogram (ECG)

For Cohorts 1 and 2, any abnormalities in ECG parameters (at screening) will be listed.

Physical Examination

Physical examination abnormalities will be reported as AEs, according to the investigator.

11.6. Planned Analyses

Note: Depending on the timing, some of the planned analyses might be combined.

11.6.1. Initial Safety Cohort (Cohort 1)

Primary Analysis

Primary analysis: analysis of safety data 28 days post-dose 2. Data collected up to the time of the visit at 28 days after the second dose of study vaccine for the last participant in Cohort 1 will be included in the analysis. This analysis will be performed on unblinded data. The blind will be maintained at the participant/site level.

As immunogenicity data from Groups 9 and 10 of the initial safety cohort (Cohort 1) will be combined with those from Groups 16 and 17 of the regimen selection cohort (Cohort 2), immunogenicity data from the initial safety cohort will be analyzed at the time of the primary analysis of the regimen selection cohort.

Analysis 28 Days Post-Month 12 Booster

This analysis will include safety and immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 28 days after the Month 12 booster dose of study vaccine for the last participant in this cohort will be included in the analysis. The blind will be maintained at the participant/site level.

11.6.2. Regimen Selection Cohort (Cohort 2)

Primary Analysis

Primary analysis: analysis of safety data 28 days post-dose 2 and immunogenicity data up to at least 28 days post-dose 1.

- This analysis should contain all safety data collected up to the time of the visit at 28 days after the second dose for the last participant in this cohort.
- Immunogenicity data from at least Groups 11 to 15 and part of Group 18 (placebo group), up to at least 28 days post-dose 1 will be included as well.[a]
- This analysis will be performed on unblinded data. The blind will be maintained at the participant/site level.

In this analysis, all available immunogenicity data of the initial safety cohort (Cohort 1) will be analyzed as well.

Additional Analysis

Additional analysis: analysis of immunogenicity data 28 days post-dose 1 for all one-dose regimens (including the one-dose regimen with separate injections) and 28 days post-dose 2 for the two-dose regimen. This analysis may include immunogenicity data available from additional timepoints.

This analysis should contain immunogenicity data up to at least day 28 post-dose 1 for one-dose regimens and 28 days post-dose 2 for the two-dose regimen. This analysis will be performed on unblinded data. The blind will be maintained at the participant/site level.

In this analysis, all available immunogenicity data of Groups 9 and 10 from the initial safety cohort (Cohort 1) and immunogenicity data of Cohort 2 included in the primary analysis will be analyzed as well.

The primary analysis of Cohort 1 and Cohort 2 and the additional analysis may be combined into one analysis.

[a] An unblinded person who is not part of the study team (or another independent party) will dictate which Day 29 samples should be analyzed by the clinical immunology laboratory. Half of the Day 29 samples of Group 18 (placebo group) will be included to ensure the blind at the level of the clinical immunology laboratory.

Based on safety and immunogenicity results available at the time of primary analysis, a sponsor committee will decide if the expanded safety cohort can be opened and which regimen will be used. In case none of the groups that are part of the primary objective meet internal criteria, regimen selection may be delayed until additional analyses will be available. The sponsor committee will consist of the CDC, Head of Clinical Development, Senior Advisors on Clinical Development, Head of Regulatory Affairs, Senior Statistician, Head of Biomarkers, Representative of Chemistry, Manufacturing Control, Head of Early Development and Translational Medicine, Head of Late Development, and other Senior Functions from the CDC. Additional factors such as data from other assays, manufacturability, and ease of administration will be taken into account to select the regimen for the expanded safety phase. More details will be described in the Statistical Analysis Plan.

Analysis 1 Year Post-first Vaccination

This analysis will include immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 12 months after the first dose of study vaccine for the last participant in this cohort will be included in the analysis. The blind will be maintained at the participant/site level.

Analysis 2 Years Post-first Vaccination (Groups 14 and 15)

This analysis will include immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 24 months after the first dose of study vaccine for the last participant in these 2 groups will be included in the analysis.

