Janssen Vaccines & Prevention B.V.

Clinical Protocol

A Randomized, Double-blind, Phase 1/2a Study to Evaluate the Safety, Tolerability and Immunogenicity of Ad26.RSV.preF in Adults 18 to 50 Years of Age and RSV-Seropositive Toddlers 12 to 24 Months of Age

Protocol VAC18194RSV2001; Phase 1/2a
Amendment 4

VAC18194 (Ad26.RSV.preF)

EudraCT NUMBER: 2017-001345-27

Status: Approved
Date: 18 April 2019
Prepared by: Janssen Vaccines & Prevention B.V.
EDMS number: EDMS-ERI-114933015, 14.0

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	06 July 2017
Amendment 1	29 August 2017
Amendment 1 / Finland-1	29 September 2017
Amendment 1 / UK-1	03 October 2017
Amendment 2	08 January 2018
Amendment 3	14 November 2018
Amendment 4	18 April 2019

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (Issued date: 18 April 2019)

The overall reason for the amendment: This protocol amendment is made to reduce the overall number of RSV-seropositive toddlers in the study from 48 to 36. The rationale for this reduction is as follows:

As of 18 April 2019, 35 seropositive toddlers have been enrolled in the current study (VAC18194RSV2001). The IDMC have reviewed available safety and immunogenicity data from the planned interim analysis, unblinded at the group level, when at least 24 toddlers had reached Day 29 or discontinued earlier. As enrollment was staggered over time, the analysis contained solicited and unsolicited AE data post-Dose 1 from 32 toddlers, of whom 30 toddlers already had post-Dose 2 data and 28 were in follow-up.

The IDMC concluded that the safety profile was acceptable and supported progression to the next study (VAC18194RSV2002) in RSV-seronegative toddlers aged 12 to 24 months in which subjects will receive half the dose of Ad26.RSV.preF used in the current study (ie, $2.5x10^{10}$ vp). In addition, blinded safety review by the sponsor of additional data since the IDMC review has not revealed any safety concerns. Study VAC18194RSV2002 has already been initiated; as of 18 April 2019, 6 seronegative toddlers have been enrolled and have received their first vaccination.

The reduction in the number of seropositive toddlers in the current study is supported by the expectation that there would be no difference in the local and systemic reactogenicity between seropositive and seronegative toddlers. The collection of safety data at the planned dose in seronegative toddlers in study VAC18194RSV2002 will therefore add to the overall safety database in this age group as planned. Furthermore, as RSV-seropositive toddlers are at limited to no risk of severe RSV disease, there would be limited value in continuation of the study.

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

Rationale: As indicated above, the number of RSV-seropositive toddlers in this study is reduced from 48 to 36.

Synopsis: Overview of Study Design; Sample Size Determination
3.1 Overview of Study Design
11.2 Sample Size Determination

Amendment 3 (Issued date: 14 November 2018)

The overall reason for the amendment: To potentially aid recruitment in the current study, this protocol amendment is made to allow enrollment of RSV seropositive toddlers who have been screened for a different clinical study of the sponsor (ie, VAC18194RSV2002) if RSV seropositivity was determined using the RSV EIA or virus neutralization assay.

Other updates and clarifications are made as specified below.

The table below gives an overview of the rationale for each change and all affected sections
Rationale: Added clarification that RSV-seropositive subjects can be enrolled if their serostatus has been confirmed by either RSV EIA or virus neutralization assay from a different study of the sponsor.
Synopsis: Other Evaluations – RSV Infection *Time and Events Schedule* *4.1.2 Inclusion Criteria – Pediatric Subjects* *9.1.4.1 Screening Phase: Days –42 to 1* *9.2.2 Other Evaluations – RSV Infection*
Rationale: Change of EIA cut-off criterion for seropositivity to titers >10 EIA units.
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Rationale: Update of preclinical information.
1.1 Background
Rationale: Update of clinical information.
1.1 Background
Rationale: Clarification of wording of Exclusion Criterion 23 for pediatric subjects.
4.2.2 Exclusion Criteria – Pediatric Subjects
Rationale: Clarification of the exclusion criterion for known allergies at screening refers to vaccines or vaccine components, but not to egg allergies.
4.2.2 Exclusion Criteria – Pediatric Subjects
Rationale: Clarification that the exclusion criterion for urticaria, eczema and atopic dermatitis relates to a moderate to severe history of these illnesses.
4.2.2 Exclusion Criteria – Pediatric Subjects
Rationale: Clarification that telephone calls to subjects for RTI monitoring after the first dose will be made during both the active and safety follow-up phases.
Synopsis: Overview of Study Design *Time and Events Schedule* *3.1 Overview of Study Design* *9.1.4.3 Safety Follow-up Phase*
Rationale: Clarification that during each 28-day post-vaccination period, all RTIs will be reported and that during the RSV season, but outside the 28-day post-vaccination period, only RTIs for which a combination of respiratory symptoms develop, will be reported.
Synopsis: RTI – Procedures Specific to Cohort 1; Other Evaluations – RSV Infection; Safety Evaluations *Time and Events Schedule* *3.2 RTI – Procedures Specific to Cohort 1* *3.4.5 Overall Benefit/Risk Assessment* *9.2.2 Other Evaluations – RSV Infection*
Rationale: Clarification that in the event of an ongoing AE or other situation precluding subject vaccination within 10 days, subjects may be vaccinated beyond the 10-day window at the discretion of the sponsor.

Time and Events Schedule
3.4.5 Overall Benefit/Risk Assessment
9.1.3.2.1 Vaccination (Days 1 and 29)
9.1.4.2.1 Vaccination (Days 1 and 29)
10.3 Contraindications to Vaccination

Rationale: Clarification that any subject who receives study vaccine beyond the Day 29 window specified in the Time and Events Schedule would not be included in the per-protocol immunogenicity analyses.

11.1 Analysis Sets

Rationale: For operational reasons, removal of the requirement for surveillance of primary care physicians, and/or hospitals' urgent care facilities to monitor for subjects seeking medical attention for an RTI.

3.4.5 Overall Benefit/Risk Assessment

Rationale: Specification that the 1 year post-first vaccination safety follow-up telephone call should take place within a ±14 days visit window.

Time and Events Schedule
9.1.2 Visit Windows

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

Amendment 2 (Issued date: 08 January 2018)

The overall reason for the amendment:
This amendment is made to increase the number of seropositive toddlers by 12 to generate additional safety data, to specify post-vaccination monitoring time and to correct minor changes, clarifications and corrections made throughout the protocol.

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

Rationale: To add 12 extra seropositive toddlers to Cohort 1.

Synopsis
3.1 Overview of Study Design
11.2 Sample Size Determination

Rationale: Removal of Attachment 3 containing information for sites in the United Kingdom (removal already effected via prior separate country-specific amendments: Clinical Trial Protocol Amendment 1 / Finland 1 – 29 September 2017 and Clinical Trial Protocol Amendment 1 / UK 1 – 03 October 2017).

3.4.2 Potential Benefits
Attachment 3

Rationale: Specification of monitoring time to be a minimum of 30 or 60 minutes post-vaccination in accordance with local approvals (change already effected via prior separate country specific amendment: Clinical Trial Protocol Amendment 1 / Finland 1 – 29 September 2017).

Synopsis
Time and Events Schedule
3.1 Overview of Study Design
3.4.5 Overall Benefit/Risk Assessment
9.1.3.2.1 Vaccination (Days 1 and 29)
9.1.4.2.1 Vaccination (Days 1 and 29)
9.2.3 Safety Evaluations

Rationale: Clarification that a least 5 toddlers in the active group are to have received first dose in a clinic setting and to have completed Visit 3 with no safety concerns before moving to vaccination of study subjects in a non-clinic setting.

Synopsis
Time and Events Schedule
3.1 Overview of Study Design
9.1.4 Screening and Study Visits – Cohort 1 (Seropositive Toddlers)

Rationale: Deletion of the wording "In addition, for a selection of tables, tabulations per dose by vaccine will be provided.", as the per dose analysis will no longer be carried out.

Synopsis
11.7 Safety Analysis

Rationale: Clarification that the unblinded pharmacist or other qualified individual will have no other study function from randomization onwards

Synopsis
3.1 Overview of Study Design
5 Study Vaccine Allocation and Blinding
6 Dosage and Administration
14.3 Storage and Handling

Rationale: To specify that the blood volume drawn for serology testing will not exceed 15mL and adjust total blood volume that will be collected.

Time and Events Schedule
9.1.1 Overview

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

Amendment 1 / UK-1 (Issued date: 03 October 2017)

The overall reason for the amendment:
This amendment is made to remove the offer of vaccination with a locally marketed vaccine with proven benefit for pediatric subjects for sites in the United Kingdom as this provision was not endorsed by the UK Central Ethics Committee.

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

Rationale: As above.

3.4.2 Potential Benefits
Attachment 3

Amendment 1 / Finland-1 (Issued date: 29 September 2017)

The overall reason for the amendment:
This amendment is to clarify that, according to the requirements of the local ethics committee in Finland, the immediate post-vaccination observation period for toddlers in Cohort 1 should be a minimum of 60 minutes.

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

Rationale: To clarify that the immediate post-vaccination observation period for toddlers in Cohort 1 should be a minimum of 60 minutes.

Synopsis
Time and Events Schedule
3.1 Overview of Study Design
3.4.5 Overall Risk/Benefit Assessment
9.1.4.2.1 Vaccination (Days 1 and 29)
9.2.3 Safety Evaluations

Rationale: Removal of Attachment 3 containing information for sites in the United Kingdom.

3.4.2 Potential Benefits
Attachment 3

Amendment 1 (Issued date: 29 August 2017)

The overall reason for the amendment:
This amendment is made to clarify that the responsibility to break the blind for emergency reasons rests solely with the investigator. Additionally, the following changes were made: the definition of probable RSV infection was removed; a reference to the Study Training Manual was deleted; the time periods for collections of concomitant and prestudy medications were clarified; stipulation that subjects should both measure and grade any induration/ swelling in the subject diary was added; addition of virus neutralization assay as an alternative assay for assessment of RSV seropositivity at screening; and other minor inconsistencies were corrected.

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

Rationale: To clarify that the responsibility to break the blind for emergency reasons rests solely with the investigator.

5 Study Vaccination Allocation and Blinding

Rationale: The definition of probable RSV infection was dependent on the results of local laboratory testing, and as only results from the central laboratory would be considered as definitive, the definition of probable RSV infection has been removed.

Synopsis
3.2 RTI – Procedures Specific to Cohort 1

Rationale: Removal of reference to the Study Training Manual as this document is no longer produced.

9.1.1 Study Evaluations - Overview

Rationale: Clarification that collection of concomitant medications will be from the time of each vaccination until 28 days after each vaccination, and that collection of pre-study therapies will be during the period up to 30 days prior to vaccination.

Synopsis
Time and Events Schedule
3.1 Overview of Study Design
8 Pre-study and Concomitant Therapy

Rationale: Addition of virus neutralization assay as an alternative assay for assessment of RSV seropositivity at screening.

Synopsis
9.2.2 Other Evaluations – RSV Infection

Rationale: Clarification that the solicited local AE induration/swelling should be both measured and graded by subjects in their diaries.

Synopsis
9.2.3 Safety Evaluations

SYNOPSIS

A Randomized, Double-blind, Phase 1/2a Study to Evaluate the Safety, Tolerability and Immunogenicity of Ad26.RSV.preF in Adults 18 to 50 Years of Age and RSV-Seropositive Toddlers 12 to 24 Months of Age

The adenovirus-vectored vaccine candidate assessed in this study is:

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

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objectives

- To assess the safety and tolerability of an intramuscular regimen of two doses of $1x10^{11}$ viral particles (vp) of Ad26.RSV.preF in adults aged 18 to 50 years.
- To assess the safety and tolerability of an intramuscular regimen of two doses of $5x10^{10}$ vp of Ad26.RSV.preF in RSV-seropositive toddlers aged 12 to 24 months.

Secondary Objective

- To assess the humoral and cellular immune responses as measured by virus neutralization assay, F-protein binding antibodies (pre-F and post-F) and intracellular cytokine staining (ICS; to assess T-helper [Th]1/Th2 subtyping).

Exploratory Objectives

- To further assess the humoral and cellular immune responses elicited by Ad26.RSV.preF. The assays to be used may 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), evaluation of the cellular immune response (interferon gamma [IFNγ] enzyme-linked immunospot [ELISpot] assay) and functional and memory immune response (by ICS), and cytokine profiles of RSV F-protein peptide-stimulated peripheral blood mononuclear cell (PBMC) supernatant.
- To assess RSV infection rates in Ad26.RSV.preF and placebo subjects.
- To monitor for severe RSV-lower respiratory tract infection (LRTI) in Cohort 1 (RSV-seropositive toddlers aged 12 to 24 months).
- To assess symptoms of respiratory illness via the respiratory tract infection (RTI) symptoms form.

Primary Endpoints – Safety and Tolerability

- Solicited local and systemic adverse events (AEs) for 7 days after each vaccination.
- Unsolicited AEs for 28 days after each vaccination (ie, from informed consent form [ICF] signature through the following 28 days post-first vaccination, and for subsequent vaccinations from time of vaccination through the following 28 days).

- Serious adverse events (SAEs) from ICF signature to the end of the study.

Secondary Endpoints – Immune Responses

The analysis of the immunogenicity of vaccine regimens will include the characterization of humoral as well as cellular responses. The focus of the immunogenicity analysis is on virus neutralizing antibodies (VNAs), F-protein antibodies (pre-F and/or post-F) and Th1/Th2 cytokine profile response.

Humoral Immune Response

- RSV neutralization A strain

  Analysis of RSV A neutralizing antibodies.

- RSV F-protein enzyme-linked immunosorbent assay (ELISA; pre- and/or post-fusion F antibodies)

  Analysis of antibodies binding to RSV F protein in post-fusion and pre-fusion form.

Cell-mediated Immune Response

- Intracellular cytokine staining or cytokine analysis*

  Analysis of CD4 and CD8 T-cell subsets and their cytokine expression patterns will be determined by flow cytometry after RSV F-protein peptide stimulation (including, but not limited to CD4/CD8, interleukin-2 [IL-2], IFNγ, tumor necrosis factor alpha (TNFα) and Th1/Th2 subtyping).

  **Cytokine analysis for Th1/Th2 profiling will be done in cases where no ICS data can be generated due to insufficient number of PBMCs for ICS assay (see exploratory endpoints below for description).*

Exploratory Endpoints – Immune Responses

Additional exploratory analyses may be performed to investigate vaccine-elicited immune responses further. These may include, but are not limited to, the following assays:

Humoral Immune Response

- RSV cross-neutralization of B and/or other A strain(s)
- F-protein antibody specificity characterization
- Adenovirus neutralization assay
- Functional and molecular antibody characterization

Cell-mediated Immune Response

- IFNγ ELISpot assay
- Cytokine analysis

Exploratory Endpoints – RSV Infection

- For Cohort 1 only, RSV infection confirmed by either reverse transcriptase polymerase chain reaction (RT-PCR), or by serology for, but not limited to, protein G and/or N if no RT-PCR is available. To detect asymptomatic RSV infections, a fold increase will be applied to call a subject

seropositive to G and/or N ELISA (or F in case of placebo subjects). Fold increases for RSV infection will be determined based on the (suspected) infection and the convalescent blood samples.

- In Cohort 1 throughout the study:
  - Severe RSV-LRTI: for subjects in Cohort 1, severe RSV-LRTI will be defined as the presence of severe LRTI as assessed by the clinical endpoint committee (CEC), and a positive assessment for RSV.
  - RSV medically-attended respiratory tract infection (MA-RTI): all subjects with RSV-RTI that is medically attended, ie, when the subject's parent/legal guardian seeks medical attention outside of normal study procedures, including health care professional's visit to the home, clinic visit, emergency room attendance, and hospital admission. (*Note*: medical attention outside normal study procedures will as much as possible also be captured on the RSV Symptoms Form.)

  Note: Data on these 2 exploratory endpoints will be collected to assess the feasibility of, and gain expertise in the collection of such events for future studies.

Hypothesis

No formal statistical hypothesis is planned. The study will evaluate whether Ad26.RSV.preF is safe, well-tolerated and immunogenic in adults and RSV-seropositive toddlers.

OVERVIEW OF STUDY DESIGN

In this document, unless otherwise specified, any reference to activities to be performed by the subject refers to adult subjects or the parent/legal guardian for pediatric subjects.

This is a multi-center, randomized, double-blind[a], Phase 1/2a study, to be conducted in 12 male and female adults aged ≥18 to ≤50 years and 36 male and female toddlers aged ≥12 to ≤24 months of age, seropositive for RSV within 42 days prior to dosing.

Subjects will be enrolled into sequential age cohorts:

- 18 to 50 year-old adults, into **Cohort 0**
- 12 to 24 month-old seropositive toddlers, into **Cohort 1**

In Cohort 0, subjects will be randomized 2:1 to receive either Ad26/Ad26 ($1x10^{11}$ vp in 0.5 mL) or placebo/placebo (saline), and in Cohort 1, subjects will be randomized 2:1 to receive either Ad26/Ad26 ($5x10^{10}$ vp in 0.25 mL) or placebo/placebo (Table 1).

The study will have three phases: a **screening phase**, an **active phase** and a **safety follow-up phase** through 1 year after the first dose. The durations of the respective phases are as follows:

[a] The administrator of the vaccine may be unblinded but will not participate in any other study evaluation from randomization onwards. The site staff or qualified professional staff who will do the observation and the subjects will be blinded.

Phase	**Cohort 0**	**Cohort 1**
Screening:	up to 4 weeks	up to 6 weeks
Active:	30 weeks • dosing on Days 1 and 29 • safety follow-up through 6 months post-final dose • immunogenicity at: ➢ pre-Dose 1 (Day 1) ➢ pre-Dose 2 (Day 29) ➢ 28 days post-Dose 2 (Day 57) ➢ 6 months post-Dose 2 (Day 211/Week 30)	30 weeks • dosing on Days 1 and 29 • safety follow-up through 6 months post-final dose • immunogenicity at: ➢ pre-Dose 1 (Day 1) ➢ pre-Dose 2 (Day 29) ➢ 28 days post-Dose 2 (Day 57) ➢ 6 months post-Dose 2 (Day 211/Week 30)
Safety follow-up:	through 1 year after the first dose	through 1 year after the first dose

The end of the active phase will be when the last subject completes the visit at 6 months after the final dose. The end of the study will be the last subject's last visit (by telephone) at the end of the safety follow-up phase.

An independent data monitoring committee (IDMC) will be established for this study to evaluate safety and tolerability data on a regular basis. An independent blinded CEC will be established for this study to assess any suspected case of severe LRTI in pediatric subjects.

First-dose Safety

For Cohort 0, 48-hour and 7-day safety will be monitored by the Principal Investigator(s) (PI[s]) and the Study Responsible Physician(s) (SRP[s])[a]; for Cohort 1, 48-hour safety will be monitored by the PI(s) and the SRP(s), and 7-day safety will be monitored by the IDMC. In the event of a significant safety finding, the IDMC will be consulted.

Note: At least 5 toddlers in the active group are to have received first dose in a clinic setting and to have completed Visit 3 with no safety concerns before moving to vaccination of study subjects in a non-clinic setting (safety information of the first 5 active toddlers will be monitored by the PI(s)/SRP(s) through Visit 3, and escalated to the IDMC in the event of a safety signal).

Enrollment will be staggered to allow safety assessments to be made 7 days after the first dose in all 12 adults in Cohort 0 before enrolling and dosing seropositive toddlers in Cohort 1. Additionally, safety assessments will be made 7 days after the first dose in the first 12 seropositive toddlers (8 actives and 4 placebos) in Cohort 1 before enrolling and dosing the remaining seropositive toddlers. These safety assessments are described more fully in Section 3.1.

In addition, 48-hour safety will be checked after dosing sentinel subjects in both cohorts (2 subjects [1 active and 1 placebo] in each cohort).

Second-dose Safety

Post-second dose 48-hour and 7-day safety assessments will be monitored by the PI(s) and the SRP(s).