11.6.3. Expanded Safety Cohort (Cohort 3)

Primary Analysis

Primary analysis: analysis of safety and immunogenicity data up to Day 29 if a one-dose regimen is selected or up to Day 85 if a two-dose regimen is selected. This analysis should at least contain safety data collected up to the time of the Day 29 visit for the last participant in this cohort in case a one-dose regimen is selected and up to the time of the Day 85 visit for the last participant in this cohort in case a two-dose regimen is selected.[a] If the corresponding immunogenicity data are not available at the time of database lock, they will be analyzed at a later timepoint. This analysis will be performed on unblinded data. The blind will be maintained at the participant/site level.

Analysis 28 Days Post-Month 12 Booster

This analysis will include safety and immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 28 days after the Month 12 booster dose of study

[a] An unblinded person who is not part of the study team (or another independent party) will dictate which Day 85 samples should be analyzed. All Day 85 samples of the two-dose regimen will be included and some Day 85 samples of each of the other groups to ensure the blind at the level of the clinical immunology laboratory.

vaccine for the last participant in this cohort will be included in the analysis. The blind will be maintained at the participant/site level.

Analysis 28 Days Post-Month 24 Booster

This analysis will include safety and immunogenicity data, and will be performed on unblinded data. Data collected up to the time of the visit at 28 days after the Month 24 booster dose of study vaccine for the last participant in this cohort will be included in the analysis. The blind will be maintained at the participant/site level.

11.6.4. Final Analysis

The final analysis at the end of the study, to be conducted on a per-cohort basis, will include safety and immunogenicity data. Data collected up to the time of the last visit for the last participant will be included in the analysis. This analysis will be performed on unblinded data.

11.7. Additional Interim Analyses

Additional interim analyses (blinded or, if occurring after the primary analysis of the respective cohort, unblinded) may be performed during the study for the purpose of informing future vaccine development-related decisions in a timely manner, or upon health authority request. If they occur, these unplanned interim analyses may replace planned analyses, depending on the timing. The results will not influence the conduct of the study in terms of early termination or later safety or immunogenicity endpoint assessments, and will only be available to a selected group of sponsor personnel.

11.8. Data Review Committee

Data Review Committee

An internal DRC will be commissioned for this study. The DRC will consist of sponsor personnel not directly involved in the conduct of the study and who have expertise in clinical study conduct and vaccines, at least one medical expert in the relevant therapeutic area, at least one statistician, and a safety expert. The DRC will convene, according to their charter, to discuss any safety issues and any situation meeting a specific study pausing rule (Section 11.9). The PI(s) and SRP/S will inform the DRC of any AE of concern.

In addition, the DRC will review all safety data collected up to the time the final participant in the initial safety cohort (Cohort 1) had his/her Day 8 visit.

It will also be possible for the DRC to review unblinded immunogenicity data during the course of the study if this is deemed necessary for future vaccine development-related decisions. If this is the case, a biomarker representative (not involved in the conduct of the study) will be part of the DRC.

After these reviews, the DRC will make recommendations regarding the continuation of the study. Conclusions of the DRC will be communicated to the investigators, the IRB/IEC and the national regulatory authorities as appropriate. Details will be provided in a separate DRC charter.

If deemed necessary for safety review, the DRC may request randomization codes and review unblinded data, if applicable.

Safety data from the primary analyses and from the analyses at 28 days after the Month 12 booster dose (in Cohorts 1 and 3) and the Month 24 booster dose (Cohort 3 only) will be shared with the DRC.

11.9. Study Vaccination Pausing Rules

The PI(s) and the SRP/S will monitor the study vaccination pausing rules. If study vaccination is considered to raise significant safety concerns, further study vaccination of participants will be suspended until DRC review is carried out and subsequent communication between the sponsor and the investigator takes place.

The occurrence of any of the following events will lead to pause in further study vaccination and trigger a meeting of the DRC to discuss study suspension, adaptation or discontinuation of further vaccination. The list is only applicable for concerned AEs that occur up to 4 weeks after each vaccination and to concerned SAEs:

1. One or more participants per cohort experience an SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine; *OR*
2. One or more participants per cohort experience anaphylaxis clearly not attributable to other causes than vaccination with any study vaccine; *OR*
3. Two or more participants per cohort experience a Grade 3 or 4 unsolicited AE of the same type, determined to be related to study vaccine, that persists for 72 hours or longer; *OR*
4. Two or more participants per cohort experience a Grade 3 or 4 solicited systemic AE of the same type, determined to be related to study vaccine, that persists for 72 hours or longer; *OR*
5. Two or more participants per cohort (in Cohorts 1 and 2 only) experience a persistent (upon repeat testing) Grade 3 or 4 laboratory abnormality related to the same laboratory parameter and considered related to study vaccine, that persists for 72 hours or longer; *OR*
6. Death of any participant, considered related to any study vaccine or if the causal relationship to study vaccine cannot be excluded.

   Note: All cases of death will be sent to the DRC. Upon their review, the DRC will decide whether a study pause is required.

After the first DRC meeting triggered by the occurrence of a given pausing rule, the DRC will convene thereafter for each additional participant meeting that pausing rule.

The DRC will review blinded data first, but is entitled to and has the right to require submission of unblinded data if deemed necessary.

To enable prompt response to a situation that would trigger pausing rule 3, 4 or 5, the investigator should update the eCRF with information on any Grade 3 or 4 AE on the same day that the AE is reported.

Also, the investigator should notify the sponsor's medical monitor (and fax/email the SAE Form to Global Medical Safety Operations, if applicable), immediately and no later than 24 hours after becoming aware of any related AE of Grade 3 or above (and update the eCRF with relevant information on the same day the AE information is collected). A thorough analysis of all Grade 3 cases will be carried out by the sponsor's medical monitor, irrespective of whether the criteria for pausing the study are met. Based on the pausing criteria, the sponsor's medical monitor will then decide whether a study pause is warranted. All sites will be notified immediately in the event of a study pause. The sponsor's medical monitor is responsible for the immediate notification of the DRC and coordination of a DRC meeting in the event of a study pause.

Vaccinations for an individual participant may be suspended for safety concerns other than those described in the pausing criteria, at the discretion of the investigator if he/she feels the participant's safety may be threatened. The sponsor's medical monitor or the PI(s) (upon consultation with the sponsor's medical monitor) may initiate a DRC review for any single event or combination of events which, in their professional opinion, could jeopardize the safety of the participants or the reliability of the data.

Vaccinations for the study may be suspended for safety concerns other than those described above, or before pausing rules are met, if, in the judgment of the DRC, participant safety may be threatened.

Resumption of vaccinations will start only upon receipt by the site of written recommendations by the DRC. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. These communications from the DRC will be forwarded by the investigator to the IRB/IEC and by the sponsor to the relevant health authorities according to local standards and regulations.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are pre-defined local (at the injection site) and systemic events for which participants are specifically questioned and which are noted by participants in their diary (see Section 9.1.1).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which participants are specifically not questioned in the participant diary.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the vaccines used in this study. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Council for Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs, whether serious or non-serious, related to the study procedures or non-investigational (concomitant) Janssen products from ICF signature onwards. All other non-serious AEs and special reporting situations will be reported from each vaccination through the following 28 days on the Adverse Event eCRF page[a] (see Section 12.3.1, All Adverse Events, for time of last AE recording). All other serious AEs will be reported from the first vaccination onwards. Clinically relevant medical events, occurring between ICF signature and time of first vaccination, are collected on the medical history eCRF page as pre-existing conditions. During the long-term follow-up phase for participants from Groups 14 and 15 in Cohort 2, only SAEs related to study vaccine, study procedures (ie, blood draws), or non-investigational (concomitant) Janssen products, and all AEs leading to discontinuation will be collected.