Administration of the second dose will also be staggered to allow safety assessments to be made 7 days after the second dose in all 12 adults in Cohort 0 before administering the second dose to seropositive toddlers in Cohort 1. Likewise, safety assessments will be made 7 days after the second dose in the first

[a] The safety of Ad26.RSV.preF in elderly subjects at $5x10^{10}$ vp and $1x10^{11}$ vp will have been established in study VAC18193RSV1003 prior to initiation of the current study; the purpose of dosing Ad26.RSV.preF in Cohort 0 in the current study is as a safety check for the new drug product formulation buffer, and consequently only PI and SRP review of Cohort 0 safety data is planned prior to dosing seropositive toddlers in Cohort 1.

12 seropositive toddlers in Cohort 1 before administering the second dose to the remaining seropositive toddlers in Cohort 1. These safety assessments are described more fully in Section 3.1. In addition, 48-hour safety will be checked after dosing sentinel subjects in both cohorts.

The sponsor will monitor post-vaccination safety on an ongoing basis by reviewing blinded safety data.

Table 1: Study Design

Cohort	Group	N	Day 1	Day 29/Week 4
ADULTS 18 to 50 years				
0	Group 1	8	Ad26.RSV.preF ($1x10^{11}$ vp)	Ad26.RSV.preF ($1x10^{11}$ vp)
	Group 2	4	Placebo	Placebo
TODDLERS 12 to 24 months: RSV seropositive				
1	Group 3	24	Ad26.RSV.preF ($5x10^{10}$ vp)	Ad26.RSV.preF ($5x10^{10}$ vp)
	Group 4	12	Placebo	Placebo

After each vaccination, all subjects will be closely observed for a minimum of 30 minutes post-vaccination, or a minimum of 60 minutes post-vaccination according to local approvals, to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs and vital signs will be documented by study-site personnel following this observation period. Subjects[a] will be given a thermometer, ruler and daily assessment (subject) diary with instructions for the proper recording of events. Each subject will record solicited local (at injection site) and systemic AEs and body temperatures, beginning on the evening of each study vaccine dosing day and on a daily basis for the following 7 days. Temperatures[b] should be taken at approximately the same time each day, preferably in the evening[c] and, for pediatric subjects, additionally whenever the child feels warm. Study-site personnel will collect and review subject diary information and confirm the entries at subsequent site visits.

Unsolicited AEs will be collected from the time of informed consent through 28 days after each dose. For both cohorts, all SAEs will be collected from ICF signature to the end of the study. 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 of these periods when associated with any SAE.

Blood will be collected for immunogenicity assessments as follows:

- Cohort 0: pre-vaccination for first and second doses, and at 28 days and 6 months after the second dose
- Cohort 1: pre-vaccination for first and second doses, and at 28 days and 6 months after the second dose

For Cohort 1, a blood sample will be taken for RSV serology at screening[d]; the baseline sample for immunogenicity may either be drawn at the same screening visit or pre-dose on Day 1, at the discretion of the investigator.

[a] In Cohort 1, activities to be performed by the subject refers to the parent/legal guardian.

[b] Recommended orally for adult subjects; rectally or axillary for pediatric subjects (actual routes to be recorded in the eCRF).

[c] All Day 8 post-vaccination diary assessments, including temperature measurements, may be collected earlier to coincide with the corresponding clinic visit.

[d] 0.5 mL of blood for serostatus assessment can be collected by venous blood sample or fingerstick, at the discretion of the investigator. If 0.5 mL is collected at screening, baseline blood draw for immunogenicity should be on Day 1.

Safety Follow-up

Parents/legal guardians of subjects in Cohort 1 will be contacted by telephone (or clinic visit) through 1 year after the first dose (including during the active phase and safety follow-up phase: every 30 days ± 7 days outside the RSV season, but every 14 days ± 3 days in season). During each 28-day post-vaccination period, calls will remind parents/legal guardians to contact the site in the event their child develops an RTI. During the RSV season, but outside the 28-day post-vaccination period, calls will remind parents/legal guardians to contact the site in the event their child develops a combination of symptoms of respiratory infection (persistent [>48 hours] clinical symptoms of rhinitis [sneezing or runny nose or congestion] and persistence [>24 hours] of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite). These calls will also check for any SAEs and associated concomitant medications since the previous visit or telephone contact.

RTI – PROCEDURES SPECIFIC TO COHORT 1

Monitoring of RTIs will take place during each 28-day post-vaccination period, and additionally during the RSV season after the first dose (even if it falls outside of the 28-day post-vaccination period). Monitoring for MA-RTIs and severe LRTIs will take place during the whole study period.

During each 28-day post-vaccination period, all RTIs will be reported, nasal turbinate samples will be collected as soon as possible after the onset of respiratory symptoms, and signs and symptoms will be recorded by the attending health care professional using the RTI Symptoms Form.

If, during the RSV season, but outside the 28-day post-vaccination period, a subject shows persistent (>48 hours) clinical symptoms of rhinitis (sneezing or runny nose or congestion) and persistence (>24 hours) of one or more of the following [30,32,41,44]: cough, abnormal breathing, fever, lethargy or decreased appetite, the study site should be notified. Nasal turbinate samples will be collected as soon as possible after the onset of these combined respiratory symptoms[a]. When nasal turbinate samples are collected, the attending health care professional will record signs and symptoms of the RTI using the RTI Symptoms Form.

Nasal turbinate samples will not be collected if less than 7 days after the previous sample collection.

Outside of the RSV season, nasal turbinate samples will only be collected from subjects with MA-RTIs or severe LRTIs.

Throughout the study, nasal turbinate samples will be collected from any subject with a MA-RTI or severe LRTI.

The criteria used to assess potential cases of RSV infection in subjects from Cohort 1 will be as follows:

- Suspected RSV infection: subject has persistent (>48 hours) clinical symptoms of rhinitis (sneezing or runny nose or congestion) and persistence (>24 hours) of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite. Occurrence of this combination of symptoms in any subject would trigger collection of a nasal turbinate sample.
- Confirmed RSV infection: subject with suspected RSV infection and positive for RSV on the basis of RT-PCR conducted centrally.

[a] These procedures should preferentially be performed at the study site. These procedures can be conducted at the subject's home by site staff or qualified professional staff if the study site has an established standard operating procedure as such. In case of emergency, the procedures can be done in a hospital.

SUBJECT POPULATION

Cohort 0: Healthy (on the basis of physical examination, medical history and vital signs measurement performed at screening) male or female adults, aged ≥18 to ≤50 years old on the day of ICF signature.

Cohort 1: Healthy (on the basis of physical examination, medical history and vital signs measurement performed at screening) male or female toddlers, aged ≥12 months to ≤24 months on the day of ICF signature and seropositive for RSV within 42 days prior to dosing.

DOSAGE AND ADMINISTRATION

Ad26.RSV.preF (JNJ-64400141) will be supplied in single-use vials. Volumes of 0.5 mL ($1x10^{11}$ vp) for adults and 0.25 mL ($5x10^{10}$ vp) for toddlers will be used for intramuscular injection into the deltoid of the non-dominant arm for adults and into either anterolateral aspect of the thigh for toddlers.

Placebo will be supplied as sterile 0.9% saline for injection.

An unblinded pharmacist, or other qualified individual will prepare the appropriate vial and syringe and provide the syringe in a blinded manner to the study vaccine administrator who will perform the injection. The unblinded pharmacist, or other qualified individual, may also perform the administration, but will have no other study function from randomization onwards[a].

For adult subjects, injections should be administered in the deltoid. For pediatric subjects, injections should be administered in the anterolateral aspect of the thigh. Alternating injection sites will be used for the vaccinations on Day 1 and Day 29.

IMMUNOGENICITY EVALUATIONS

Humoral and cellular immunogenicity evaluations are summarized in Table 2 and Table 3, respectively. Sample collection and processing will be performed by the staff at the clinical sites according to current versions of approved standard operating procedures.

Table 2: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Secondary endpoints	
RSV neutralization A	Analysis of neutralizing antibodies to the A strain
F-protein antibody (ELISA; pre- and/or post-fusion)	Analysis of antibodies binding to RSV F protein in post-fusion and/or pre-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 VNA
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including ADCC, ADCP, avidity, Fc characteristics, Ig isotype, functional VNA and protective antibody assessments

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

[a] The unblinded pharmacist, or other qualified individual, may also perform the administration, but will have no other study function from randomization onwards.

Table 3: Summary of Immunogenicity Assays (Cellular)

Assay	Purpose
Secondary endpoints	
Flow cytometry (ICS)*	Analysis of T-cell responses to RSV F-protein peptides for Th1/Th2 subtyping
Exploratory endpoints	
IFNγ ELISpot	T-cell IFNγ responses to RSV F-protein peptides
ICS	Analysis of T-cell responses to RSV F-protein peptide-stimulated PBMCs (including but not limited to, CD4/CD8, IL2, INFγ, TNFα, activation markers and memory)
Cytokine analysis	Analysis of secreted cytokines in RSV F peptide-stimulated PBMC supernatant, including, but not limited to, measurement of Th1/Th2 cytokine balance

ELISpot = enzyme-linked immunospot; F = fusion; ICS = intracellular cytokine staining; IFNγ = interferon gamma; IL = interleukin; PBMC = peripheral blood mononuclear cell; Th = T-helper (cell); RSV = respiratory syncytial virus; TNFα = tumor necrosis factor alpha

* Cytokine analysis for Th1/Th2 profiling will be done in cases where no ICS data can be generated due to insufficient number of PBMCs for ICS assay

In addition to RT-PCR performed on a nasal turbinate sample collected at the time of infection, any immunogenicity blood sample collected from any Cohort 1 subject who subsequently develops a suspected RTI may also be assayed by a serological assay (eg, ELISA specific to RSV protein G and/or N) to confirm RSV infection.

For adults, nasal turbinate samples, collected pre-dose on Days 1 and 29, 7 days post-Dose 1 (Day 8) and 28 days post-Dose 2 (Day 57) will be used to assess any immunoglobulin (Ig) or cellular immune component.

OTHER EVALUATIONS – RSV INFECTION

RSV seropositivity of Cohort 1 subjects will be assessed by RSV enzyme immunoassay (EIA) or virus neutralization assay at screening. The cut-off for seropositivity by EIA is a titer >10 EIA units and the cut-off by virus neutralization assay is a titer >4. *Note*: RSV-seropositive toddlers may be recruited if RSV seropositivity was assessed via either of these assays in a different study of the sponsor.

Nasal turbinate samples, taken from any Cohort 1 subject with an RTI during each 28-day post-vaccination period, and from any Cohort 1 subject with a specified combination[a] of respiratory symptoms during the RSV season (but outside of the 28-day post-vaccination period), and from any Cohort 1 subject with a MA-RTI or severe LRTI during the whole study period, will be assessed for the presence of RSV infection by RT-PCR.

In addition, scheduled blood samples may be assessed for the presence of RSV antibodies by serology.

SAFETY EVALUATIONS

On a daily basis, for 7 days after each vaccination, each adult subject and each pediatric subject's parent/legal guardian will be asked to record the following AEs via the diary card:

- Solicited local AEs *for all subjects*: erythema (measured using the ruler supplied), swelling/induration (measured using the ruler supplied and graded using the functional scale), and pain/tenderness.

[a] Persistent (>48 hours) clinical symptoms of rhinitis (sneezing or runny nose or congestion) and persistence (>24 hours) of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite.

- Solicited systemic AEs *for adult subjects*: fatigue, headache, myalgia, arthralgia, chills, nausea and fever (ie, body temperature ≥38 °C); *for pediatric subjects*: loss of appetite, vomiting, diarrhea, decreased activity/lethargy, irritability/crying and fever (ie, body temperature ≥38 °C).

Body temperature[a] should be measured by the same method and at approximately the same time each day, preferably in the evening and, for pediatric subjects, additionally whenever the child feels warm using the thermometer supplied. All diary assessments, including body temperature 7 days after the first and second vaccinations may be collected earlier to coincide with the Day 8 clinic visit.

The investigator will review each subject's diary at the subsequent in-clinic visit; diary information will be transcribed by the study personnel into the electronic case report form (eCRF).

The investigator or study-site staff will document any reported unsolicited AEs and perform causality evaluations from the time of ICF signature through 28 days after the final vaccination. For both cohorts, all SAEs will be collected from ICF signature to the end of the study.

When nasal turbinate samples are collected from subjects with an RTI during each 28-day post-vaccination period, and from subjects with a specified combination of respiratory symptoms during the RSV season, but outside the 28-day post-vaccination period, the attending health care professional will record signs and symptoms of the RTI using the RTI Symptoms Form. RTIs, preferably as a diagnosis, will also be reported on the AE page of the eCRF if they occur within 28 days following vaccination. Any RTI fulfilling the criteria of an SAE would be reported as such during the entire study. Any severe LRTI will be reported using the SAE reporting system and SAE form, regardless of whether the event fulfills the criteria of an SAE.

STATISTICAL METHODS

Sample Size Determination

The number of subjects chosen for this study will provide a preliminary safety and immunogenicity 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 site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated.

The following table shows the probabilities of observing at least one AE at given true AE rates:

True AE rate	Probability of observing at least one AE in N subjects			
	N=4	N=8	N=12	N=24
0.5%	2%	4%	6%	11%
1%	4%	8%	11%	21%
2.5%	10%	18%	26%	46%
5%	19%	34%	46%	71%
10%	34%	57%	72%	92%
25%	68%	90%	97%	100%
50%	94%	100%	100%	100%

[a] Recommended orally for adult subjects; rectally or axillary for pediatric subjects (actual routes to be recorded in the eCRF).

Planned Analyses

The following analyses will be performed:

- **Cohort 0**: primary analysis will be performed when all subjects have reached Day 57 (28 days post-Dose 2) or discontinued earlier. All available safety and immunogenicity data gathered so far will be included in the analysis; unblinded at the group level.
- **Cohort 1**: interim analysis will be performed when at least 24 subjects have reached Day 29 (28 days post-Dose 1) or discontinued earlier. All available safety and immunogenicity data gathered so far will be included in the analysis; unblinded at the group level.
- **Cohort 1**: primary analysis will be performed when all subjects have reached Day 57 (28 days post-Dose 2) or discontinued earlier. All available safety and immunogenicity data gathered so far will be included in the analysis; unblinded at the group level.
- **Final analysis of both cohorts**; at the end of the study, 1 year after the first dose; unblinded

Additional interim analyses (blinded or unblinded at the group level) may be performed during the study for the purpose of informing future vaccine-related decisions in a timely manner, or upon health authority request. 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, excluding sponsor personnel involved in data collection or data management.

Immunogenicity Analyses

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% confidence interval (CI) for ELISA and virus neutralization assays; median and quartiles for ELISpot and ICS) will be calculated for continuous immunologic parameters at all timepoints. Graphical representations of immunologic parameters will be made as applicable.

Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters as applicable.

Safety Analyses

No formal statistical testing of safety data is planned. All safety data will be analyzed descriptively by regimen.

TIME AND EVENTS SCHEDULE – COHORT 0: ADULTS

Phase	Screening	Active								Safety FU
Clinic Visit #	1	2	3	4	5	6	7	8	Exit [c]	*Telephone call at 1 year after the first dose*
Visit Timing		Vac 1	Vac 1 + 3 d	Vac 1 + 7 d	Vac 2	Vac 2 + 7 d	Vac 2 + 28 d	Vac 2 + 6 mo		
Visit Week		0		1	4	5	8	30		
Target Visit Day ±window	-28 to 1	1	4±1 [e]	8±2 [g]	29±3	36±2 [e]	57±3	211±14		365±14
Visit Type	Screening	VACCINE 1	Safety (Telephone)	Safety	VACCINE 2	Safety	Safety and Immuno.	Safety and Immuno.	Early Exit	Safety FU (Telephone)
Written informed consent [h]	●									
Inclusion/exclusion criteria	●									
Demographics	●									
Medical history/pre-study meds	●									
Body height and weight	●									
Physical examination	●	❶❷		❷	❶❷	❷	❷	❷	❷	
Vital signs [i] incl. body temperature	●	❸		●	❸	●	❿	❿	●	
Serum pregnancy test [k]	●									
Serology (HIV-1/2, hepatitis B/C) [x]	● 15									
Randomization		❶								
Inclusion/exclusion criteria check [n]		❶			❶					
Prevaccination symptoms [q]		❶			❶					
Urine pregnancy test [k]		❶			❶					
Safety lab blood sample, mL	❾ 10	❶ 5		● 5					❻	
Cellular immunity, mL		❶ 40			❶ 40		● 40	● 40	❺ 40	
Humoral immunity, mL		❶ 40			❶ 40		● 10	● 10	❺ 10	
Nasal turbinate sample		●		●	●		●		❺	
Vaccination		●			●					
30 minute or 60 minute post-vaccination observation [r]		●			●					
Solicited AE recording		----- *Continuous* -----			- *Continuous* -				❻	
Unsolicited AE recording	---------- *Continuous* ----------								❼	
SAE recording	---------- *Continuous* ----------									●
Concomitant meds [s]	---------- *Continuous* ----------									●
Subject diary distribution [v]		●			●					

Phase	Scree-ning	---------- Active ----------								Safety FU
Clinic Visit #	1	2	3	4	5	6	7	8	Exit [c]	*Telephone call at 1 year after the first dose*
Visit Timing		Vac 1	Vac 1 + 3 d	Vac 1 + 7 d	Vac 2	Vac 2 + 7 d	Vac 2 + 28 d	Vac 2 + 6 mo		
Visit Week		0		1	4	5	8	30		
Target Visit Day ±window	-28 to 1	1	4±1 [e]	8±2 [g]	29±3	36±2 [e]	57±3	211±14		365±14
Visit Type	Screening	VACCINE 1	Safety (Telephone)	Safety	VACCINE 2	Safety	Safety and Immuno.	Safety and Immuno.	Early Exit	Safety FU (Telephone)
Subject diary review			❽	●		●				
Approx. daily blood draw, mL	25	85	–	5	80	–	50	50	50	–
Approx. cumulative blood draw, mL	25	110	110	115	195	195	245	**295**	–	–

(*footnotes on page 25*)

TIME AND EVENTS SCHEDULE – COHORT 1: SEROPOSITIVE TODDLERS

Phase	Screening	Active									Safety FU[a]
Clinic Visit #	1	2	3	4	5	6	7	8	9[b]	Exit[d]	*During both the active and safety FU phases: FU outside RSV season at 30-day intervals; FU in season at 14-day intervals*
Visit Timing		Vac 1	Vac 1 + 3 d	Vac 1 + 7 d	Vac 2	Vac 2 + 3 d	Vac 2 + 7 d	Vac 2 + 28 d	Vac 2 + 6 mo		
Visit Week		0		1	4		5	8	30		
Target Visit Day ±window	-42 to 1	1	4±1[f]	8±2[g]	29±3	32±1[f]	36±2	57±3	211±14		
Visit Type	Screening	VACCINE 1	Safety (Telephone)	Safety	VACCINE 2	Safety (Telephone)	Safety	Safety and Immuno.	Safety and Immuno.	Early Exit	Safety FU (Telephone)
Written informed consent[h]	●										
Inclusion/exclusion criteria	●										
Demographics	●										
Medical history/pre-study meds	●										
Body height and weight	●	❶			❶			●	●	●	
Physical examination	●	❶❷		❷	❶❷		❷	❷	❷	❷	
Vital signs[j] incl. body temperature	●	❸		●	❸		●	❿	❿	❻	
RSV serostatus testing[l,m]	● 0.5 mL										
Randomization		❶									
Inclusion/exclusion criteria check[o]		❶			❶						
Prevaccination symptoms[q]		❶			❶						
Cellular immunity	❹ 4 mL				❶ 4 mL					❿ 4 mL	
Humoral immunity[p]	❹ 1 mL				❶ 1 mL			● 2 mL	● 2 mL	❿ 1 mL	
Vaccination[w]		●			●						
30 minute or 60 minute post-vaccination observation[r]		●			●						
Solicited AE recording		----- *Continuous* -----			----- *Continuous* -----					❻	
Unsolicited AE recording	---------- *Continuous* ----------									❼	
SAE recording	---------- *All SAEs* ----------										●
Concomitant meds[s]	---------- *Continuous* ----------										●
RTIs[t]	---------- *Continuous* ----------										
RTI Symptoms Form[u]	---------- *Continuous* ----------										
Severe LRTIs; MA-RTIs	---------- *Continuous* ----------										