Note: For all cohorts, AE reporting starts from Day 1 onwards. Clinically relevant medical events before the vaccination on Day 1 should be reported as medical history.

[a] AEs that start more than 28 days after a vaccination, but that are still present at the time of the next vaccination will also be recorded.

Any RTI that is not due to RSV infection will be reported as an AE if it occurs between the time of any vaccination through the following 28 days. Any RTI recorded as an AE in the eCRF will be excluded from any AE analysis if the central laboratory RT-PCR is subsequently found to be positive for RSV. RTIs arising from RSV infection will not be reported as (S)AEs in the Clinical Study Report as they are endpoints of the study but will be tabulated separately.

Serious Adverse Event

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

* Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the vaccine and the event (eg, death from anaphylaxis), the event must be reported as a suspected unexpected serious adverse reaction (SUSAR) by the sponsor to health authorities and by the investigator to the IRB/IEC according to regulatory and local requirements.

Any RTI fulfilling the criteria of an SAE will be reported as such during the entire study period if RT-PCR indicates it is not an RSV-RTI. If the RT-PCR is positive for RSV the event should not be reported as an SAE. If RT-PCR information is not available within 24 hours of knowledge of the event, the event will be reported as an SAE, but will be subsequently downgraded from SAE status if it later turns out to be RT-PCR positive for RSV.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.RSV.preF and RSV preF protein, expectedness of an AE will be determined by whether or not it is listed in the respective Investigator's Brochure.[17,18]

Adverse Event Associated With the Use of Vaccine

An AE is considered associated with the use of the vaccines if the attribution is related by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Every effort should be made by the investigator to explain any AE and assess its potential causal relationship, ie, to administration of the vaccine or to alternative causes (eg, natural history of the underlying diseases, concomitant therapy). This applies to all AEs (serious or non-serious).

Causality of AEs should be assessed by the investigator based on the following:

Related: there is suspicion that there is a relationship between the vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the vaccine contributed to the AE.

Unrelated: there is no suspicion that there is a relationship between the vaccine and the AE; there are other more likely causes and administration of the vaccine is not suspected to have contributed to the AE.

By definition, all solicited AEs at the injection site (local) will be considered related to vaccine administration.

12.1.3. Severity Criteria

All AEs and laboratory data reported as AEs will be coded for severity using the toxicity grading table in Attachment 1. *Note*: Laboratory values within central laboratory normal ranges (even if within a toxicity grade range), or laboratory values outside normal ranges that are not clinically significant in the judgment of the investigator, should not be recorded as AEs.

For AEs not identified in the toxicity grading table, the following guidelines will be applied:

Mild (Grade 1):	Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
Moderate (Grade 2):	Sufficient discomfort is present to cause interference with normal activity.
Severe (Grade 3):	Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.
Potentially life-threatening (Grade 4):	Symptoms causing inability to perform basic self-care functions, *OR* Medical or operative intervention indicated to prevent permanent impairment, persistent disability.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

The toxicity grading scale used for laboratory assessments is based on the FDA toxicity grading table (see Attachment 1), consistent with the assessment grading used throughout the protocol. If a laboratory value falls within the grading as specified in the FDA table, but also within the laboratory normal limits, the value is considered as normal. For hemoglobin, both the actual value and the change from reference will be graded.

The severity of solicited AEs will be graded in the diary by the participant based on the severity assessment provided in the diary and then verified by the investigator using the FDA toxicity grading table (see Attachment 1).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study vaccine that may require expedited reporting or safety evaluation include, but are not limited to:

- Suspected abuse/misuse of a sponsor study vaccine
- Accidental or occupational exposure to a sponsor study vaccine
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study vaccine, eg, name confusion)
- Exposure to a sponsor study vaccine from breast-feeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, that are related to study-related procedures or that are related to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated ICF is obtained onwards.

All other AEs and special reporting situations will be reported until 28 days (including relevant visit window, if applicable) after first dose of vaccine and thereafter, pre-dose on the vaccination day, and for 28 days (including relevant visit window, if applicable) following each subsequent vaccination. Unsolicited AEs with the onset date outside the time frame defined above (>28 days after previous vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded on the eCRF AE page.

All SAEs and AEs leading to discontinuation from the study/vaccination (regardless of the causal relationship) are to be reported from the moment of first vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up.

Clinically relevant medical events occurring between ICF signature and date of first vaccination will be collected on the Medical History eCRF page as pre-existing conditions.

Solicited AEs will be recorded by each participant in the participant diary for 7 days after each vaccination. The investigator will review each participant's diary at the subsequent in-clinic visit and discuss the information from the diary with the participant. The diary information will be transcribed by the study-site personnel in the diary forms in the eCRF.

The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

The investigator will monitor and check the study data, including all AE and clinical laboratory data, as they become available and will make determinations regarding the severity of the adverse experiences and their relation to vaccine. All AEs will be deemed related to vaccine or not related to vaccine, according to Section 12.1.2.

The investigator must review both post-injection reactogenicity and other AEs to insure the prompt and complete identification of all events that require expedited reporting as SAEs, invoke pausing rules or are other serious and unexpected events.

All AEs, regardless of seriousness, severity, or presumed relationship to the vaccine, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to the vaccine. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

Each participant will be provided with a "wallet (study) card" and instructed to carry this card for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

SAEs related to the study procedures or non-investigational (concomitant) Janssen products will be reported from ICF signature throughout the rest of the study. All other SAEs will be reported from first vaccination throughout the rest of the study.

SAEs must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event. During the long-term follow-up phase for participants from Groups 14 and 15 in Cohort 2, only SAEs related to study vaccine, study procedures (ie, blood draws), or non-investigational (concomitant) Janssen products, and all AEs leading to discontinuation will be collected.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the vaccine or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or healthcare practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or an AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). *Note*: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered as SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study during the entire study period, whether or not the event is expected or associated with the vaccine, is considered an SAE and must be reported.

12.3.3. Pregnancy

All initial reports of pregnancy in female participants and in partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form.

Pregnancies in partners of male participants included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and immunogenicity of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (see Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. VACCINE INFORMATION

14.1. Physical Description of the Vaccines

A human replication-incompetent adenovirus-vectored vaccine candidate and RSV preF protein, manufactured and provided under the responsibility of the sponsor, will be assessed in this study:

Ad26.RSV.preF (JNJ-64400141)

Ad26.RSV.preF is a replication-incompetent Ad26 containing a DNA transgene that encodes the pre-fusion conformation-stabilized F protein derived from the RSV A2 strain.

For this study, Ad26.RSV.preF will be formulated as a solution for intramuscular injection and will be supplied as a frozen liquid to be thawed prior to use. Ad26.RSV.preF will be supplied in single-use vials (2×10^{11} vp/mL). Refer to the Investigational Product Preparation Instructions for details on dosing preparation.

Refer to the Investigator's Brochure for details of the components of Ad26.RSV.preF and a list of excipients.[18]

RSV preF protein (JNJ-64213175)

RSV preF protein is a pre-fusion conformation-stabilized F protein derived from the RSV A2 strain.

For this study, RSV preF protein will be formulated as a solution for intramuscular injection. RSV preF protein will be supplied in a single-use vial. Refer to the Investigational Product Preparation Instructions for details on dosing preparation.

Refer to the Investigator's Brochure for details of the components of RSV preF protein and a list of excipients.[17]

Note: RSV preF protein clinical trial material will be labelled as "RSV-F Vaccine".

Placebo

Placebo for Ad26.RSV.preF and RSV preF protein will be supplied as sterile saline for intramuscular injection in vials.

14.2. Packaging and Labelling

Vaccines will be manufactured and packaged in accordance with Current Good Manufacturing Practice. Vaccines will be packaged and labeled under the responsibility of the sponsor. Vaccine labels will contain information to meet the applicable regulatory requirements.