TIME AND EVENTS SCHEDULE – COHORT 1: SEROPOSITIVE TODDLERS

Phase	Screening	Active									Safety FU[a]
Clinic Visit #	1	2	3	4	5	6	7	8	9[b]	Exit[d]	*During both the active and safety FU phases: FU outside RSV season at 30-day intervals; FU in season at 14-day intervals*
Visit Timing		Vac 1	Vac 1 + 3 d	Vac 1 + 7 d	Vac 2	Vac 2 + 3 d	Vac 2 + 7 d	Vac 2 + 28 d	Vac 2 + 6 mo		
Visit Week		0		1	4		5	8	30		
Target Visit Day ±window	-42 to 1	1	4±1[f]	8±2[g]	29±3	32±1[f]	36±2	57±3	211±14		
Visit Type	Screening	VACCINE 1	Safety (Telephone)	Safety	VACCINE 2	Safety (Telephone)	Safety	Safety and Immuno.	Safety and Immuno.	Early Exit	Safety FU (Telephone)
Subject diary distribution[v]		●			●						
Subject diary review			❽	●		❽	●				
Approx. daily blood draw, mL	5.5		–	–	5.0	–	–	2.0	2.0	5.0	–
Approx. cumulative blood draw, mL	5.5		5.5	5.5	10.5	10.5	10.5	12.5	**14.5**	–	–

❶ pre-dose; ❷ abbreviated physical examination only at the discretion of the investigator (based on health status of subject); ❸ pre- and post-dose; ❹ baseline immunogenicity blood draw can take place *either* at screening *or* prior to vaccination on Day 1, at the discretion of the investigator; ❺ if at least 14 days after the previous blood draw for immunogenicity; ❻ if within 7 days of the previous vaccination; ❼ if within 28 days of the last vaccination; ❽ check of diary during the telephone call; ❾ laboratory tests at screening are to be done within 28 days of randomization; ❿ at the discretion of the investigator (based on health status of subject); ⓫ If before Day 29 collect 4 mL cellular + 1 mL humoral; if after Day 29 collect 2 mL humoral only.

a. Safety follow-up during both the active and safety follow-up phases through 1 year after the first dose: telephone call (or clinic visit) to parent(s)/legal guardian(s) of Cohort 1 subjects– every 30 days ± 7 days outside the RSV season, but every 14 days ± 3 days in season. Final Telephone call 1 year post-first dose will be at Day 365 ± 14 days.
b. If Visit 9 occurs during the RSV season, an additional visit will be made by telephone at the end of the RSV season to collect safety information
c. For those subjects who are unable to continue participation in the study up to Visit 8, but for whom consent is not withdrawn, an exit visit will be conducted as soon as possible
d. For those subjects who are unable to continue participation in the study up to Visit 9, but for whom consent is not withdrawn, an exit visit will be conducted as soon as possible
e. On Days 3 and 31, a telephone call will *additionally* be made to sentinel subjects in Cohort 0 to collect safety information
f. On Days 3 and 31, a telephone call will *additionally* be made to parent(s)/legal guardian(s) of sentinel subjects in Cohort 1 to collect safety information
g. If any subject in Cohort 0, or any of the first 12 subjects in Cohort 1 come in earlier than Day 8 for Visit 4 (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
h. Signing of the ICF should be done before any study-related activity
i. Systolic and diastolic blood pressure, respiratory rate, heart rate, body temperature
j. Respiratory rate, heart rate, body temperature
k. For women of childbearing potential only

l. 0.5 mL of blood for serostatus assessment can be collected at screening by venous blood sample or fingerstick, at the discretion of the investigator. If 0.5 mL is collected at screening, baseline blood draw for immunogenicity should be on Day 1.
m. *Note*: RSV-seropositive toddlers may be recruited if RSV seropositivity was assessed via RSV EIA or virus neutralization assay in a different study of the sponsor.
n. Cohort 0: to include exclusion criteria 1, 4, 8, 9, 10, 11, 15, 16 and 17
o. Cohort 1: to include exclusion criteria 21, 22, 25, 26, 28, and 32
p. Blood for cellular immunity will also provide plasma for humoral assessments
q. Investigator must check for acute illness or body temperature ≥38.0 °C at the time of vaccination. If before the first vaccination, the subject may be enrolled at a later date if within the screening window (otherwise, rescreening is required), or be withdrawn at the discretion of the investigator and after consultation with the sponsor. If before the second vaccination, the subject may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator and after consultation with the sponsor. In the event of an ongoing AE or other situation precluding subject vaccination within 10 days, subjects may be vaccinated beyond the 10-day window at the discretion of the sponsor.
r. Subjects will be closely observed for a minimum of 30 minutes post-vaccination, or a minimum of 60 minutes post-vaccination according to local approvals. Any unsolicited, solicited local and systemic AEs, and vital signs will be documented by study-site personnel following this observation period
s. 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
t. Monitoring of RTIs will take place during each 28-day post-vaccination period, and additionally during the RSV season after the first dose (even if it falls outside of the 28-day post-vaccination period). During each 28-day post-vaccination period, nasal turbinate samples will be collected for all RTIs. If, during the RSV season, but outside the 28-day post-vaccination period, a subject shows persistent (>48 hours) clinical symptoms of rhinitis (sneezing or runny nose or congestion) and persistence (>24 hours) of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite, the study site should be informed and nasal turbinate samples will be collected for these subjects. *Note*: Nasal turbinate samples will not be collected if less than 7 days after the previous sample collection
u. When nasal turbinate samples are collected, the attending health care professional will record signs and symptoms of the RTI using the RTI Symptoms Form
v. At Visit 2, rulers and thermometers will be distributed to subjects in Cohort 0, and to parent(s)/legal guardian(s) of subjects in Cohort 1
w. At least 5 toddlers in the active group are to have received first dose in a clinic setting and to have completed Visit 3 with no safety concerns before moving to vaccination of study subjects in a non-clinic setting (safety information of the first 5 active toddlers will be monitored by the PI(s)/SRP(s) through Visit 3, and escalated to the IDMC in the event of a safety signal).
x. Blood draw for serology testing will not exceed 15mL

Note: Body temperatures for Cohort 0 recommended to be measured orally; body temperatures for Cohort 1 recommended to be measured either rectally or axillary (actual routes to be recorded in the eCRF)

AE = adverse event; d = day; eCRF = electronic case report form; EIA = enzyme immunoassay; FU = follow-up; HIV = human immunodeficiency virus; ICF = informed consent form; LRTI = lower respiratory tract infection; mo = month; MA-RTI = medically-attended respiratory tract infection; RT-PCR = reverse transcriptase polymerase chain reaction; RSV = respiratory syncytial virus; RTI = respiratory tract infection; SAE = serious adverse event; vac = vaccination

ABBREVIATIONS

Ad26	adenovirus serotype 26
Ad35	adenovirus serotype 35
AE	adverse event
BMI	body mass index
CEC	Clinical Endpoint Committee
CI	confidence interval
CS	circumsporozoite
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eDC	electronic data capture
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
ERD	enhanced respiratory disease
FA	Full Analysis (set)
FDA	(US) Food and Drug Administration
FI	formalin-inactivated
FIH	first-in-human
GCP	Good Clinical Practice
β-hCG	β-human chorionic gonadotropin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	intracellular cytokine staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFNγ	interferon gamma
Ig	immunoglobulin
IL	interleukin
IRB	Institutional Review Board
IWRS	interactive web response system
LRTI	lower respiratory tract infection
MA-RTI	medically-attended respiratory tract infection
PBMC	peripheral blood mononuclear cell
PI	principal investigator
PPI	Per-protocol Immunogenicity (set)
PQC	Product Quality Complaint
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SRP	study responsible physician
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th	T-helper (cell)
TNFα	tumor necrosis factor alpha
UK	United Kingdom
US	United States
VNA	virus neutralizing antibody

vp	viral particles
WHO	World Health Organization

1. INTRODUCTION

A human adenovirus-vectored vaccine candidate which has shown promise in preclinical animal models of respiratory syncytial virus (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 for the pre-fusion conformation-stabilized F protein (pre-F) derived from the RSV A2 strain.

For the most comprehensive nonclinical and clinical information regarding Ad26.RSV.preF, refer to the latest version of the Investigator's Brochure for Ad26.RSV.preF.[1]

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 considered to be the most important cause of serious acute respiratory illness in infants and children under 5 years of age.[18,39,44] Globally, in 2005, RSV was responsible for an estimated 3.4 million hospitalizations worldwide in children under 5 years of age. Furthermore, 66,000 to 199,000 children younger than 5 years died from RSV-associated acute lower respiratory tract infection (LRTI) in 2005, and 99% of these deaths occurred in developing countries.[32] Nevertheless, the disease burden due to RSV in developed countries is substantial, with RSV infection during childhood linked to the development of wheezing, airway hyperreactivity and asthma.[36,38,40,42,43] In the United States (US), the infection rate was 68.8% in children younger than 12 months of age and 82.6% during the second year of life. Virtually all children had been infected at least once by 24 months of age, and about one half had experienced 2 infections.[16] In the US, RSV infection in children under 5 years of age is the cause of 57,000 to 175,000 hospitalizations, 500,000 emergency room visits, and approximately 500 deaths each year.[35,39,44] In children under 1 year of age, RSV is the most important cause of bronchiolitis, and RSV hospitalization is highest among children under 6 months of age.[6,18]

Despite the high disease burden, no licensed vaccine is available for RSV. The first vaccine candidate for 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.[31]

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.[3] The 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 from immunization of adults with Ad26-vectored human immunodeficiency virus (HIV) vaccine (Ad26.ENVA.01), and of adults and infants with an adenovirus serotype 35 (Ad35)-vectored tuberculosis (TB) vaccine (Ad35.TB-S). These data show predominantly interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα) production in $CD4^+$ and $CD8^+$ T cells.[2,5,34] Furthermore, in mice, Ad26- and Ad35-vectored vaccines with circumsporozoite (CS) transgene inserts (Ad26.CS.01 and Ad35.CS.01), when administered as single immunizations or in combination as a heterologous prime-boost regimen at dose levels ranging from $1x10^8$ viral particles (vp) to $1x10^{10}$ vp, induce predominantly $CD8^+$ T-cell responses, as well as mainly immunoglobulin (Ig) G2a antibody responses, indicative of a Th1-biased response.[37]

Thus, in contrast with the Th2-skewed profile of FI-RSV vaccine, which has been associated with ERD upon infection with RSV, the likely Th1 profile of an adenoviral-vectored RSV vaccine reduces the likelihood of disease enhancement in RSV-seronegative infants.

Ad26.RSV.FA2 Clinical Data

Ad26 encoding for the wild-type RSV FA2, Ad26.RSV.FA2, has been evaluated in studies VAC18192RSV1001 and VAC18192RSV1003 (N = 48 and 32, respectively, of which 35 and 24 subjects, respectively, received Ad26.RSV.FA2) in adults at doses of $5x10^{10}$ vp. All subject visits have been completed in both studies.

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 and of median duration 1 to 3 days; most unsolicited AEs and most laboratory abnormalities were mild to moderate in severity. No serious adverse events (SAEs) were reported and no AEs led to withdrawal from study vaccine.

Single vaccination with $5x10^{10}$ vp Ad26.RSV.FA2 raised 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 candidate vaccine assessed in this study is Ad26.RSV.preF, ie, a replication-incompetent Ad26-containing a DNA transgene that encodes for the pre-fusion conformation-stabilized F protein derived from the RSV A2 strain.

First-in-human (FIH) clinical studies (VAC18192RSV1001 [FIH for Ad35.RSV.FA2] and VAC18192RSV1003 [FIH for Ad26.RSV.FA2]) have been completed with vaccines

Ad26.RSV.FA2 and Ad35.RSV.FA2 (ie, 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 F 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.[15,17] This evidence in the design of the candidate RSV vaccine (Ad26.RSV.preF) in which the adenoviral vector encodes for 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 conformation encoded by this vector differs by only five amino acids from the wild-type F protein used in the FA2 construct.[25] This change in the transgene confers more stability to the pre-fusion form of the protein.[25] This change also induces higher immune responses against pre-fusion epitopes because the majority of neutralizing antibodies target the pre-fusion protein conformation.[27,33] 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.[47]

Ad26.RSV.preF Preclinical Data

In preclinical studies in mice and cotton rats, Ad26.RSV.preF is immunogenic, 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+ IFNγ+ T cells. The immune response following Ad26.RSV.preF immunization was T-helper 1 (Th1)-biased, based on the ratio of the Th1 cytokine IFNγ to Th2 cytokines, and on the ratio of RSV F-specific IgG2a/IgG1 antibodies. Also, in neonatal mice, Ad26.RSV.preF was immunogenic and induced both humoral and cellular responses, with similar Th1 bias. In rodent models, single immunization with Ad26.RSV.preF induced dose-dependent protection in the upper and lower respiratory tract from RSV challenge with the RSV A2 strain (in cotton rats and mice) and the RSV B strain (in cotton rats only). Histopathologic features of ERD were not observed in the lung after RSV challenge of mice and cotton rats vaccinated with Ad26.RSV.preF over a large dose range, including vaccine doses that were fully protective, as well as non-protective vaccine doses at which RSV replication in the lung was observed.[47]

Ad26.RSV.preF Clinical Data

Ad26.RSV.preF is currently under evaluation in three other ongoing clinical studies: Phase 1 study (VAC18193RSV1003), and two Phase 2a studies (VAC18193RSV2002 and VAC18193RSV2003) (Table 4).

Table 4: Other Ongoing Clinical Studies with Ad26.RSV.preF

Study Identifier	Clinical Phase	Vaccine	N Planned	Study Population
VAC18193RSV1003	1	Ad26.RSV.preF	72	Adult subjects aged 60 years and older
VAC18193RSV2002	2a	Ad26.RSV.preF	44-70	Adult subjects aged 18 to 50 years
VAC18193RSV2003	2a	Ad26.RSV.preF	180	Adult subjects aged 60 years and older

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. Subjects have been randomized in parallel to one of five study groups and have received two intramuscular injections as follows:

- Group 1 – $5x10^{10}$ vp Ad26.RSV.preF on Day 1 and 1 year later;
- Group 2 – $5x10^{10}$ vp Ad26.RSV.preF on Day 1 and placebo 1 year later;
- Group 3 – $1x10^{11}$ vp Ad26.RSV.preF on Day 1 and 1 year later;
- Group 4 – $1x10^{11}$ vp Ad26.RSV.preF on Day 1 and placebo 1 year later;
- Group 5 – placebo on Day 1 and 1 year later.

Safety and immunogenicity data from the unblinded (at the study group level) analysis 28 days post-dose 1 from all 72 subjects 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.

For Study VAC18193RSV1003, Ad26.RSV.preF was provided in a different buffer (Formulation Buffer 1[a]) from the one to be used in the current study (Formulation Buffer 2[b]). The formulation buffer was changed to enhance the Ad26.RSV.preF drug product stability at 2 to 8 °C for storage purposes in future studies. The new formulation buffer was considered well-

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tolerated when tested in a nonclinical single-dose intramuscular safety study in rabbits,[47] and will be assessed in Cohort 0 before commencement of dosing Cohort 1 in the current study.

Safety Data Supporting Dose Selection from Other Ad26-based Vaccines

In addition to the two completed studies with Ad26.RSV.FA2 and one ongoing study with Ad26.RSV.preF, the dose levels for Ad26.RSV.preF used in this study are supported by experience in adults with other Ad26 vaccines encoding for different antigens (EnvA [in Ad26.ENVA.01 against HIV];[4,5] CS protein [in Ad26.CS.01 against malaria];[10,34] and Ebola glycoprotein [in Ad26.ZEBOV against Ebola virus][29]). Note that, in general, at a given dose level, no significant changes in the safety profiles of Ad26-based vaccines have been seen when the transgene has been changed.

In completed clinical studies,[a] the safety of Ad26.ENVA.01, Ad26.CS.01 and Ad26.RSV.FA2 has previously been evaluated in at least 293 adult subjects, of whom 243 have received $5x10^{10}$ vp, and found to be well-tolerated. In addition, four Phase 1 studies with Ad26.ZEBOV have been completed in adults: 291 subjects have received Ad26.ZEBOV at $5x10^{10}$ vp and $1x10^{11}$ vp without significant safety issues: 15 subjects have received $1x10^{11}$ vp (25 doses administered), and 276 subjects have received $5x10^{10}$ vp. The safety data from these Ebola studies showed no safety concerns at $5x10^{10}$ vp and $1x10^{11}$ vp. Overall, these clinical data are supportive of dosing Ad26.RSV.preF at $5x10^{10}$ vp and $1x10^{11}$ vp in the current study.

To date, Ad26-vectored vaccines have only been tested in adults and the elderly (ie, subjects ≥18 years); Ad35-vectored vaccines have been tested in 904 subjects, including 555 adults and 349 infants. Data from Bacillus Calmette-Guérin (BCG)-primed infants immunized with Ad35 encoding for TB antigens (AERAS-402) indicated that the highest immune responses were obtained following administration of $1x10^{11}$ vp. The safety of this Ad35-based TB vaccine was acceptable when tested in infants aged 14 weeks and older at doses from $1.5x10^{8}$ vp to $1x10^{11}$ vp.

Study Design

In the current study, homologous regimens will be evaluated in subjects in two sequential cohorts.

- In 18 to 50 year-old adults (Cohort 0):

  $1x10^{11}$ vp Ad26.RSV.preF (or placebo) on Days 1 and 29
- In 12 to 24 month-old RSV-seropositive toddlers (Cohort 1):

  $5x10^{10}$ vp Ad26.RSV.preF (or placebo) on Days 1 and 29

[a] Safety data from these studies are summarized in a separate report (Adenoviral Vaccine Safety Database V2.0, December 2016) which is available on request.

A dose of $1x10^{11}$ vp will be used for adults in Cohort 0 based on an acceptable safety profile of Ad26.RSV.preF at $1x10^{11}$ vp from the unblinded (at the group level) interim analysis 28 days post-Dose 1 from all 72 elderly subjects in study VAC18193RSV1003, in addition to supporting safety data from dosing Ad26.ZEBOV at $1x10^{11}$ vp.

A dose of $5x10^{10}$ vp will be used for toddlers in Cohort 1 as this is the anticipated dose to be used in a future study in 12-24 month-old seronegative toddlers. Dosing ranging would occur in a future study in 6 to 12 month-old seronegative subjects.

Enrollment and dosing will be staggered to allow safety assessments to be made in adults before enrolling and dosing seropositive toddlers, as described fully in Section 3.1 below.

An independent data monitoring committee (IDMC) will be established for this study to evaluate safety and tolerability data on a regular basis. Refer to Section 11.9.1, for details.

An independent blinded clinical endpoint committee (CEC) will be established for this study to assess any suspected case of severe lower LRTI in pediatric subjects. Refer to Section 11.9.2, for details.

1.2. Overall Rationale for the Study

This study seeks to evaluate the safety and immunogenicity of Ad26.RSV.preF at a dose of $5x10^{10}$ vp in RSV-seropositive toddlers aged 12 to 24 months (Cohort 1). As this is the first study using Ad26.RSV.preF in Formulation Buffer 2, the reactogenicity profile of Ad26.RSV.preF in this new formulation buffer will be first assessed in an adult run-in cohort (Cohort 0) before dosing the toddlers.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

The primary objectives are:

- To assess the safety and tolerability of an intramuscular regimen of two doses of $1x10^{11}$ vp of Ad26.RSV.preF in adults aged 18 to 50 years.
- To assess the safety and tolerability of an intramuscular regimen of two doses of $5x10^{10}$ vp of Ad26.RSV.preF in RSV-seropositive toddlers aged 12 to 24 months.

Secondary Objective

The secondary objective is:

- To assess the humoral and cellular immune responses as measured by virus neutralization assay, F-protein binding antibodies (pre-F and post-F) and intracellular cytokine staining (ICS; to assess Th1/Th2 subtyping).

Exploratory Objectives

The exploratory objectives are:

- To further assess the humoral and cellular immune responses elicited by Ad26.RSV.preF. The assays to be used may 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), evaluation of the cellular immune response (IFNγ enzyme-linked immunospot [ELISpot] assay) and functional and memory immune response (by ICS), and cytokine profiles of RSV F-protein peptide-stimulated peripheral blood mononuclear cell (PBMC) supernatant.
- To assess RSV infection rates in Ad26.RSV.preF and placebo subjects
- To monitor for severe RSV-LRTI in Cohort 1 (RSV-seropositive toddlers aged 12 to 24 months)
- To assess symptoms of respiratory illness via the respiratory tract infection (RTI) symptoms form

2.1.2. Endpoints

Primary Endpoints – Safety and Tolerability

- Solicited local and systemic AEs for 7 days after each vaccination.
- Unsolicited AEs for 28 days after each vaccination (ie, from informed consent form [ICF] signature through the following 28 days post-first vaccination, and for subsequent vaccinations from time of vaccination through the following 28 days).
- SAEs from ICF signature to the end of the study.