No vaccine can be repacked or relabeled without prior approval from the sponsor.

Further details for vaccine packaging and labeling can be found in the Investigational Product Preparation Instructions.

14.3. Storage and Handling

Vaccines must be stored in a secured location under controlled temperature with no access for unauthorized personnel. The study refrigerator/freezer must be equipped with a continuous temperature monitor and alarm, and with back-up power systems. If a vaccine is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected vaccine can be used or will be replaced. The affected vaccine must be quarantined and not used until further instruction from the sponsor is received.

The vaccines will be prepared by the unblinded site pharmacist, or other qualified individual and administered by a vaccine administrator.

Note: The unblinded pharmacist, or other qualified individual, may also perform administration of the vaccines, but will have no other study function following dosing.

Further details for vaccine storage, preparation, handling and stability can be found in the Investigational Product Preparation Instructions.

14.4. Vaccine Accountability

The investigator is responsible for ensuring that all vaccines received at the site is inventoried and accounted for throughout the study. All vaccines administered to the participant must be documented on the vaccine accountability form. All vaccines will be stored and disposed of according to the sponsor's instructions.

Vaccines must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused vaccines must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused vaccines will be documented on a vaccine return form. When the study site is an authorized destruction unit and vaccine supplies are destroyed on-site, this must also be documented on a vaccine return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for vaccine accountability purposes.

Vaccines should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Vaccines will be supplied only to participants participating in the study. Vaccines may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense vaccines from, nor store them at, any sites other than the study site agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for Ad26.RSV.preF[18]

- Investigator's Brochure for RSV preF protein[17]
- Investigational Product Preparation Instructions/Investigational Product Procedures Manual
- Laboratory Manual (including procedures for collection of nasal samples)
- Trial Center File
- IWRS Manual
- Electronic Data Capture (eDC) Manual/eCRF completion guidelines and randomization instructions
- Sample ICF
- Participant diaries
- Rulers
- Thermometers
- Nasal swab kits
- RTI Symptoms Forms
- Contact information page(s)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume drawn from each participant will not exceed the US Department of Health and Human Services Office for Human Research Protections, and FDA guidelines of 550 mL in any 8-week period.[36,37]

Risks Related to Vaccination

Participants may exhibit local signs/symptoms associated with vaccination, including erythema, swelling/induration, and pain/tenderness. These local reactions will be monitored, but generally are short-term and do not require treatment.

Participants may exhibit general signs/symptoms associated with vaccination, including fatigue, headache, myalgia, arthralgia, chills, nausea, and fever. These side effects will be monitored, but are generally short-term and do not require treatment.

Syncope can occur in association with administration of injectable vaccines. Syncope can be accompanied by falls. Procedures should be in place to avoid falling injury. If syncope develops, participants should be observed until the symptoms resolve.

Participants may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, hives or even difficulty breathing. Severe reactions, including anaphylaxis, are rare but can occur with any vaccine. Participants with a known allergy, or a history of anaphylaxis or other serious adverse reactions to vaccines or vaccine components (including any of the constituents of the vaccines) will be excluded from the study. Sites should have medical treatment available in case of severe allergic reactions following vaccine administration.

Risks Related to Adenoviral-vectored Vaccines

Safety data available from completed clinical studies in adults with other Ad26-vectored vaccine candidates, in which Ad26 with different inserts has been evaluated at dose levels ranging from 1×10^{9} vp to 1×10^{11} vp, indicate that no safety concerns would be anticipated from vaccination with Ad26.RSV.preF at doses of 5×10^{10} vp and 1×10^{11} vp.[14,15]

Local AEs (moderate injection site pain/tenderness, moderate to severe redness at the injection site) and systemic AEs (headache, chills, joint pain, muscle pain, tiredness/generally not feeling well/fatigue, fever) have been reported after vaccination with Ad26-vectored vaccines. In a few participants, transient laboratory abnormalities have been observed, including changes in neutrophils. Laboratory changes including decreased hemoglobin, decreased platelets, and moderate elevations in liver transaminases were observed that were not associated with any clinical findings and appear to be transient based on no reported persistent abnormalities in any of the participants.