Secondary Endpoints – Immune Responses

The analysis of the immunogenicity of vaccine regimens will include the characterization of humoral as well as cellular responses. The focus of the immunogenicity analysis is on virus neutralizing antibodies (VNAs), F-protein antibodies (pre-F and/or post-F) and Th1/Th2 cytokine profile response.

Humoral Immune Response

- RSV neutralization A strain

  Analysis of RSV A neutralizing antibodies.

- RSV F-protein enzyme-linked immunosorbent assay (ELISA; pre- and/or post-fusion F antibodies)

  Analysis of antibodies binding to RSV F protein in post-fusion and pre-fusion form.

Cell-mediated Immune Response

- Intracellular cytokine staining or cytokine analysis*

  Analysis of CD4 and CD8 T-cell subsets and their cytokine expression patterns will be determined by flow cytometry after RSV F-protein peptide stimulation (including, but not limited to CD4/CD8, interleukin-2 [IL-2], IFNγ, TNFα and Th1/Th2 subtyping).

  **Cytokine analysis for Th1/Th2 profiling will be done in cases where no ICS data can be generated due to insufficient number of PBMCs for ICS assay (see exploratory endpoints below for description)*

Exploratory Endpoints – Immune Responses

Additional exploratory analyses may be performed to investigate vaccine-elicited immune responses further. These may include, but are not limited to, the following assays:

Humoral Immune Response

- RSV cross-neutralization of B and/or other A strain(s)

  The strain cross-neutralizing capacity of the vaccine-induced immune response will be assessed.

- 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.

- Adenovirus neutralization assay

  This assay assesses neutralizing antibody responses against the adenoviral vector.

- Functional and molecular antibody characterization

  Functional characterization of antibodies may be performed in assays including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).[9] A molecular characterization of vaccine-elicited antibodies will include antibody avidity, Fc characterization and Ig isotype, functional VNA and protective antibody assessments.

Cell-mediated Immune Response

- IFNγ ELISpot assay

  An ELISpot assay is used to quantify the amount of PBMCs able to produce IFNγ upon RSV F-protein peptide antigen stimulation.

- Cytokine analysis

  Cytokine profiles of (in vitro) stimulated PBMC supernatant will be analyzed to assess the quantity and quality of the elicited immune responses, including Th1/Th2 balance. Analysis will include, but is not limited to, IFNγ, IL-2, IL-4, IL-5, IL-13, and TNFα.

Exploratory Endpoints – RSV Infection

- For Cohort 1 only, RSV infection confirmed by either reverse transcriptase polymerase chain reaction (RT-PCR), or by serology for, but not limited to, protein G and/or N if no RT-PCR is available. To detect asymptomatic RSV infections, a fold increase will be applied to call a subject seropositive to G and/or N ELISA (or F in case of placebo subjects). Fold increases for RSV infection will be determined based on the (suspected) infection and the convalescent blood samples.
- In Cohort 1 throughout the study:
  - Severe RSV-LRTI
  - RSV medically-attended respiratory tract infection (MA-RTI)

Refer to Section 9.2 for evaluations related to endpoints.

2.2. Hypothesis

No formal statistical hypothesis is planned. The study will evaluate whether Ad26.RSV.preF is safe, well-tolerated and immunogenic in adults and RSV-seropositive toddlers.

3. STUDY DESIGN AND RATIONALE

In this document, unless otherwise specified, any reference to activities to be performed by the subject refers to adult subjects or the parent/legal guardian for pediatric subjects.

3.1. Overview of Study Design

This is a multi-center, randomized, double-blind[a], Phase 1/2a study, to be conducted in 12 male and female adults aged ≥18 to ≤50 years and 36 male and female toddlers aged ≥12 to ≤24 months of age, seropositive for RSV within 42 days prior to dosing.

Subjects will be enrolled into sequential age cohorts:

- 18 to 50 year-old adults, into **Cohort 0**
- 12 to 24 month-old seropositive toddlers, into **Cohort 1**

[a] The administrator of the vaccine may be unblinded but will not participate in any other study evaluation from randomization onwards. The site staff or qualified professional staff who will do the observation and the subjects will be blinded.

In Cohort 0, subjects will be randomized 2:1 to receive either Ad26/Ad26 (at $1x10^{11}$ vp) or placebo/placebo, and in Cohort 1, subjects will be randomized 2:1 to receive either Ad26/Ad26 (at $5x10^{10}$ vp) or placebo/placebo (Table 5).

The standard dose ($5x10^{10}$ vp) is the dose the most commonly used in previous studies and other programs with good safety and immunogenicity profiles. The high dose ($1x10^{11}$ vp) has been shown in study VAC18192RSV1003 to be well tolerated in elderly subjects and at least as immunogenic, and is therefore appropriate for adults in this study. The standard dose is thought to be the proper dose to start with for preliminary ERD assessment in toddlers as ERD could be linked to a suboptimal immune response. The high dose will be first tested in further studies in seropositive toddlers, before being used in seronegative infants. Dose ranging will be performed in 6-12M seronegative, closer to the target population.

The study will have three phases: a **screening phase**, an **active phase** and a **safety follow-up phase** through 1 year after the first dose. The durations of the respective phases are as follows:

Phase	**Cohort 0**	**Cohort 1**
Screening:	up to 4 weeks	up to 6 weeks
Active:	30 weeks • dosing on Days 1 and 29 • safety follow-up through 6 months post-final dose • immunogenicity at: ➢ pre-Dose 1 (Day 1) ➢ pre-Dose 2 (Day 29) ➢ 28 days post-Dose 2 (Day 57) ➢ 6 months post-Dose 2 (Day 211/Week 30)	30 weeks • dosing on Days 1 and 29 • safety follow-up through 6 months post-final dose • immunogenicity at: ➢ pre-Dose 1 (Day 1) ➢ pre-Dose 2 (Day 29) ➢ 28 days post-Dose 2 (Day 57) ➢ 6 months post-Dose 2 (Day 211/Week 30)
Safety follow-up:	through 1 year after the first dose	through 1 year after the first dose

The end of the active phase will be when the last subject completes the visit at 6 months after the final dose. The end of the study will be the last subject's last visit (by telephone) at the end of the safety follow-up phase.

First-dose Safety

For Cohort 0, 48-hour and 7-day safety will be monitored by the Principal Investigator(s) (PI[s]) and the Study Responsible Physician(s) (SRP[s])[a]; for Cohort 1, 48-hour safety will be monitored by the PI(s) and the SRP(s), and 7-day safety will be monitored by the IDMC. In the event of a significant safety finding, the IDMC will be consulted.

Note: At least 5 toddlers in the active group are to have received first dose in a clinic setting and

[a] The safety of Ad26.RSV.preF in elderly subjects at $5x10^{10}$ vp and $1x10^{11}$ vp will have been established in study VAC18193RSV1003 prior to initiation of the current study; the purpose of dosing Ad26.RSV.preF in Cohort 0 in the current study is as a safety check for the new drug product formulation buffer, and consequently only PI and SRP review of Cohort 0 safety data is planned prior to dosing seropositive toddlers in Cohort 1.

to have completed Visit 3 with no safety concerns before moving to vaccination of study subjects in a non-clinic setting (safety information of the first 5 active toddlers will be monitored by the PI(s)/SRP(s) through Visit 3, and escalated to the IDMC in the event of a safety signal).

Enrollment will be staggered to allow safety assessments to be made 7 days after the first dose in all 12 adults in Cohort 0 before enrolling and dosing seropositive toddlers in Cohort 1. Additionally, safety assessments will be made 7 days after the first dose in the first 12 seropositive toddlers (8 actives and 4 placebos) in Cohort 1 before enrolling and dosing the remaining seropositive toddlers, as indicated below (see also Figure 1). In addition, 48-hour safety will be checked after dosing sentinel subjects in both cohorts. The sentinel cohort approach with 2 subjects (1 active and 1 placebo) in each cohort is taken to ensure active and placebo subjects are included in the evaluations, taking into account the blinding. The observation at 48 hours post-dose is primarily to rule out anaphylaxis or cytokine storm.

- Enroll and dose 2 sentinel subjects (adults) in Cohort 0: 1 of these 2 sentinel subjects will receive Ad26.RSV.preF.
- After satisfactory completion of 48-hour safety review after the first dose for these 2 Cohort 0 subjects, the remaining 10 subjects in Cohort 0 will be enrolled and receive the first dose. The PI(s)/SRP(s) will assess post-first dose reactogenicity by review of 7-day safety data for all 12 Cohort 0 subjects.
- After satisfactory completion of this safety review, 2 sentinel subjects (seropositive toddlers) in Cohort 1 will be enrolled and receive the first dose: one of these 2 sentinel subjects will receive Ad26.RSV.preF.
- After satisfactory completion of 48-hour safety review after the first dose for these 2 Cohort 1 subjects, 10 more subjects in Cohort 1 will be enrolled and receive the first dose. The IDMC will assess post-first dose reactogenicity by review of 7-day safety data for the first 12 Cohort 1 subjects (8 actives and 4 placebos).
- After satisfactory completion of this safety review, the remaining subjects in Cohort 1 will be enrolled and receive the first dose.

In all post-first dose 48-hour and 7-day safety reviews, safety data for review will include solicited and unsolicited AEs and SAEs. Additionally, for Cohort 0 safety laboratory data will be included in the 7-day safety review. In the absence of clinically relevant findings, enrollment and dosing for the next cohort of subjects will continue as described above.

Second-dose Safety

Post-second dose 48-hour and 7-day safety assessments will be monitored by the PI(s) and the SRP(s). Administration of the second dose will also be staggered to allow safety assessments to be made 7 days after the second dose in all 12 adults in Cohort 0 before administering the second dose to seropositive toddlers in Cohort 1. Likewise, safety assessments will be made 7 days after the second dose in the first 12 seropositive toddlers in Cohort 1 before administering the second dose to the remaining seropositive toddlers in Cohort 1. In addition, 48-hour safety will be

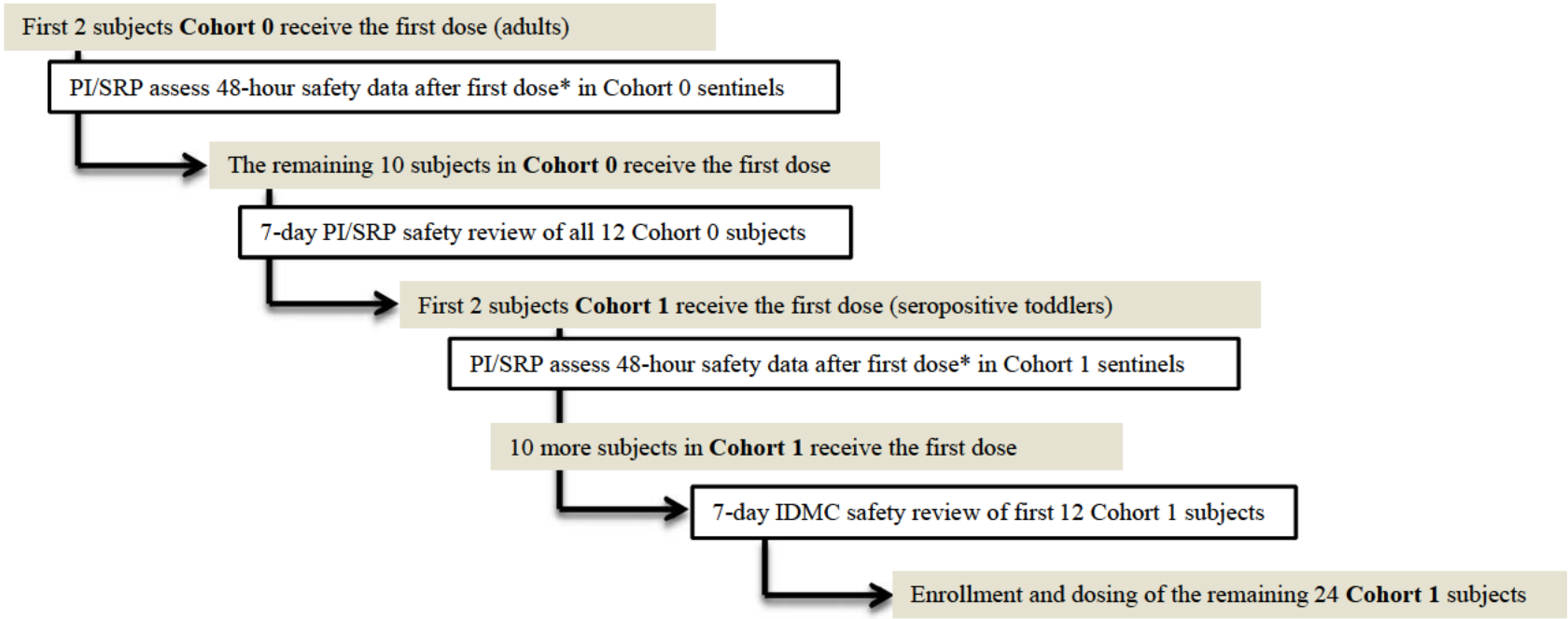
checked after dosing sentinel subjects in both cohorts. Safety data for review will include solicited and unsolicited AEs and SAEs. In the absence of clinically relevant findings, enrollment and dosing for the next cohort of subjects will continue as described above.

The sponsor will monitor post-vaccination safety on an ongoing basis by reviewing blinded safety data.

Table 5: Study Design

Cohort	Group	N	Day 1	Day 29/Week 4
ADULTS 18 to 50 years				
0	Group 1	8	Ad26.RSV.preF ($1x10^{11}$ vp)	Ad26.RSV.preF ($1x10^{11}$ vp)
	Group 2	4	Placebo	Placebo
TODDLERS 12 to 24 months: RSV seropositive				
1	Group 3	24	Ad26.RSV.preF ($5x10^{10}$ vp)	Ad26.RSV.preF ($5x10^{10}$ vp)
	Group 4	12	Placebo	Placebo

Figure 1: Enrollment and First Dose Strategy



*Two Cohort 0 sentinel subjects, and the parent/legal guardian of 2 sentinel subjects from Cohort 1 will be contacted on Day 3 by telephone to collect safety information.

After each vaccination, all subjects will be closely observed for a minimum of 30 minutes post-vaccination, or a minimum of 60 minutes post-vaccination according to local approvals, to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs and vital signs will be documented by study-site personnel following this observation period. Subjects[a] will be given a thermometer, ruler and daily assessment (subject) diary with instructions for the proper recording of events. Each subject will record solicited local (at injection site) and systemic AEs and body temperatures, beginning on the evening of each study vaccine dosing day and on a daily basis for the following 7 days. Temperatures[b] should be taken at approximately the same time each day, preferably in the evening[c] and, for pediatric subjects, additionally whenever the child feels warm. Study-site personnel will collect and review subject diary information and confirm the entries at subsequent site visits.

Unsolicited AEs will be collected from the time of informed consent through 28 days after each dose. For both cohorts, all SAEs will be collected from ICF signature to the end of the study. 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 of these periods when associated with any SAE.

Blood will be collected for immunogenicity assessments as follows:

- Cohort 0: pre-vaccination for first and second doses, and at 28 days and 6 months after the second dose
- Cohort 1: pre-vaccination for first and second doses, and at 28 days and 6 months after the second dose

For Cohort 1, a blood sample will be taken for RSV serology at screening[d]; the baseline sample for immunogenicity may either be drawn at the same screening visit or pre-dose on Day 1, at the discretion of the investigator.

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

Diagrams of the entire study design by cohort are provided in Figure 2 (Cohort 0) and Figure 3 (Cohort 1).

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[a] In Cohort 1, activities to be performed by the subject refers to the parent/legal guardian.

[b] Recommended orally for adult subjects; rectally or axillary for pediatric subjects (actual routes to be recorded in the eCRF).

[c] All Day 8 post-vaccination diary assessments, including temperature measurements, may be collected earlier to coincide with the corresponding clinic visit.

[d] 0.5 mL of blood for serostatus assessment can be collected by venous blood sample or fingerstick, at the discretion of the investigator. If 0.5 mL is collected at screening, baseline blood draw for immunogenicity should be on Day 1.

Figure 2: Schematic Overview of the Study for Cohort 0

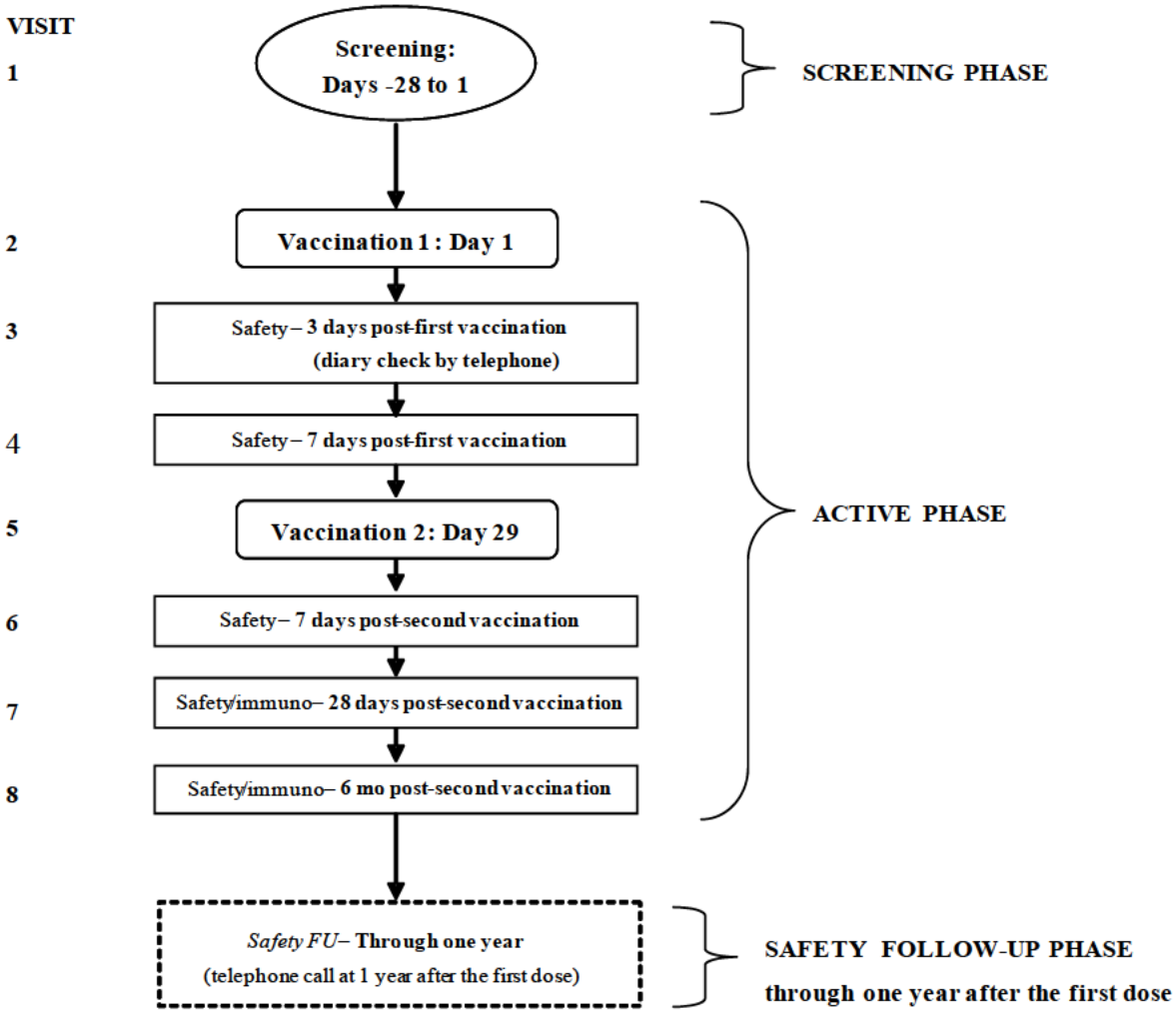
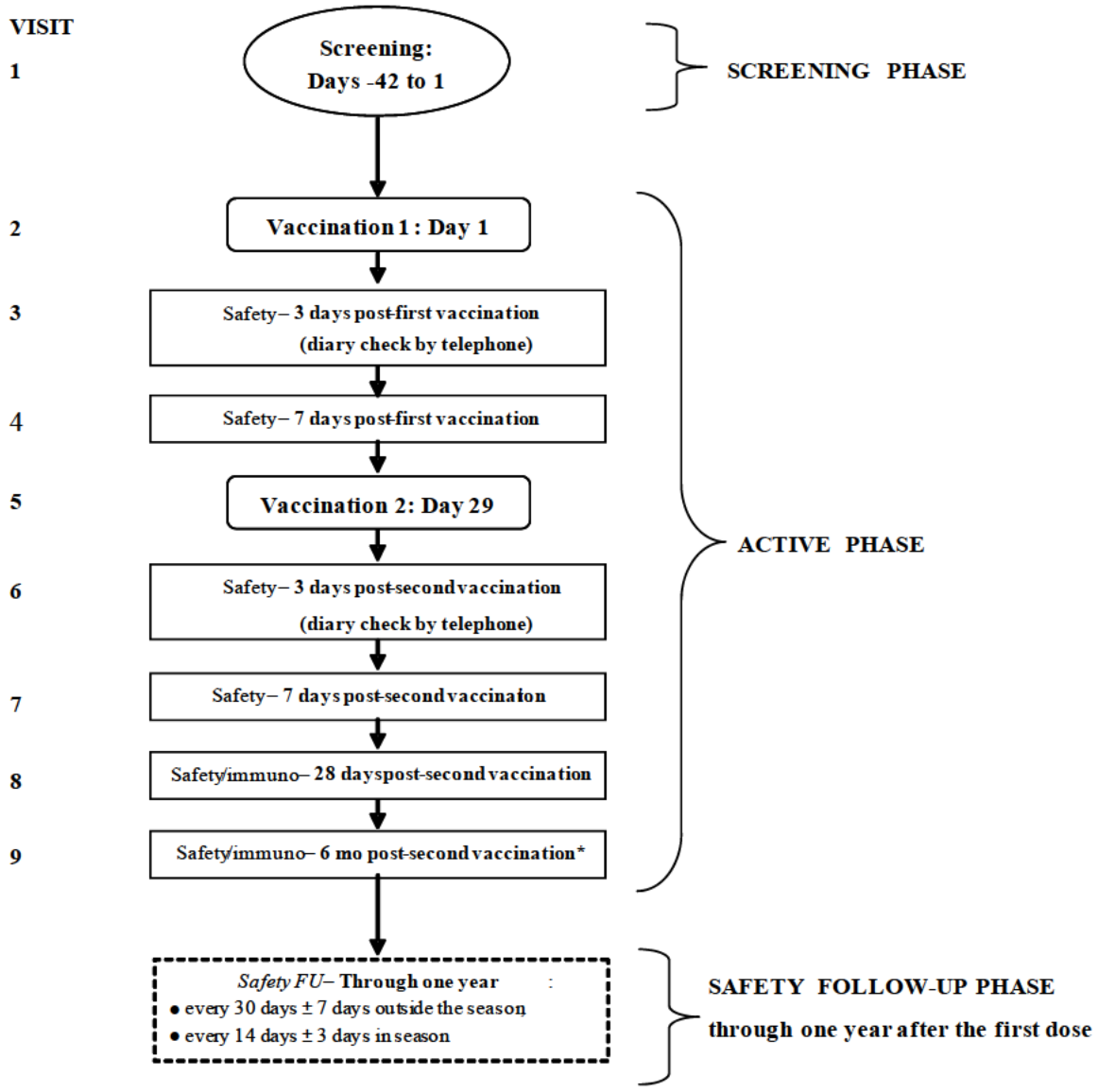


Figure 3: Schematic Overview of the Study for Cohort 1



*If Visit 9 occurs during the RSV season, an additional visit will be made by telephone at the end of the RSV season to collect safety information

Safety Follow-up

Parent(s)/legal guardian(s) of subjects in Cohort 1 will be contacted by telephone (or clinic visit) through 1 year after the first dose (including during the active phase and safety follow-up phase: every 30 days ± 7 days outside the RSV season, but every 14 days ± 3 days in season). During each 28-day post-vaccination period, calls will remind parents/legal guardians to contact the site in the event their child develops an RTI. During the RSV season, but outside the 28-day post-vaccination period, calls will remind parents/legal guardians to contact the site in the event their child develops a combination of symptoms of respiratory infection (persistent [>48 hours] clinical symptoms of rhinitis [sneezing or runny nose or congestion] and persistence [>24 hours] of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased

appetite). These calls will also check for any SAEs and associated concomitant medications since the previous visit or telephone contact.

3.2. RTI – Procedures Specific to Cohort 1

Monitoring of RTIs will take place during each 28-day post-vaccination period, and additionally during the RSV season after the first dose (even if it falls outside of the 28-day post-vaccination period). Monitoring for MA-RTIs and severe LRTIs will take place during the whole study period.

During each 28-day post-vaccination period, all RTIs will be reported, nasal turbinate samples will be collected as soon as possible after the onset of respiratory symptoms, and signs and symptoms will be recorded by the attending health care professional using the RTI Symptoms Form.

If, during the RSV season, but outside the 28-day post-vaccination period, a subject shows persistent (>48 hours) clinical symptoms of rhinitis (sneezing or runny nose or congestion) and persistence (>24 hours) of one or more of the following[30,32,41,44]: cough, abnormal breathing, fever, lethargy or decreased appetite, the study site should be notified. Nasal turbinate samples will be collected as soon as possible after the onset of these combined respiratory symptoms[a]. When nasal turbinate samples are collected, the attending health care professional will record signs and symptoms of the RTI using the RTI Symptoms Form.

Nasal turbinate samples will not be collected if less than 7 days after the previous sample collection.

Outside of the RSV season, nasal turbinate samples will only be collected from subjects with MA-RTIs or severe LRTIs (for definition of MA-RTI and severe LRTI, please refer to Section 11.3.1).

Throughout the study, nasal turbinate samples will be collected from any subject with a MA-RTI or severe LRTI.

The criteria used to assess potential cases of RSV infection in subjects from Cohort 1 will be as follows:

- Suspected RSV infection: subject has persistent (>48 hours) clinical symptoms of rhinitis (sneezing or runny nose or congestion) and persistence (>24 hours) of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite.

  Occurrence of this combination of symptoms in any subject would trigger collection of a nasal turbinate sample.

[a] These procedures should preferentially be performed at the study site. These procedures can be conducted at the subject's home by site staff or qualified professional staff if the study site has an established standard operating procedure as such. In case of emergency, the procedures can be done in a hospital.

- Confirmed RSV infection: subject with suspected RSV infection and positive for RSV on the basis of RT-PCR conducted centrally.

Data on the clinical course of infection including information regarding oxygenation status, supplemental oxygen requirements and specific drug treatments should be collected, as well as any other concurrent respiratory illness present at the time of the diagnosis of the event and up to symptom resolution.

To ensure the rapid follow-up of any severe LRTI or MA-RTI, study sites will need to make arrangements with primary care physicians, emergency departments and/or hospitals' urgent care facilities to be notified when a subject is being seen. Further details will be provided in the Trial Center File. Any parent/legal guardian who seeks medical attention for their child due to an RTI should make the attending health care professional aware that their child is taking part in an RSV vaccine study. Each child's parent/legal guardian will be given a wallet card with key study information and site contact details (see Section 12.3.1). These details should be shared with the attending health care professional.

Note: Any RTI falling within the 28-day post-vaccination period will be reported as an unsolicited AE, preferably as a diagnosis. Any RTI fulfilling the criteria of an SAE would be reported as such during the entire study. Any severe LRTI will be reported using the SAE reporting system and SAE form, regardless of whether the event fulfills the criteria of an SAE.

3.3. Study Design Rationale

Dose Selection

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

Availability of Safety Data Prior to Dosing

Two initial FIH studies (VAC18192RSV1001, N = 48; VAC18192RSV1003, N = 32) in healthy adults examining homologous and heterologous regimens of $5x10^{10}$ vp of Ad26.RSV.FA2 and $5x10^{10}$ vp of Ad35.RSV.FA2 have been completed. Both Ad26.RSV.FA2 and Ad35.RSV.FA2 were shown to be safe and immunogenic.

One subsequent FIH study (VAC18193RSV1003, N = 72) in elderly adults in stable health examining homologous regimens of $5x10^{10}$ vp and $1x10^{11}$ vp of Ad26.RSV.preF is ongoing. This study uses Formulation Buffer 1. All 72 subjects have been randomized and have received the first dose. Based on acceptable safety and immunogenicity data from the unblinded (at the group level) interim analysis 28 days post-Dose 1 from all 72 subjects in this study, the current study will be initiated firstly for adults 18 to 50 years of age. After 7-day safety has been verified by the PI/SRP in the first 12 adults, enrollment of seropositive toddlers 12-24 months of age will commence.

3.4. Risk/Benefit Section

3.4.1. Known Benefits

The clinical benefits of vaccination with Ad26.RSV.preF have yet to be established.

3.4.2. Potential Benefits

Ad26.RSV.preF is under development for prophylaxis of RSV, however vaccine efficacy has not yet been investigated. There is no direct medical benefit to the subject for participation in this clinical study. Although study subjects 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.

3.4.3. Known Risks

Single doses of $5x10^{10}$ vp or $1x10^{11}$ vp of Ad26.RSV.preF are under investigation in the ongoing FIH Phase 1 study VAC18193RSV1003 in elderly subjects. Preliminary safety data from an unblinded[a] interim analysis 28 days post-Dose 1 from 41 subjects who received Ad26.RSV.preF or placebo did not reveal any safety concerns at either dose level.

3.4.4. Potential Risks

The following potential risks for Ad26.RSV.preF will be monitored during the study.

Risks Related to Vaccines

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

Subjects may exhibit general signs and symptoms associated with administration of a vaccine, or vaccination with placebo, including fatigue, headache, myalgia, arthralgia, chills and nausea in adult subjects, and loss of appetite, vomiting, diarrhea, decreased activity/lethargy, irritability/crying in pediatric subjects. These side effects will be monitored, but are generally short-term and do not require treatment.

Subjects 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. Subjects with 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) will be excluded from the study. Sites should have medical treatment and medically qualified staff available in case of severe allergic reactions following vaccine administration.

[a] At the group level.

Risks Related to Adenoviral-vectored Vaccines

Safety data available from 10 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 $1x10^9$ vp to $1x10^{11}$ vp, indicate that no safety concerns would be anticipated from vaccination with Ad26.RSV.preF at doses of $5x10^{10}$ vp and $1x10^{11}$ vp.

Local AEs (moderate injection site pain and tenderness, and moderate to severe redness at the injection site) and systemic AEs (headache, chills, joint pain, muscle pain, tiredness/generally not feeling well/fatigue and fever) have been reported after vaccination with Ad26-vectored vaccines. In a few subjects, transient laboratory abnormalities have been seen, 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 subjects.

For further details on the safety profiles of other Ad26-vectored vaccine candidates, see the Ad26.RSV.preF Investigator's Brochure.[1]

An Ad35-vectored vaccine (AERAS-402) has been tested in two completed clinical studies in infants: data from these studies indicate acceptable safety at doses from $1.5x10^8$ vp to $1x10^{11}$ vp in infants aged 14 weeks and older.

Risks Related to RSV Vaccines

In the 1960s, a FI-RSV vaccine was associated with ERD in young children, characterized by an increased rate of RSV-mediated, severe LRTI in the vaccinated individuals compared with the control group.[8,13,21,22] Children aged between 2 months and 7 years of age were vaccinated; the risk of ERD was highest among children under 6 months of age. In the study with the most severe outcomes, RSV infection was confirmed in 20/31 (65%) children who received the FI-RSV vaccine, with 16/20 children requiring hospitalization due to severe LRTI (52% of all FI-RSV vaccinees, representing 80% of those being RSV-infected). In contrast, while RSV infection was observed in 21/40 (53%) children who received a control vaccine, only one hospitalization due to severe LRTI (2.5% of all control vaccinees, representing 5% of those being RSV-infected) was required. Two of the FI-RSV vaccinated children died.[22] ERD is characterized by increased pulmonary inflammatory response and mucin production leading to reduced oxygen exchange in the lungs.

Although the mechanisms for ERD are not fully understood, it is thought that FI-RSV: 1) may have failed to induce adequate neutralizing antibody titers; 2) may have led to an overproduction of binding antibodies promoting immune complex deposition and hypersensitivity reactions; 3) may have failed to induce adequate numbers of memory CD8 T cells important for viral clearance; and 4) may have induced a Th2-skewed allergic type T cell response.[31]

In general, adenoviral-vectored vaccines have been shown to promote a Th1-biased response.[37] Single immunization with low doses of Ad26.RSV.preF protects cotton rats from challenge with the vaccine-homologous RSV-A2 and the heterologous B Wash strain, without induction of any histopathological signs of ERD. This Th1 profile of Ad26.RSV.preF reduces the likelihood of disease enhancement in RSV-seronegative infants.

Risks from Collection of Nasal Turbinate Samples

Collection of nasal turbinate samples may cause a nosebleed.

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.

Pregnancy and Birth Control (Cohort 0 Only)

The effect of the study vaccine on a fetus or nursing baby is unknown so women of childbearing potential are required to agree to practice effective birth control measures for sexual intercourse from signing the ICF until at least 3 months after the last vaccination (see Section 4.1). Use of hormonal contraception should start at least 28 days before the first administration of study vaccine. Women who are pregnant or breast-feeding, or are planning to become pregnant while enrolled in the study until 3 months after the final dose of study vaccine, will be excluded from the study.

Subjects 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 as in immunocompetent individuals. However, the magnitude, breadth, and persistence of the immune response to vaccination may be reduced or absent in immunocompromised persons. Subjects with abnormal function of the immune system will be excluded from the study.

Concomitant Vaccination

Concomitant vaccination might have an influence on both safety profile and immunogenicity of Ad26.RSV.preF. Likewise, Ad26.RSV.preF might have an influence on both safety profile and immunogenicity of any concomitant vaccination. As a result, vaccination with live attenuated vaccines within 28 days of a study vaccination (ie, before and after) is prohibited. Other vaccines (eg, influenza, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before (or at least 14 days after) administration of study vaccine. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine. *Note*: Planning for routine childhood vaccinations will be available from the site to ensure that these can be taken at appropriate times during the study.

Unknown Risks

There may be other serious risks that are not known.

3.4.5. Overall Benefit/Risk Assessment

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:

Preliminary safety data from the ongoing clinical studies and safety data generated with the related vaccines containing different inserts revealed no significant safety issues.

- Only subjects who meet all inclusion criteria and none of the exclusion criteria (specified in Section 4) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of subjects in the study.
- Safety will be closely monitored throughout the study:
  - After each vaccination, subjects will remain in the clinic and be closely observed by study staff for at least total 30 minutes post-vaccination, or a minimum of 60 minutes post-vaccination according to local approvals, or longer if deemed necessary by the investigator, to monitor the development of any acute reactions. Any unsolicited, solicited local or systemic AEs will be documented during this period. Subjects will use a diary to document solicited local and systemic AEs in the evening after each vaccination and then daily for the next 7 days at approximately the same time each day.
  - Subjects will undergo safety follow-up by study staff 72 hours after each vaccination by telephone.
  - Unsolicited AEs will be documented from immediately prior to until 28 days after each vaccination. All SAEs will be recorded from signing the ICF through 1 year after the first vaccination.
  - Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable endpoint is reached.
- Several safety measures are included in this protocol to minimize the potential risk to subjects, including the following:
  - Enrollment will be staggered to allow safety assessments to be made 7 days after the first dose in all 12 adults before enrolling and dosing seropositive toddlers. Additionally, safety assessments will be made 7 days after the first dose in the first 12 seropositive toddlers (8 actives and 4 placebos) before enrolling and dosing the remaining seropositive toddlers. For Cohort 0, 7-day safety will be monitored by the PI and SRP; for Cohort 1, 7-day safety will be monitored by the IDMC. In addition, 48-hour safety will be checked by the PI and SRP after dosing sentinel subjects in both cohorts. These safety assessments at 48 hours and 7 days post-first dose are described more fully in Section 3.1.
  - For all subjects, there are pre-specified rules that would result in pausing of further vaccinations if predefined conditions occur, preventing exposure of new subjects to study vaccine until the PI/SRP and/or IDMC reviews all safety data (see Section 11.10).

- Subjects will discontinue study vaccine for the reasons included in Section 10.2.
- If acute illness (excluding minor illnesses such as diarrhea) or fever (body temperature ≥38.0°C) occur at the scheduled time for the first vaccination, the subject may be enrolled at a later date[a], or be withdrawn at the discretion of the investigator and after consultation with the sponsor.
- If acute illness (excluding minor illnesses such as diarrhea) or fever (body temperature ≥38.0°C) occur at the scheduled time for the second vaccination, the subject may be vaccinated up to 10 days beyond the scheduled vaccination, or be withdrawn from further vaccination at the discretion of the investigator and after consultation with the sponsor. In the event of an ongoing AE or other situation precluding subject vaccination within 10 days, subjects may be vaccinated beyond the 10-day window at the discretion of the sponsor.
- Contraindications to vaccination are included in Section 10.3.
- Careful monitoring will be in place to check for incidence of any severe RSV-LRTI in Cohort 1. During each 28-day post-vaccination period all suspected cases of RSV infection will be identified for follow-up, and nasal turbinate samples will be analyzed. During the RSV season, but outside the 28-day post-vaccination period, suspected cases of RSV infection will be identified for follow-up from a defined set of clinical symptoms; nasal turbinate samples will be analyzed for identification and confirmation of RSV infection. Individual cases of severe LRTI may be reviewed by the IDMC.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following two 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 subject in the study. Waivers are not allowed.

Screening for eligible subjects will be performed within 28 days before administration of the first dose of study vaccine for Cohort 0, and within 42 days before administration of the first dose of study vaccine for Cohort 1. Each potential subject must satisfy all of the following criteria to be enrolled in the study.

4.1. Inclusion Criteria

4.1.1. Adult Subjects

1 Each subject must sign an 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.

[a] If within the screening window. Otherwise, rescreening is required.

2 Subject is a man or woman, ≥18 to ≤50 years old on the day of ICF signature.

3 Subject must be in good health, without significant medical illness, on the basis of physical examination, medical history, and vital signs measurement.

4 Subject must be healthy on the basis of clinical laboratory tests performed at screening. If the results of the laboratory screening tests are outside the local laboratory normal reference ranges and additionally within the limits of toxicity Grade 1 according to the US Food and Drug Administration (FDA) toxicity tables (ie, for tests in the FDA table[a]), the subject 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 subject's source documents and initialed by the investigator.

Note: If laboratory screening tests are out of local 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.

5 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

Before randomization, a woman must be either:

a. Not of childbearing potential defined as:
   i. Premenarchal: *a premenarchal state is one in which menarche has not yet occurred.*
   ii. postmenopausal: *amenorrhea for at least 12 months without an alternative medical cause.*
   iii. permanently sterile: *permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.*

b. Of childbearing potential and
   i. practicing an acceptable effective method of contraception. Acceptable methods for this study include:
      - hormonal contraception;
      - intrauterine device;
      - intrauterine hormone-releasing system;
      - male or female condom with or without spermicide;
      - cap, diaphragm or sponge with a vaginal spermicide;
      - vasectomized partner (the vasectomized partner should be the sole partner for that subject);
      - sexual abstinence*.

[a] 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).

Sexual abstinence is considered an effective method **only if defined as refraining from heterosexual intercourse from signing the informed consent until 3 months after the last dose of study vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*

ii. agrees to remain on an effective method of contraception from signing the informed consent until 3 months after the last dose of study vaccine. Use of hormonal contraception should start at least 28 days before the first administration of study vaccine.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active,) a woman must begin an acceptable effective method of contraception, as described above.

6 All women of childbearing potential must:

a. Have a negative highly sensitive serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening
b. Have a negative urine β-hCG pregnancy test immediately prior to each study vaccine administration

7 From the time of first vaccination through 3 months after the final vaccination, subject agrees not to donate blood.

4.1.2. Pediatric Subjects

8 Each child's parent/legal guardian must sign an ICF indicating that he/she understands the purpose of and procedures required for the study, are willing for his/her child to participate in the study and attend all scheduled visits, and are willing and able to comply with all study procedures, including maintaining contact with the site for 1 year following the first dose, and adhere to the prohibitions and restrictions specified in this protocol.