For further details on the safety profiles of other Ad26-vectored vaccine candidates, see the Ad26.RSV.preF Investigator's Brochure.[18]

Risks Related to RSV preF Protein

This study will be the FIH study for RSV preF protein. No clinical data are available to date.

For the most comprehensive nonclinical information regarding RSV preF protein, refer to the latest version of the Investigator's Brochure for RSV preF protein.[17]

Risks from Blood Draws

Blood drawing may cause pain/tenderness, bruising, bleeding, lightheadedness, dizziness, vasovagal response, and, rarely, infection at the site where the blood is taken.

Risks from Collection of Nasal Samples

Collection of nasal samples may cause a nosebleed.

Participants with Immuno-suppression/Reduced Immune Response

Limited evidence indicates that inactivated vaccines (or non-replicating viral vaccines) generally have the same safety profile in immunocompromised patients and immunocompetent individuals. However, the magnitude, breadth, and persistence of the immune response to vaccination may be reduced or absent in immunocompromised persons. Participants with abnormal function of the immune system will be excluded from the study.

Concomitant Vaccination

Concomitant vaccination might have an influence on both the safety profile and immunogenicity of Ad26.RSV.preF and/or RSV preF protein. Likewise, Ad26.RSV.preF and/or RSV preF protein might have an influence on both the safety profile and immunogenicity of any concomitant vaccination. As a result, vaccination with live attenuated vaccines within 28 days of a vaccination in this study (ie, before and after) is prohibited. Other licensed vaccines (ie, not live: eg, influenza, tetanus, hepatitis A or B, or rabies) should be given at least 14 days before or 14 days after each study vaccination to avoid potential confusion of adverse reactions and potential immune interference. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the vaccines in this study.

Potential Benefits

Ad26.RSV.preF and RSV preF protein are under development for prophylaxis of RSV, however, vaccine efficacy has not yet been evaluated. There is no direct medical benefit to the participant for participation in this study. Although study participants may benefit from clinical testing and physical examination, they may receive no direct benefit from participation. Others may benefit from knowledge gained in this study that may aid in the development of an RSV vaccine.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments

- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- Investigator's Brochures (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure(s) and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the vaccine
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site

- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Additional informed consent for participants progressing to the long-term follow-up phase (participants in Groups 14 and 15 in Cohort 2) will be required. Information relevant to participating in the follow-up phase of the study will be provided to the participant in a timely manner, and written informed consent for participation in this phase will be obtained. Additional

informed consent will also be required for participants in Cohort 3 who will receive the Month 24 booster.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand Ad26.RSV.preF and RSV preF protein, to understand RSV, and to develop tests/assays related to Ad26.RSV.preF and RSV preF protein and RSV. The research may begin at any time during the study or the post-study storage period. Included are samples from participants who were screened but not randomized which may also be used to develop tests/assays related to Ad26.RSV.preF, RSV preF protein, and RSV.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (see Section 10.2).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of vaccines to the study site:

- Protocol and amendment(s), if any, signed and dated by the PI(s).
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a

member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the PI(s), where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all sub-investigators.
- Documentation of sub-investigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and date of birth. In cases where the participant is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a participant screening log, which reports on all participants who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and immunogenicity parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; vaccine

receipt/dispensing/return records; vaccine administration information; and date of study completion and reason for early discontinuation of vaccine or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The participant diary used to collect information regarding solicited events after vaccination will be considered source data. At the visits at 7 days after each vaccination, information from the participant diary will be reviewed by the investigator; diary information will be transcribed by study-site personnel into the eCRF as described in the eCRF Completion Guidelines.