Note: For each subject, at least one parent, or legal guardian, according to local regulations, must give written consent.

9 Criterion amended per Amendment 3:

9.1 Subject is male or female, whose age on the day of ICF signature is ≥12* months to ≤24 months and who is seropositive for RSV.

Note: RSV-seropositive toddlers may be recruited if RSV seropositivity was assessed via RSV EIA or virus neutralization assay in a different study of the sponsor. In the event that a subject is not able to be randomized during the 42-day screening period, eg, due to illness or other circumstances, a subject may be rescreened and reconsented. However, a new serostatus blood sample would not be needed if the previous sample was deemed seropositive.

*Window of up to minus 2 weeks

10 Subject is the product of a normal term pregnancy ≥37 weeks, with a minimum birth weight of 2.5 kg.

11 Subject must be in good health without any significant medical illness on the basis of physical examination, medical history, and vital signs performed at screening.

12 Subject has received all routine immunizations appropriate for his or her age according to local guidelines.

13 Each child's parent(s)/legal guardian(s) must have access to a consistent means of contact either by telephone contact or email/computer.

4.2. Exclusion Criteria

4.2.1. Adult Subjects

1. Subject has acute illness (this does not include minor illnesses such as diarrhea) or temperature ≥38.0 ºC/100.4 °F within 24 hours prior to the first dose of study vaccine.
2. Subject has a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
3. Subject 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. Subject has had major surgery (per the investigator's judgment), within 12 weeks before dosing, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 6 months after the last dose of study vaccine. *Note*: Subjects with planned surgical procedures to be conducted under local or locoregional anesthesia and not judged as major by the investigator may participate.
5. Subject has chronic active hepatitis B or hepatitis C infection, documented by hepatitis B surface antigen and hepatitis C antibody, respectively.
6. Subject has HIV type 1 or type 2 infection.
7. Subject has had major psychiatric illness and/or drug or alcohol abuse which in the investigator's opinion would compromise the subject's safety and/or compliance with the study procedures.
8. Subject has current or past abuse of recreational or narcotic drugs or alcohol, which in the investigator's opinion would compromise the subject's safety and/or compliance with the study procedures.
9. Subject 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, hepatitis B or rabies) should be given at least 14 days before or 14 days after each study vaccination.

10. Subject 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 this study. *Note: Participation in an observational clinical study (ie, with no intervention) is allowed upon approval of the sponsor.*
11. Subject has received treatment with Ig in the 2 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.
12. Subject 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).
13. Subject has a history of chronic urticaria (recurrent hives), eczema and/or atopic dermatitis.
14. Subject has a history of acute polyneuropathy (eg, Guillain-Barré syndrome).
15. Subject 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)
    - Administration of antineoplastic and immunomodulating agents or radiotherapy during the study and within 6 months before first administration of study vaccine
16. Subject has a contraindication to intramuscular injections and blood draws, eg, bleeding disorders.
17. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study vaccine.
18. Subject 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.
19. Subject cannot communicate reliably with the investigator.
20. Subject who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or are unlikely to complete the full course of vaccination and observation.

4.2.2. Pediatric Subjects

21. Subject has moderate or severe illness (this does not include minor illnesses such as diarrhea) or temperature ≥38.0 ºC/100.4 °F within 24 hours prior to the first dose of study vaccine; enrollment at a later date is permitted.

22. Subject's weight is below 10th percentile according to World Health Organization (WHO) pediatric growth and weight charts.[7]

23. Criterion amended per Amendment 3:

    23.1 Subject has any clinically significant acute or chronic medical condition that, in the opinion of the investigator, would preclude participation: eg, history of seizure disorders, bleeding/clotting disorder, autoimmune disease, active malignancy, systemic infections, congenital heart disease, history of any pulmonary condition requiring medication, atopy, reactive airway disease, medically-confirmed wheezing, bronchoconstriction or treatment with a β2 agonist, cystic fibrosis, bronchopulmonary dysplasia, chronic pulmonary disease, medically-confirmed apnea, hospitalization for respiratory illness, or mechanical ventilation for respiratory illness.

24. Subject has major congenital anomalies or known cytogenetic disorders (eg, Down's syndrome).

25. Subject has had major surgery within the 4 weeks prior to randomization or has planned major surgery through the course of the study.

26. Subject is in receipt of, or planning to receive, live attenuated vaccine (eg, measles, mumps and rubella [MMR] or varicella, but excluding rotavirus vaccine) within 28 days of each study vaccination (ie, before and after); other vaccines (eg, influenza, pertussis, polio or rotavirus) should be given at least 14 days before or 14 days after each study vaccination. *Note*: Planning for routine childhood vaccinations will be available from the site to ensure that these can be taken at appropriate times during the study.

27. Subject has known or suspected immunodeficiency, such as known HIV infection.

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

29. Criterion amended per Amendment 3:

    29.1 Subject has a known allergy to vaccines or vaccine components (including any of the constituents of the study vaccine), or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine components (including any of the constituents of the study vaccine). *Note*: subjects with egg allergies can be enrolled.

30. Criterion amended per Amendment 3:

    30.1 Subject has a history of the following moderate to severe chronic conditions: urticaria (recurrent hives), eczema and/or atopic dermatitis.

31. Subject has a history of acute polyneuropathy (eg, Guillain-Barré syndrome).

32. Subject has chronic or recurrent use of immunomodulators/suppressors, eg, cancer chemotherapeutic agents, oral or parenteral corticosteroids for at least 5 days within 42 days prior to randomization, or planned during the course of the study.
33. Subject has a history of receipt of blood products or Ig within 3 months of randomization. Subject has been in receipt of palivizumab/Synagis® or received any other vaccine or monoclonal/polyclonal antibody in a previous RSV study at any time prior to randomization.
34. Subject has a contraindication to intramuscular injections and blood draws, eg, bleeding disorders.
35. Subject has a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
36. Subject's parent(s)/legal guardian(s) cannot communicate reliably with the investigator.
37. Subject is a family member of either the investigator, study-site employee, or employee of the sponsor.

Note: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject'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 subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects 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. Refer to Section 8, for details regarding prohibited and restricted therapy 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 4.1.1 and Section 4.2.1, respectively, for adult subjects, and Section 4.1.2 and Section 4.2.2, respectively, for pediatric subjects).
3. Vaccination with live attenuated vaccines within 28 days of a study vaccination (ie, before and after) is prohibited. Other vaccines (eg, influenza, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before (or at least 14 days after) administration of study vaccine in order 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 study vaccine.
4. *Cohort 1 only*: Subjects should receive all routine immunizations according to applicable national guidelines. A subject will not postpone, forego or delay the receipt of any recommended vaccine according to local schedules (eg, in Europe, the applicable national

immunization schedules,[11] and the equivalent in other countries) due to participation in the current study. All subjects should receive routine immunizations according to schedule.

5. STUDY VACCINE ALLOCATION AND BLINDING

Study Vaccine Allocation

Central randomization will be implemented in this study. Within each cohort, subjects will be randomly assigned to one of the two groups 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. Initially 2 sentinel subjects (one Ad26.RSV.preF and one placebo) will be enrolled to monitor for any unexpected severe adverse reaction to the vaccine. Therefore, the randomization of the first block will be phased to accommodate this. The remainder of the blocks will be filled to have an overall 2:1 randomization ratio. No stratification will be applied. The interactive web response system (IWRS) will assign a unique code, which will dictate the group assignment for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

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

Any randomized subject 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 subject will be assigned to the same group as the original (discontinued) subject. The replacement subject's randomization number will equal the randomization number of the discontinued subject +2000.

Blinding

The investigator will not be provided with randomization codes until the final analysis is performed. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Unblinding (ie, at the subject level) will only occur at the time of database lock of the final analysis. 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 its designee to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its 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. In the event the blind is broken, the sponsor must be informed as soon as

possible. The date, time and reason for the unblinding must be documented by the IWRS, in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

The subjects, study-site personnel, and investigator, and sponsor personnel will be blinded to study vaccine allocation throughout the study, except for the pharmacist or qualified staff member with primary responsibility for study vaccine preparation and dispensing. The pharmacy and preparation of study vaccines will be monitored by an independent study vaccine monitor (see Section 17.8).

Note: the unblinded pharmacist, or other qualified individual, may also perform the vaccine administration, but will have no other study function from randomization onwards.

The primary analysis, and any other interim analysis performed before the final analysis, will be performed on data unblinded at the group level[a]; there will be no unblinding at the subject level. These data will only be available to a selected group of sponsor personnel, excluding sponsor personnel involved in data collection or data management.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

If the randomization code is broken by the investigator or the study-site personnel, the subject 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 subject should not discontinue further study vaccine administration and may remain in the study (if the randomization code is still blinded to the study-site personnel and the subject).

6. DOSAGE AND ADMINISTRATION

Ad26.RSV.preF (JNJ-64400141) will be supplied in single-use vials. Volumes of 0.5 mL ($1x10^{11}$ vp) for adults and 0.25 mL ($5x10^{10}$ vp) for toddlers will be used for intramuscular injection.

Placebo will be supplied as sterile 0.9% saline for injection.

An unblinded pharmacist, or other qualified individual will prepare the appropriate vial and syringe and provide the syringe in a blinded manner to the study vaccine administrator who will perform the injection.

[a] To preserve the blind at the subject level, dummy subject identification numbers will be used to link the data to the randomization codes. The results of this analysis will only be distributed to sponsor personnel not directly involved in data collection and data management.

Note: the unblinded pharmacist, or other qualified individual, may also perform the administration, but will have no other study function from randomization onwards.

Further details on study vaccine preparation will be provided in the Investigational Product Preparation Instructions.

For adult subjects, injections should be administered in the deltoid. For pediatric subjects, injections should be administered in the anterolateral aspect of the thigh. Alternating injection sites will be used for the vaccinations on Day 1 and Day 29.

7. STUDY VACCINE COMPLIANCE

Study vaccine will be administered intramuscularly by a study vaccine administrator – a trained and qualified study nurse, medical doctor, or otherwise qualified health care professional. The date and time of each study vaccine administration will be recorded in the eCRF.

8. PRE-STUDY AND CONCOMITANT THERAPY

Pre-study therapies administered 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 time of each vaccine administration through 28 days after each vaccination, and additionally outside of these periods when associated with an SAE meeting the criteria outlined in Section 12.3.2. Information on concomitant use of herbal supplements or vitamins will not be collected.

Use of any experimental medication (including experimental vaccines other than the study vaccine) during the study is not allowed.

Subjects can receive medications such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), or antihistamines as needed, although their use must be documented and use of these medications as routine prophylaxis prior to study vaccination is discouraged, unless if specified by the sponsor. (*Note*: The use of EMLA® Cream [2.5% lidocaine and 2.5% prilocaine] as a topical anesthetic will not be prohibited during the study.)

For adult subjects: 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 (*Note*: ocular, topical or inhaled steroids are allowed). Antineoplastic and immunomodulating agents or radiotherapy are prohibited in the 6 months prior to screening and during the study.

For pediatric subjects: chronic or recurrent use of immunomodulators/suppressors, eg, cancer chemotherapeutic agents, oral or parenteral corticosteroids for at least 5 days within 42 days prior to randomization, or planned during the course of the study.

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

Vaccination with live attenuated vaccines within 28 days of a study vaccination (ie, before and after) is prohibited. Other licensed vaccines (ie, not live) should be given at least 14 days before or at least 14 days after administration of study vaccine in order 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 study vaccine.

For pediatric subjects: planning for routine childhood vaccinations will be available from the site to ensure that these can be taken at appropriate times during the 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 EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

Evaluation of the safety/tolerability of the vaccine regimens will include physical assessment by study-site personnel, and subject reports on signs and symptoms following vaccinations. Additional visits may be required if in the investigator's opinion, further clinical or laboratory evaluation is needed.

Each Cohort 0 subject, and each Cohort 1 subject's parents/legal guardian or caregiver will be provided with a thermometer, ruler, and subject diary to measure and record body temperature and solicited local (at injection site) and systemic events.

The diary includes instructions how to capture the data and grading scales to assess severity of the symptoms. Study staff are responsible for providing appropriate training for diary completion to avoid missing or incorrect data. The diary will be reviewed by the study personnel at visits indicated on the Time and Events Schedule.

For Cohort 0, at each visit/telephone call, each adult subject should be informed that, in the event of developing a combination of symptoms of respiratory infection (persistent [>48 hours] clinical symptoms of rhinitis [sneezing or runny nose or congestion] and persistence [>24 hours] of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite), they should contact the site as soon as possible.

For Cohort 1 only, at each visit/telephone call, each subject's parents/legal guardian or caregiver should be informed that, in the event that their child develops a combination of symptoms of respiratory infection (persistent [>48 hours] clinical symptoms of rhinitis [sneezing or runny nose or congestion] and persistence [>24 hours] of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite), they should contact the site as soon as possible.

The Time and Events Schedule summarizes the frequency and timing of safety and immunogenicity measurements applicable to this study.

The total blood volume to be collected from each subject in Cohort 0 over approximately 34 weeks from screening will be approximately 295 mL.

The total blood volume to be collected from each subject in Cohort 1 over approximately 36 weeks from screening will be approximately 14.5 mL.

9.1.2. Visit Windows

For the following visits, windows will be allowed as indicated:

- Second vaccination: ± 3 days (both cohorts)
- 3 days post-vaccination safety only visit: ± 1 day
- 7 days post-vaccination safety only visit: ± 2 days
- 28 days post-final vaccination safety and immunogenicity visit: ± 3 days
- 6 months post-final vaccination safety and immunogenicity visit: ± 14 days
- 1 year post-first vaccination safety follow-up telephone call: ± 14 days

9.1.3. Screening and Study Visits – Cohort 0 (Adults)

9.1.3.1. Screening Phase: Days –28 to 1

Only healthy subjects without acute illness or fever and complying with the inclusion and exclusion criteria specified in Section 4.1.1 and Section 4.2.1, respectively, will be included into the study. The investigator will provide detailed information on the study to the subjects and will obtain written informed consent prior to each subject's participation in the study. All the procedures described in the Time and Events Schedule will only take place after written informed consent has been obtained.

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

- Physical examination including vital signs measurement (systolic and diastolic blood pressure, respiratory rate, heart rate and body temperature) and height and weight
- Demographic information
- Medical history
- Review of pre-study medications
- Review of inclusion/exclusion criteria
- Serology testing (HIV type 1 or type 2, hepatitis B, hepatitis C)

- Blood sampling for hematology and biochemistry laboratory testing
- Women of childbearing potential: serum β-hCG pregnancy testing

General eligibility for this clinical study will be dependent on results of laboratory tests and the medical assessment. Study subjects who qualify for inclusion based on the medical history, physical examination, and laboratory results 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.

Subjects with laboratory values not meeting eligibility criteria at the screening visit may have one repeat testing at the discretion of the investigator if the abnormality is not clinically significant and may be a testing aberrancy. Enrollment of a subject with laboratory values representing toxicity Grades 1 or 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 9.2.3.2.

After laboratory data, medical history and physical examination data have been reviewed for completeness and adherence to inclusion and exclusion criteria, the subject can be deemed eligible for the study.

Unsolicited AEs will be recorded on the AE page of the eCRF from the signing of the ICF until 28 days after the first vaccination and from the second vaccination through the following 28 days, together with information about any concomitant medications. SAEs will be collected from ICF signature through 1 year after the first dose.

9.1.3.2. Active Phase – Day 1 to Day 211

9.1.3.2.1. Vaccination (Days 1 and 29)

Visit 2: Day 1/Day of Randomization/Vaccination 1

After re-check of inclusion and exclusion criteria[a], abbreviated physical examination (at the discretion of the investigator) and measurement of vital signs, eligible subjects will be randomized as described in Section 5. If medical status and/or physical examination suggest significant changes have occurred since screening, the laboratory tests will be repeated and the Day 1 visit re-scheduled, or the subject excluded from the study if he/she fails to meet the inclusion and exclusion criteria. Pre-dose samples for baseline immunogenicity assessments as well as pre-dose samples for safety laboratory testing (hematology and biochemistry) and a nasal turbinate sample for immunogenicity assessment will be collected. All women must have a negative urine pregnancy test pre-dose. Before the first vaccination, the investigator must check for any symptoms of an acute illness or body temperature ≥38.0 °C. In such a situation, the

[a] To include exclusion criteria 1, 4, 8, 9, 10, 11, 15, 16 and 17.

subject may be enrolled at a later date[a], or be withdrawn at the discretion of the investigator and after consultation with the sponsor.

Administration of first dose of study vaccine.

Subjects will be closely observed for a minimum of 30 minutes post-vaccination, or a minimum of 60 minutes post-vaccination according to local approvals, to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs and vital signs will be documented in the eCRF by study-site personnel following this observation period.

Subjects will be provided with a subject diary, thermometer, and ruler to measure and record body temperature, solicited local and systemic AEs for 7 days post-vaccination.

Visit 5: Day 29/Vaccination 2

Verification of selected eligibility criteria,[b,c] abbreviated physical examination (at the discretion of the investigator) and measurement of vital signs will be performed for all subjects pre-vaccination. Pre-dose samples for immunogenicity assessments as well as a nasal turbinate sample for immunogenicity assessment will be collected. All women must have a negative urine pregnancy test pre-dose. Before the second vaccination, the investigator must check for any symptoms of an acute illness or body temperature ≥38.0 °C. In such a situation, the subject may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator and after consultation with the sponsor. In the event of an ongoing AE or other situation precluding subject vaccination within 10 days, subjects may be vaccinated beyond the 10-day window at the discretion of the sponsor.

Administration of second dose of study vaccine.

Subjects will be closely observed for a minimum of 30 minutes post-vaccination, or a minimum of 60 minutes post-vaccination according to local approvals, to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs and vital signs will be documented in the eCRF by study-site personnel following this observation period.

Subjects will be provided with a subject diary, thermometer, and ruler to measure and record body temperature, solicited local and systemic AEs for 7 days post-vaccination.

[a] If within the screening window. Otherwise, rescreening is required.

[b] To include fever and any acute illness that precludes vaccination; also receipt of any routine immunizations.

[c] To include exclusion criteria 1, 4, 8, 9, 10, 11, 15, 16 and 17.

9.1.3.2.2. Post-first Vaccination Follow-Up

Sentinel Subjects: 48 Hours Post-first Vaccination

At 48 hours after the first vaccination, a telephone call will be made to sentinel subjects only to collect safety information (solicited and unsolicited AEs, SAEs and concomitant medications).

Visits 3 and 4 (3 and 7 Days Post-first Vaccination)

Visit 3 at 3 days post-vaccination will be a telephone call to check subject diaries and to collect safety information (solicited and unsolicited AEs, SAEs and concomitant medications).

Visit 4 at 7 days post-vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, and recording of any AEs/SAEs and concomitant medications. Samples for safety laboratory testing (hematology and biochemistry) and a nasal turbinate sample for immunogenicity assessment will be collected. The subject diary will be reviewed and collected. If Visit 4 occurs before the end of Day 8 (ie, before the end of the post-vaccination diary period), review of the diary will still take place, but the diary will be returned by the subject at Visit 5.

Note: If any of the 12 Cohort 0 subjects come in earlier than Day 8 for Visit 4 (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.

9.1.3.2.3. Post-second Vaccination Follow-Up

Sentinel Subjects: 48 Hours Post-second Vaccination

At 48 hours after the second vaccination, a telephone call will be made to sentinel subjects only to collect safety information (solicited and unsolicited AEs, SAEs and concomitant medications).

Post-second Vaccination: Visits 6 and 7 (7 Days and 28 Days Post-second Vaccination)

Visit 6 at 7 days after the second vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, and recording of any AEs/SAEs and concomitant medications. The subject diary will be reviewed and collected. If Visit 6 occurs before the end of the diary period after the second vaccination, review of the diary will still take place, but the diary will be returned by the subject at Visit 7.

Visit 7 at 28 days after the second vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement (at the discretion of the investigator), recording of any unsolicited AEs/SAEs and concomitant medications. Blood samples for immunogenicity assessments, as well as a nasal turbinate sample for immunogenicity assessment will be collected.

9.1.3.2.4. Final Visit – 6 Months After the Second Vaccination

Visit 8 at 6 months after the second vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement (at the discretion of the investigator), recording of any SAEs and associated concomitant medications. Blood samples will be collected for immunogenicity assessments.

9.1.3.2.5. Early Withdrawal – Early Exit Visit

For those subjects 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 required at the final visit (Section 9.1.3.2.4) will be performed. Samples for safety laboratory testing (hematology and biochemistry) will only be collected if the early exit is within 7 days of the first vaccination. Samples for immunogenicity assessments will only be collected if the early exit is at least 14 days after the previous blood draw for immunogenicity. A nasal turbinate sample for immunogenicity assessment will be collected if the early exit is within 14 days of the previous vaccination.

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

9.1.3.3. Safety Follow-up Phase: Cohort 0 – After Day 211

During the safety follow-up phase, any SAEs and associated concomitant medications will be reported through 1 year after the first dose.

Adults will be contacted by telephone call at the end of the safety follow-up phase.

The follow-up phase will include all subjects who received at least one dose of study vaccine.

9.1.4. Screening and Study Visits – Cohort 1 (Seropositive Toddlers)

Note: It is possible for any visit for a pediatric subject to be conducted in the subject's home if the study site has an established standard operating procedure as such. However, at least 5 toddlers in the active group are to have received first dose in a clinic setting and to have completed Visit 3 with no safety concerns before moving to vaccination of study subjects in a non-clinic setting (safety information of the first 5 active toddlers will be monitored by the PI(s)/SRP(s) through Visit 3, and escalated to the IDMC in the event of a safety signal).

9.1.4.1. Screening Phase: Days –42 to 1

Only healthy subjects without acute illness or fever and complying with the inclusion and exclusion criteria specified in Section 4.1.2 and Section 4.2.2, respectively, will be included into the study. The investigator will provide detailed information on the study to the subject's parent/legal guardian and will obtain his/her written informed consent prior to each subject's participation in the study. All the procedures described in the Time and Events Schedule will only take place after written informed consent has been obtained.

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

- Physical examination including vital signs measurement (respiratory rate, heart rate, body temperature) and height and weight
- Demographic information
- Medical history
- Review of pre-study medications
- Review of inclusion/exclusion criteria
- Blood sample for immunogenicity testing*
- Blood sample for RSV antibody testing**

*Collection of blood samples for immunogenicity assessments can be either at screening, or pre-dose on Day 1 at the discretion of the investigator.

**0.5 mL of blood for serostatus assessment can be collected at screening by venous blood sample or fingerstick, at the discretion of the investigator. If 0.5 mL is collected at screening, the baseline blood draw for immunogenicity should be on Day 1.

RSV seropositivity of Cohort 1 subjects will be assessed by RSV EIA or virus neutralization assay at screening. *Note*: RSV-seropositive toddlers may be recruited if RSV seropositivity was assessed via either of these assays in a different study of the sponsor. In the event that a subject is not able to be randomized during the 42-day screening period, eg, due to illness or other circumstances, a subject may be rescreened and reconsented. However, a new serostatus blood sample would not be needed if the previous sample was deemed seropositive.

General eligibility for this clinical study will be dependent on results of the medical assessment. Study subjects who qualify for inclusion based on the medical history and physical examination will be scheduled for enrollment and first vaccination (Visit 2) within 42 days. If necessary, the screening visit may be split into several visits.

After medical history and physical examination data have been reviewed for completeness and adherence to inclusion and exclusion criteria, the subject can be deemed eligible for the study.

Unsolicited AEs will be recorded on the AE page of the eCRF from the signing of the ICF until 28 days after the first vaccination and from the second vaccination through the following 28 days, together with information about any concomitant medications. SAEs (and any associated concomitant medications) will be collected from ICF signature through 1 year after the first dose.

9.1.4.2. Active Phase – Day 1 to Day 211

9.1.4.2.1. Vaccination (Days 1 and 29)

Visit 2: Day 1/Day of Randomization/Vaccination 1

After re-check of inclusion and exclusion criteria,[a] abbreviated physical examination (at the discretion of the investigator) and measurement of vital signs, body height and weight, eligible subjects will be randomized as described in Section 5. If medical status and/or physical examination suggests significant changes have occurred since screening, either the Day 1 visit can be re-scheduled, or the subject excluded from the study if he/she fails to meet the inclusion and exclusion criteria. Before the first vaccination, the investigator must check for any symptoms of an acute illness or body temperature ≥38.0 °C. In such a situation, the subject may be enrolled at a later date[b], or be withdrawn at the discretion of the investigator and after consultation with the sponsor.

Collection of blood samples for immunogenicity assessments can be either at screening, or pre-dose on Day 1 at the discretion of the investigator. If 0.5 mL of blood for RSV serology only is collected at screening, blood draw for immunogenicity should be on Day 1.

Administration of first dose of study vaccine.

Subjects will be closely observed for a minimum of 30 minutes post-vaccination, or a minimum of 60 minutes post-vaccination according to local approvals, to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs and vital signs will be documented in the eCRF by study-site personnel following this observation period.

A subject diary, thermometer, and ruler will be provided to measure and record body temperature and solicited local and systemic AEs for 7 days post-vaccination.

Visit 5: Day 29/Vaccination 2

After verification of selected eligibility criteria,[c] abbreviated physical examination (at the discretion of the investigator) and measurement of vital signs, body height and weight will be performed for all subjects pre-vaccination. Pre-dose samples for immunogenicity assessments will be collected. Before the second vaccination, the investigator must check for any symptoms of an acute illness. In such a situation, the subject may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator and after consultation with the sponsor. In the event of an ongoing AE or other situation precluding

[a] Exclusion criterion 21, 22, 25, 26, 28, and 32.

[b] If within the screening window. Otherwise, rescreening is required.

[c] Exclusion criterion 21, 22, 25, 26, 28 and 32.

subject vaccination within 10 days, subjects may be vaccinated beyond the 10-day window at the discretion of the sponsor.

Administration of second dose of study vaccine.

Subjects will be closely observed for a minimum of 30 minutes post-vaccination, or a minimum of 60 minutes post-vaccination according to local approvals, to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs and vital signs will be documented in the eCRF by study-site personnel following this observation period.

A subject diary, thermometer, and ruler will be provided to measure and record body temperature and solicited local and systemic AEs for 7 days post-vaccination.

9.1.4.2.2. Post-first Vaccination Follow-Up

Sentinel Subjects: 48 Hours Post-first Vaccination

At 48 hours after the first vaccination, a telephone call will be made to the parent/legal guardian or caregiver of sentinel subjects only to collect safety information (solicited and unsolicited AEs, SAEs and concomitant medications).

Visits 3 and 4 (3 and 7 Days Post-first Vaccination)

Visit 3 at 3 days post-vaccination will be a telephone call to check subject diaries and to collect safety information (solicited and unsolicited AEs, SAEs and concomitant medications).

Visit 4 at 7 days post-vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, and recording of any AEs/SAEs, concomitant medications and RTIs. The subject diary will be reviewed and collected. If Visit 4 occurs before the end of Day 8 (ie, before the end of the post-vaccination diary period), review of the diary will still take place, but the diary will be returned by the subject's parent/guardian or caregiver at Visit 5.

Note: If any of the first 12 Cohort 1 subjects come in earlier than Day 8 for Visit 4 (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.

9.1.4.2.3. Post-second Vaccination Follow-Up

Sentinel Subjects: 48 Hours Post-second Vaccination

At 48 hours after the second vaccination, a telephone call will be made to the parent/legal guardian or caregiver of sentinel subjects only to collect safety information (solicited and unsolicited AEs, SAEs and concomitant medications).

Post-second Vaccination: Visits 6, 7, 8 and 9 (3, 7 and 28 Days and 6 Months Post-second Vaccination)

Visit 6 at 3 days post-vaccination will be a telephone call to check subject diaries and to collect safety information (solicited and unsolicited AEs, SAEs and concomitant medications).

Visit 7 at 7 days after the second vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, and recording of any AEs/SAEs, concomitant medications and RTIs. The subject diary will be reviewed and collected. If Visit 7 occurs before the end of the diary period after the second vaccination, review of the diary will still take place, but the diary will be returned by the subject's parent/guardian or caregiver at Visit 8.

Visit 8 at 28 days after the second vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement (at the discretion of the investigator), measurement of body height and weight, recording of any unsolicited AEs/SAEs, concomitant medications, and RTIs. Blood samples will be collected for immunogenicity assessments.

Visit 9 at 6 months after the second vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement (at the discretion of the investigator), measurement of body height and weight, recording of any SAEs and associated concomitant medications, and RTIs. Blood samples will be collected for immunogenicity assessments. Visit 9 (Day 211) will be the final visit of the active phase for Cohort 1 subjects. *Note*: If Visit 9 occurs during the RSV season, an additional visit will be made by telephone at the end of the RSV season to collect safety information.

9.1.4.2.4. Early Withdrawal – Early Exit Visit

For those subjects who are unable to continue participation in the study up to Day 211, but for whom consent is not withdrawn, an early exit visit will be conducted as soon as possible. In the event of early withdrawal from the study, all procedures required at Visit 9 (Section 9.1.4.2.3) will be performed. Samples for immunogenicity assessments will be collected at the early exit visit as follows: if the early exit visit is before Day 29, 4 mL for cellular assessments and 1 mL for humoral assessments will be collected; if the early exit visit is after Day 29, only 2 mL for humoral assessments will be collected.

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

9.1.4.3. Safety Follow-up Phase: Cohort 1 – After Day 211

Each subject's parent/legal guardian or caregiver will be contacted by telephone call (or clinic visit) through 1 year after the first dose, including during the active phase and safety follow-up phase (every 30 days ± 7 days outside the RSV season, but every 14 days ± 3 days in season).

During each 28-day post-vaccination period, calls will remind parents/legal guardians to contact the site in the event their child develops an RTI. During the RSV season, but outside the 28-day post-vaccination period, calls will remind parents/legal guardians to contact the site in the event their child develops a combination of symptoms of respiratory infection (persistent [>48 hours] clinical symptoms of rhinitis [sneezing or runny nose or congestion] and persistence [>24 hours] of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite). These calls will also check for SAEs and associated concomitant medications, any MA-RTIs or severe LRTIs, and any subsequent medical care that may have been sought, since the previous visit or telephone contact (includes contacts with subjects who received at least one dose of study vaccine but withdrew from further dosing).

The follow-up phase will include all subjects who received at least one dose of study vaccine.

9.2. Study Evaluations

9.2.1. Immunogenicity

Venous blood samples will be collected for the determination of humoral and cellular responses, respectively, according to the Time and Events Schedules. 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 evaluations are summarized in Table 6 and Table 7, respectively.

Table 6: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Secondary endpoints	
RSV neutralization A	Analysis of neutralizing antibodies to the A strain
F-protein antibody (ELISA; pre- and/or post-fusion)	Analysis of antibodies binding to RSV F protein in post-fusion and/or pre-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 VNA
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including ADCC, ADCP, avidity, Fc characteristics, Ig isotype, functional VNA and protective antibody assessments

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

Table 7: Summary of Immunogenicity Assays (Cellular)

Assay	Purpose
Secondary endpoints	
Flow cytometry (ICS)*	Analysis of T-cell responses to RSV F-protein peptides for Th1/Th2 subtyping
Exploratory endpoints	
IFNγ ELISpot	T-cell IFNγ responses to RSV F-protein peptides
ICS	Analysis of T-cell responses to RSV F-protein peptide-stimulated PBMCs (including but not limited to, CD4/CD8, IL2, INFγ, TNFα, activation markers and memory)
Cytokine analysis	Analysis of secreted cytokines in RSV F peptide-stimulated PBMC supernatant, including, but not limited to, measurement of Th1/Th2 cytokine balance

ELISpot = enzyme-linked immunospot; F = fusion; ICS = intracellular cytokine staining; IFNγ = interferon gamma; IL = interleukin; PBMC = peripheral blood mononuclear cell; Th = T-helper (cell); RSV = respiratory syncytial virus; TNFα = tumor necrosis factor alpha
* Cytokine analysis for Th1/Th2 profiling will be done in cases where no ICS data can be generated due to insufficient number of PBMCs for ICS assay

In addition to RT-PCR performed on a nasal turbinate sample collected at the time of infection, any immunogenicity blood sample collected from any Cohort 1 subject who subsequently develops a suspected RTI may also be assayed by a serological assay (eg, ELISA specific to RSV protein G and/or N) to confirm RSV infection.

For adults, nasal turbinate samples, collected pre-dose on Days 1 and 29, 7 days post-Dose 1 (Day 8) and 28 days post-Dose 2 (Day 57) will be used to assess any Ig or cellular immune component.

Instructions for the collection, handling, storage, and shipment of blood and nasal turbinate samples for immunogenicity assay are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of blood and nasal turbinate 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. Other Evaluations – RSV Infection

RSV seropositivity of Cohort 1 subjects will be assessed by RSV EIA or virus neutralization assay at screening. The cut-off for seropositivity by EIA is a titer >10 EIA units and the cut-off by virus neutralization assay is a titer >4. *Note*: RSV-seropositive toddlers may be recruited if RSV seropositivity was assessed via either of these assays in a different study of the sponsor.

Nasal turbinate samples, taken from any Cohort 1 subject with an RTI during each 28-day post-vaccination period, and from any Cohort 1 subject with a combination of respiratory symptoms[a] during the RSV season (but outside of the 28-day post-vaccination period), and from any Cohort 1 subject with a MA-RTI or severe LRTI during the whole study period, will be assessed for the presence of RSV infection by RT-PCR. The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

[a] Persistent (>48 hours) clinical symptoms of rhinitis (sneezing or runny nose or congestion) and persistence (>24 hours) of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite.

In addition, scheduled blood samples may be assessed for the presence of RSV antibodies by serology.

9.2.3. Safety Evaluations

Any reference to activities to be performed by the subject refers to adult subjects or the parent/legal guardian for pediatric subjects.

Any clinically relevant changes occurring from ICF signature until 28 days after the first vaccination, and from the time of subsequent vaccinations through the following 28 days, must be recorded on the eCRF. Any clinically significant abnormalities, including those persisting at the end of the study/early withdrawal, will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Time and Events Schedule.

Adverse Events

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative). AEs will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

For solicited AEs, the following applies:

- **Solicited Adverse Events**

Information related to solicited events as defined in Section 12.1.1, will be recorded by subjects in a diary for 7 days after each vaccination. Each subject 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, or a minimum 60-minute post-vaccination assessment of solicited events at the site (according to local approvals). Diary information will be transcribed by the study personnel in the appropriate eCRF pages.

Injection Site (Local) Adverse Events

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

- **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 and/or movement of the limb. Due to subjective nature of the reaction, the severity assessment of pain/tenderness is self-reported (if a subject is unable to provide self-report, other reporters include parent/care giver or health care provider).[14]

- **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 either 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 health care professional's assessment, both symptoms have been combined to allow self-assessment by the subjects. Both 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.[23,24]

Systemic Adverse Events

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

Fever is defined as endogenous elevation of body temperature ≥38° C, as recorded in at least one measurement.[28]

[a] Recommended orally for adult subjects; rectally or axillary for pediatric subjects (actual routes to be recorded in the eCRF).

[b] All Day 8 post-vaccination diary assessments, including temperature measurements, may be collected earlier to coincide with the corresponding clinic visit.

Subjects will also be instructed on how to note daily in the diary for 7 days post-vaccination symptoms of the following events: *for adult subjects* – fatigue, headache, myalgia, arthralgia, chills, nausea and fever (ie, body temperature ≥38 °C); *for pediatric subjects* – loss of appetite, vomiting, diarrhea, decreased activity/lethargy, irritability/crying and fever (ie, body temperature ≥38 °C).

The severity of these solicited systemic AEs will be graded by the investigator according to the criteria presented in Section 12.1.3, Severity Criteria.

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

9.2.3.1. Respiratory Tract Infections

RTIs will be reported as follows:

- During the 28-day period after each vaccination, all RTIs will be reported.
- During the RSV season, but outside the 28-day period after each vaccination, RTIs will be reported for which a combination of respiratory symptoms[a] develop.
- Outside the RSV season, only MA-RTIs and severe LRTIs will be reported (ie, for the whole study period).

RTIs, preferably as a diagnosis, will also be reported on the AE page of the eCRF if they occur within 28 days following vaccination. Any RTI fulfilling the criteria of an SAE would be reported as such during the entire study. Any severe LRTI will be reported using the SAE reporting system and SAE form, regardless of whether the event fulfills the criteria of an SAE.

9.2.3.2. Clinical Laboratory Tests – Cohort 0 Only

Blood samples for serum chemistry and hematology will be collected at screening, pre-vaccination on Day 1 and on Day 8. The following tests will be performed by a local laboratory (*parameters only measured at screening):

- **Hematology Panel**

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

[a] Persistent (>48 hours) clinical symptoms of rhinitis (sneezing or runny nose or congestion) and persistence (>24 hours) of one or more of the following: cough, abnormal breathing, fever, lethargy or decreased appetite.

- **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 assess systematically any clinical significance. The laboratory reports must be filed with the source documents.

Laboratory values will be initially evaluated by the investigator according to local laboratory criteria. Abnormal values outside the local 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" (see Attachment 1). Laboratory values within local laboratory normal limits will not be FDA graded and will be considered as normal.

Reporting Laboratory Abnormalities as AEs

Any clinically significant abnormal laboratory value within 28 days post-vaccination that falls outside of the local 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 AEs.

Any laboratory value falling within the local 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.

Note: Values for parameters falling within the local laboratory normal range should not be reported as AEs.

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 the investigator's judgment, however Grade 3 abnormalities should be retested within 48 hours. Any clinically significant abnormalities (including those persisting at the end of the study or at early withdrawal) will be followed by the investigator until resolution or until a clinically stable endpoint is reached (see Section 12.3).

Screening Procedures

For entry into the study, each subject must be healthy on the basis of clinical laboratory tests performed at screening. Enrollment of a subject with laboratory values outside of the local laboratory normal range representing FDA toxicity Grade 1 is allowed if the investigator considers the values reasonable for the population under study and not clinically significant.

Additional Clinical Laboratory Assessments

Additional clinical laboratory assessments (HIV type 1 or type 2, hepatitis B, hepatitis C serology) will be performed locally at screening for Cohort 0 only.

9.2.3.3. Vital Signs

Blood pressure (Cohort 0 only) 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):

- Heart rate (beats per minutes, bpm), respiratory rate (breaths per minute), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg)
- Body temperature (oral route recommended for Cohort 0, rectal or axillary route recommended for Cohort 1)

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

9.2.3.4. Physical Examination

Full physical examination, including length/height and body weight, will be carried out at screening. At all other visits, an abbreviated, symptom-directed examination will be performed by the investigator based on any clinically relevant issues, clinically relevant symptoms and medical history. Symptom-directed physical examination may be repeated if deemed necessary by the investigator.

Note: For Cohort 0, physical examination will only be required at the screening visit.

Physical examinations will be performed by the investigator or appropriately trained delegate. Any abnormalities or changes in severity noted during the review of body systems should be documented in the eCRF.

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

10.1. Completion

A subject will be considered to have completed study vaccination if he or she has received all study vaccinations. A subject will be considered to have completed the study if he or she has completed assessments through to the end of the study (see Section 17.9.1).

10.2. Discontinuation of Study Vaccine/Withdrawal from the Study

Discontinuation of Study Vaccine

A subject will not be automatically withdrawn from the study if they have to discontinue from study vaccination before the end of the study vaccine regimen.

Subjects will be discontinued from study vaccine administration for the reasons listed below. These subjects must not receive any additional dose of study vaccine but should continue other study procedures, eg, safety follow-up:

- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- Pregnancy (Cohort 0 only)
- Any related SAE
- Any related AE, worsening of health status or intercurrent illness that, in the opinion of the investigator, requires study vaccine discontinuation

Withdrawal from the Study

Each subject has the right to withdraw (*Cohort 1*: "subject's parent/legal guardian has the right to withdraw their child") from the study at any time for any reason without affecting the right to treatment by the investigator. Although the subject (*Cohort 1*: "subject's parent/legal guardian") is 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 subject's rights.

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

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

Any unnecessary study discontinuation should be avoided. Should a subject be withdrawn, all efforts should be made to complete and report the observations as thoroughly as possible. Whenever a subject is withdrawn from the study, independent of the reason, a final evaluation should be completed for that subject and the major reason for which the subject was withdrawn must be stated. If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/ withdrawal. The measures taken to follow up must be documented.

When a subject is withdrawn 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 subject may not be assigned to another subject. In general, subjects who withdraw will not be replaced, unless that subject was randomized but did not receive any study vaccine. However, any randomized subject 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.