An electronic source (eSource) system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

17.5. Case Report Form Completion

CRFs are prepared and provided by the sponsor for each participant in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg,

hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The end of the study will be the last participant's last visit 24 months after the first vaccination (Cohort 1 and Cohort 2 [Groups 11-13 and Groups 16-18]) or the last participant's last visit 36 months after the first vaccination (Cohort 2 [Groups 14-15] and Cohort 3). The study is considered completed with the last visit for the last participant participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study vaccine development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding Ad26.RSV.preF and RSV preF protein or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Ad26.RSV.preF and RSV preF protein, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per-protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multi-center) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish

information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multi-center study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multi-center study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multi-center study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

18. APPENDIX 1: GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

- When site visits are not possible due to local/national guidelines, sites should collect the assessments via telephone visits or home-based visits, if the participant allows. The actual visit date and the type of visit (ie, telephone or home-based visit) should be captured in the eCRF. Procedures that cannot be performed during a home-based visit (eg, clinical assessments, blood samples, nasal samples and physical examination), should be excluded. The missed procedures should be recorded as "missed due to COVID-19".
- When planning for vaccination visits, local/national or institutional guidelines will be followed. The study vaccine should be administered by an (unblinded) pharmacist or other

qualified individual at the study site. If this is not possible, a solution may be considered in consultation with the sponsor and taking into consideration participant safety. Of note, if a scheduled study vaccination is not possible at the scheduled visit time, the vaccination should occur within 3 weeks after the scheduled visit.

- A revised ICF arising from this amendment needs to be signed by the participants during a site visit or home-based visit, if the participant allows. When a site or home-based visit is not possible due to local/national guidelines, the participant can sign the paper ICF and mail the signed document to the site.

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Attachment 1: Toxicity Tables

Adapted from the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007).

A: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to Touch	Discomfort with Movement	Significant discomfort at rest	ER visit or Hospitalization
Erythema/redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever** (°C) Fever** (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg****	141 – 150	151 – 160	> 160	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) - mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate - breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.

** Oral body temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 and 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

**** Revised by the sponsor.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 gms/24 hours	4 - 5 stools or 400 - 800 gms/24 hours	6 or more watery stools or > 800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities	Sufficient discomfort is present to cause interference with normal activity	Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability

B: Tables for Laboratory Abnormalities

The grading scale used for laboratory assessments is based on the FDA Guidance document "Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". Any laboratory value shown as a "graded" value in the table that is within the central laboratory normal ranges will not be graded for severity or recorded as an AE. For hemoglobin, both the actual value and the change from reference will be graded. For the change from reference, the corresponding actual value should also be at least Grade 1.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4) **
Sodium - hyponatremia - mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium - hypernatremia - mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium - hyperkalemia - mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium - hypokalemia - mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose - hypoglycemia - mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose - hyperglycemia fasting - mg/dL	100 – 110	111 – 125	> 125	Insulin requirements or hyperosmolar coma
Random glucose - mg/dL	110 – 125	126 – 200	> 200	
Blood urea nitrogen BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine - mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium - hypocalcemia - mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium - hypercalcemia - mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium - hypomagnesemia - mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous - hypophosphatemia - mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK - mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin - Hypoalbuminemia - g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4) **
Total protein - hypoproteinemia - g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate - increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver function tests - ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin - when accompanied by any increase in liver function test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	--
Pancreatic enzymes - amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

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

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

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

Hematology *	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 (female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (male) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1,500	1,501 – 5,000	> 5,000	Hypereosinophilic
Platelets decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT - increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT - increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

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

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

INVESTIGATOR AGREEMENT

VAC18193 (JNJ-64400141)
Clinical Protocol VAC18193RSV1004 Amendment 6

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study vaccine, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Vaccines & Prevention B.V.

Signature: PPD PPD Reason: I am approving this document. Date: 2020.11.06 17:43:04 +01'00' Adobe Acrobat version: 11.0.20 Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 133
Approved, Date: 6 November 2020