If a subject withdraws early from the study, assessments for early withdrawal should be obtained (see Section 9.1.3.2.5 and Section 9.1.4.2.4).

Subjects 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 subject may withdraw consent for use of samples for future research (refer to 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:

- 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 time of vaccination.

If any of these events occur at the scheduled time for the first vaccination, enrollment at a later date is permitted[a] at the discretion of the investigator and after consultation with the sponsor. If any of these events occur at the scheduled time for the second vaccination, the subject may be vaccinated up to 10 days beyond the scheduled vaccination, or be withdrawn from further vaccination at the discretion of the investigator and after consultation with the sponsor. In the event of an ongoing AE or other situation precluding subject vaccination within 10 days, subjects may be vaccinated beyond the 10-day window at the discretion of the sponsor.

Note: Medically indicated vaccines should be given at least 14 days before or 14 days after study vaccine administration (see Section 4.3).

[a] If within the screening window. Otherwise, rescreening is required.

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 (SAP).

Planned analyses are described in Section 11.8.

11.1. Analysis Sets

The **Full Analysis Set (FA)** includes all subjects who were randomized and received at least one dose of study vaccine, regardless of the occurrence of protocol deviations. Vaccination assignment will follow the as-treated principle. All safety analyses will be based on the FA set. As a sensitivity analysis, key immunogenicity tables will also be based on the FA set.

The **Per-protocol Immunogenicity Set (PPI**) will include all randomized and vaccinated subjects for whom immunogenicity data are available, excluding subjects with major protocol deviations expecting to impact the immunogenicity outcomes.

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

- If subjects miss one or more doses, but continue the planned visit schedule, samples taken after the planned but missed dose(s) will not be taken into account;
- For subjects who experience a natural RSV infection (based on RT-PCR, or other sources), samples taken after the natural infection are not be taken into account.
- Any subject who receives study vaccine beyond the Day 29 window specified in the Time and Events Schedule would not be included in the per-protocol immunogenicity analyses.

The analysis of immunogenicity will be based on the PPI set.

11.2. Sample Size Determination

The number of subjects chosen for this study will provide a preliminary safety and immunogenicity 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 site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated.

The following table shows the probabilities of observing at least one AE at given true AE rates:

True AE rate	Probability of observing at least one AE in N subjects			
	N=4	N=8	N=12	N=24
0.5%	2%	4%	6%	11%
1%	4%	8%	11%	21%
2.5%	10%	18%	26%	46%
5%	19%	34%	46%	71%
10%	34%	57%	72%	92%
25%	68%	90%	97%	100%
50%	94%	100%	100%	100%

11.3. Criteria for Exploratory Endpoints

11.3.1. Definitions for Exploratory Endpoints

The exploratory endpoints shown below will be collected to assess the feasibility of, and gain expertise in the collection of such events for future studies.

- RSV MA-RTI: All subjects with RSV-RTI that is medically attended, ie when the subject's parent/legal guardian seeks medical attention outside of normal study procedures, including health care professional's visit to the home, clinic visit, emergency room attendance, and hospital admission. (*Note*: medical attention outside normal study procedures will as much as possible also be captured on the RSV Symptoms Form.)
- Severe LRTI: For subjects in Cohort 1, severe RSV-LRTI will be defined as the presence of severe LRTI as assessed by the CEC, and a positive assessment for RSV.

11.3.1.1. Presence of Severe LRTI as Assessed by the CEC

For subjects with an SAE related to respiratory disease, the CEC will determine the presence or absence of severe LRTIs by reviewing all available clinical information related to respiratory disease, with a special focus on the following characteristics ("WHO" criteria[30]):

- Respiratory infection defined as cough or difficulty breathing

AND

- LRTI defined as fast breathing or oxygen saturation (SpO2) <95%

AND

- ≥1 of the severe disease feature:
  - oximetry <93%
  - lower chest wall indrawing

11.3.1.2. Determination of RSV Positivity

- A subject is considered RSV positive if he/she has a positive RT-PCR for RSV on nasal turbinate samples (central laboratory).

- If a RT-PCR test result for RSV is missing (ie, not available or not conclusive), the CEC will assess RSV positivity using all available clinical and laboratory information.

11.4. Subject Information

For all subjects, demographic characteristics (eg, age, height, weight, body mass index [BMI], race, and gender), and other baseline characteristics (eg, physical examination, medical history, and concomitant diseases) will be tabulated and summarized with descriptive statistics. BMI will only be calculated for Cohort 0 (adults). For the toddlers, the weight and length percentiles according to the WHO pediatric growth and weight charts will be tabulated.[7]

11.5. Immunogenicity Analyses

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% confidence interval [CI] for ELISA and virus neutralization assays; median and quartiles for ELISpot and ICS) will be calculated for continuous immunologic parameters at all timepoints. Graphical representations of immunologic parameters will be made as applicable.

Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters as applicable.

The primary analysis set for immunogenicity is the PPI set. As a sensitivity analysis, key tables will also be based on the FA set. Depending on their occurrence, the effect of missed doses or natural infections might be further explored. Note that they will be included in the tables showing the FA set.

11.6. RSV Infection

Incidence of any RSV infection, as described in Section 3.2, in Ad26.RSV.preF and placebo subjects will be summarized by descriptive statistics.

11.7. Safety Analyses

No formal statistical testing of safety data is planned. 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 after vaccination up to 28 days post-vaccination, and all SAEs, will be included in the analysis. For each AE, the percentage of subjects who experience at least one occurrence of the given event will be summarized by group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects 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 moment of subsequent vaccinations for studies using multiple doses.

Solicited local (at injection site) and 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 subjects with at least one solicited local (at injection site) or systemic AE will be presented. Frequencies of unsolicited AEs, separately for all and vaccination-related only, will be presented by System Organ Class and preferred term.

Clinical Laboratory Tests (Cohort 0 Only)

Laboratory abnormalities will be determined according to the FDA Guidance document (see Attachment 1), or in accordance with the normal ranges for the clinical laboratory parameter if no grades are available. 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.

Vital Signs

A tabulation of the distribution of temperatures per half degree intervals will be provided. For heart rate and respiratory rate, the percentage of subjects with values beyond clinically relevant limits will be summarized.

Physical Examination

Physical examination abnormalities will be listed.

11.8. Planned Analyses

The following analyses will be performed:

- **Cohort 0**: primary analysis will be performed when all subjects have reached Day 57 (28 days post-Dose 2) or discontinued earlier. All available safety and immunogenicity data gathered so far will be included in the analysis; unblinded at the group level.
- **Cohort 1**: interim analysis will be performed when at least 24 subjects have reached Day 29 (28 days post-Dose 1) or discontinued earlier. All available safety and immunogenicity data gathered so far will be included in the analysis; unblinded at the group level.
- **Cohort 1**: primary analysis will be performed when all subjects have reached Day 57 (28 days post-Dose 2) or discontinued earlier. All available safety and immunogenicity data gathered so far will be included in the analysis; unblinded at the group level.
- **Final analysis of both cohorts**; at the end of the study, 1 year after the first dose; unblinded

Additional interim analyses (blinded or unblinded at the group level) may be performed during the study for the purpose of informing future vaccine-related decisions in a timely manner, or upon health authority request. 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, excluding sponsor personnel involved in data collection or data management.

11.9. Data Review Committees

11.9.1. Independent Data Monitoring Committee (IDMC)

An IDMC will be established to review safety data, and as needed on an ad hoc basis to ensure the continuing safety of the subjects enrolled in this study. The IDMC will convene to discuss any situation that meets a study vaccination pausing rule (see Section 11.10).

The IDMC will also monitor severe LRTI. The presence of severe LRTI will be determined by the CEC, a separate committee (see Section 11.9.2). The outcome of the adjudication of the CEC as well as the determination of RSV positivity will be provided to the IDMC.

The IDMC will monitor severe LRTI as detailed in the IDMC charter.

The IDMC will consist of members independent of the sponsor, including at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter. An external statistician independent of the sponsor and not involved in the interim, primary, and final analyses of the study will prepare the data and perform all analyses for review by the IDMC.

In any case(s) under review, the IDMC will review blinded data first, but is entitled to and has the right to require submission of unblinded data if deemed necessary.

Individual treatment information and other information essential to maintaining the blinded and controlled study design including the detailed results of the IDMC analyses will not be revealed to anyone outside of the IDMC.

Details on the intervals of the safety evaluations and on how the integrity of the study will be maintained when the blind is broken with an IDMC analysis will be provided in the IDMC charter.

Safety data from the interim and primary analyses will be shared with the IDMC.

If any question arises related to safety, the IDMC will be convened.

11.9.2. Clinical Endpoint Committee (CEC)

The CEC is an independent panel consisting of external medical experts with relevant experience in RSV in children. At all times during the study, the CEC will stay blinded, and hence CEC members will not be part of the IDMC. Full details of CEC responsibilities, authorities, and procedures will be documented in its charter.

The presence of severe LRTI will be determined by the CEC. By review of all available clinical and laboratory information, including clinical information from SAE forms related to respiratory disease, the CEC will decide whether a given situation concerns a severe LRTI. The outcome of the adjudication of the CEC, as well as the determination of RSV positivity, will be provided to the IDMC.

For subjects with an SAE related to respiratory disease, the CEC will determine the presence or absence of severe LRTIs by reviewing all available clinical information related to respiratory disease, with a special focus on the following characteristics ("WHO" criteria[30]):

- Respiratory infection defined as cough or difficulty breathing

AND

- LRTI defined as fast breathing or oxygen saturation (SpO2) <95%

AND

- ≥1 of the severe disease feature:
  - oximetry <93%
  - lower chest wall indrawing

11.10. Study Vaccination Pausing Rules

The PIs and the SRP will monitor the study vaccination pausing rules. If study vaccination is considered to raise significant safety concerns, further vaccination of subjects will be suspended until IDMC review is carried out and subsequent communication between the sponsor and the investigators takes place.

The occurrence of any of the following events will lead to suspension of further study vaccination, and trigger a meeting of the IDMC to discuss study suspension, adaptation or discontinuation of further vaccination:

1. One or more subjects in the same 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 subjects in the same cohort experience anaphylaxis clearly not attributable to other causes than vaccination with study vaccine; *OR*
3. Two or more subjects in the same 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 subjects in the same 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 subjects in Cohort 0 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 subject, regardless of causality.

Note: The count of subjects for each pausing rule will be across all study sites. After the first IDMC meeting triggered by the occurrence of a given pausing rule, the IDMC will convene thereafter for each additional subject meeting that pausing rule.

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

If any of the above specific pausing rules are met, the IDMC will make recommendations regarding the continuation of the study to the sponsor. Study suspensions or terminations will occur within 5 working days after the decision is made, unless local regulations specify a shorter timeframe. Local regulatory authorities including IECs/IRBs will be informed within the appropriate regulatory-mandated timeframes. A study may be resumed only upon approval of a substantial amendment to the initial study application by the local regulatory authorities and IECs/IRBs. The sponsor will communicate conclusions regarding study continuation to the investigators, the IECs/IRBs and the national regulatory authorities as appropriate.

Vaccinations for an individual subject may be suspended for safety concerns other than those described above, at the discretion of the investigator if he/she feels the subject's safety may be threatened. The investigator may ask for a review meeting to be held for any single event or combination of multiple events which, in his/her professional opinion, jeopardize the safety of the subjects 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 investigator, subject safety may be threatened. The sponsor should be notified that the IDMC will need to be convened.

Central randomization will be implemented in this study. Central randomization ensures that study recruitment and dosing can be effectively halted simultaneously across all sites in the event of a situation meeting any of the pausing rules. Sponsor activities and responsibilities related to temporary study suspension and restart are described in the Sponsor's applicable standard operating procedures (SOPs).[19,20]

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, 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 AEs and SAEs

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. For some studies, subjects are not always able to provide valid verbal responses to open-ended questions. In these circumstances, another method of detecting these events is specified.

Solicited Adverse Events

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

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which subjects are specifically not questioned in the subject 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 subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with study vaccine. 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 Conference on 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 unsolicited AEs starting with the signing of the ICF for 28 days after the first vaccination, and from the time of subsequent vaccinations through the following 28 days, and solicited AEs from the time of each vaccination for 7 days post-vaccination (refer to Section 12.3.1, All Adverse Events, for time of last AE recording). For both cohorts, all SAEs will be collected from ICF signature to the end of the study. RTIs, preferably as a diagnosis, will be reported on the AE page of the eCRF if they occur within 28 days following vaccination; any RTI fulfilling the criteria of an SAE would be reported as such during the entire study period. Any severe LRTI will be reported using the SAE reporting system and SAE form, regardless of whether the event fulfills the criteria of an SAE.

Serious Adverse Event

An SAE based on ICH and European Union (EU) 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 subject 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 subject 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 study 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.

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, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.[1]

Adverse Event Associated With the Use of the Vaccine

An AE is considered associated with the use of the vaccine 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 study vaccine or to alternative causes (eg, natural history of the underlying diseases, concomitant therapy). This applies to all AEs, whether 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 study vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the study vaccine contributed to the AE.

Unrelated: there is no suspicion that there is a relationship between the study vaccine and the AE; there are other more likely causes and administration of the study 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 the study 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 (for Cohort 0), and in Attachment 2 (for Cohort 1). *Note*: For Cohort 0, laboratory values within local 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 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 subject (eg, laboratory abnormalities).

For Cohort 0, the toxicity grading scale used for laboratory assessments is based on the FDA toxicity grading table, 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 subject based on the severity assessment provided in the diary and then verified by the investigator using the respective toxicity grading table.

12.2. Special Reporting Situations

Safety events of interest on a sponsor study vaccine that may require expedited reporting and/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 subject/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

Unsolicited AEs and special reporting situations will be reported from the time a signed and dated ICF is obtained until 28 days (including relevant visit window, if applicable) after first dose of study vaccine, and thereafter, for 28 days (including relevant visit window, if applicable) after each subsequent dose of study vaccine. Unsolicited AEs with the onset date outside the time frame defined above (>28 days after previous study vaccination) that are ongoing on the day of the subsequent vaccination should be recorded on the eCRF AE page.

Solicited AEs will be recorded by each subject in the subject diary for 7 days after each dosing. The investigator will review each subject's diary at the subsequent in-clinic visit; diary information will be transcribed by the study personnel in the on-site assessment 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 data (and clinical laboratory data for Cohort 0), as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study vaccine. All AEs will be deemed related to study vaccine or not related to study 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 study 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 study 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.

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

- Study number
- Statement, in the local language(s), that the subject 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
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring from ICF signature until the end of the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

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 subject'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 study vaccine or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care 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 the course of a subject'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 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 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 subject in a study during the entire study period, whether or not the event is expected or associated with the study vaccine, is considered an SAE and must be reported.

12.3.3. Pregnancy (Cohort 0 Subjects)

All initial reports of pregnancy in female subjects or partners of male subjects 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 SAE Form.

Because the effect of the study vaccine on sperm is unknown, pregnancies in partners of male subjects 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 efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, 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 (refer to Section 12.3.2, Serious Adverse Events). 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. STUDY VACCINE INFORMATION

14.1. Physical Description of Study Vaccine

A human replication-incompetent adenovirus-vectored vaccine candidate, 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 for 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. Ad26.RSV.preF will be supplied as a colorless frozen liquid to be thawed prior to use. Ad26.RSV.preF will be filled in stoppered and sealed 2 mL single-use glass vials. Injection volumes of 0.5 mL ($1x10^{11}$ vp) for adults and 0.25 mL ($5x10^{10}$ vp) for toddlers will be used. Refer to the Investigator's Brochure for details of the components of Ad26.RSV.preF and a list of excipients.

Placebo

Placebo will be supplied as sterile 0.9% saline for injection in 2 mL ampoules.

14.2. Packaging and Labeling

All study vaccines were manufactured and packaged in accordance with Current Good Manufacturing Practice. All study vaccines will be packaged and labeled under the responsibility of the sponsor. Study vaccine labels will contain information to meet the applicable regulatory requirements.

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

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

14.3. Storage and Handling

Vials 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. Study refrigerators/freezers should be equipped with back-up power systems. In the event that study vaccine is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected study vaccine can be used or will be replaced. The affected study vaccine must be quarantined and not used until further instruction from the sponsor is received.

For adult subjects, injections should be administered in the deltoid. For pediatric subjects, injections should be administered in the anterolateral aspect of the thigh. Alternating injection sites will be used for the vaccinations on Day 1 and Day 29. The study vaccine will be prepared by the unblinded site pharmacist, or other qualified individual and administered by a study vaccine administrator.

Note: the unblinded pharmacist, or other qualified individual, may also perform the administration, but will have no other study function from randomization onwards.

Further details for study 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 study vaccine received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the subject must be documented on the vaccine accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions.

Study vaccine 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 study vaccine must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study vaccine will be documented on the vaccine return form. When the study site is an

authorized destruction unit and study vaccine supplies are destroyed on-site, this must also be documented on the vaccine return form.

Potentially hazardous materials such as used ampoules, 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.

Study vaccine should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study vaccine will be supplied only to subjects participating in the study. Returned study vaccine must not be dispensed again, even to the same subject. Study vaccine may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study vaccine from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for Prophylactic RSV Vaccine
- Investigational Product Preparation Instructions/Investigational Product Procedures Manual
- Laboratory Manual (including procedures for collection of nasal turbinate samples)
- Trial Center File
- IWRS Manual
- Electronic Data Capture (eDC) Manual/eCRF completion guidelines and randomization instructions
- Sample ICF
- Subject diaries
- Rulers
- Thermometers
- RTI Symptoms Forms
- Contact information page(s)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Cohort 0 only: Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects 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 subjects 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 adult subject will not exceed the US Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), and FDA guidelines of 550 mL in any eight-week period.[44,45]

Cohort 1 only: The parents/legal guardian of potential subjects will be fully informed of the risks and requirements of the study and, during the study, will be given any new information that may affect their decision for their child to continue participation. They will be told that their consent for their child 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 parents/legal guardian who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be able to enroll their child in the study.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. For the purposes of this study, all references to subjects who have provided consent refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process.

The total blood volume drawn from each pediatric subject will not exceed the most stringent (European Medicines Agency) guidelines for pediatric subjects in clinical trials: blood loss should not exceed 3% of total blood volume over four weeks, and it should not exceed 1% of total blood volume at any single time.[12]

See Section 3.4 for the benefit-risk assessment.

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.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects 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 subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects 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 subjects
- 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 subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject 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 subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure 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 study vaccine

- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects 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 subjects, 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

In this section, any reference to activities to be performed by the subject refers to adult subjects or the parent/legal guardian for pediatric subjects.

Each subject 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 subject 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 subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects 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 subject will receive. Finally, they will be told that the investigator will maintain a subject 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 subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject 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 subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects 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 subjects confidential.

The informed consent obtained from the subject (or parent/legal guardian for pediatric subjects) 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 subject (or parent/legal guardian for pediatric subjects) 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, including samples from subjects who were screened but not randomized, will only be used to understand Ad26.RSV.preF, to understand RSV, and to develop tests/assays related to Ad26.RSV.preF and RSV. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to 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 subjects, 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 study vaccine to the study site:

- Protocol and amendment(s), if any, signed and dated by the PI.
- 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, subject 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, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.
- Genetically modified organism (GMO) and/or Institutional Biosafety Committee (IBC) approval, if applicable.

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

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator 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. Subject Identification, Enrollment, and Screening Logs

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

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

The investigator must also complete a subject screening log, which reports on all subjects 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: subject 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; study vaccine administration information; and date of study completion and reason for early discontinuation of study 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 subject 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 subject diary will be reviewed by the investigator; diary information will be transcribed by study personnel into the eCRF as described in the eCRF Completion Guidelines.

An 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

Case report forms are prepared and provided by the sponsor for each subject 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 subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject 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 subject, 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 active phase will be when the last subject completes the visit 6 months after the final dose (Visit 8 Cohort 0; Visit 9 for Cohort 1). The end of the study will be the last subject's last visit (by telephone) at the end of the safety follow-up phase (1 year after the first dose). The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject 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 subjects 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. Subject 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 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 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 subject 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.

Arrangements on publication policy will be addressed in the Clinical Trial Agreement.

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.

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47. Data on file.

Attachment 1: Toxicity Tables for Cohort 0

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 visit or hospitalization
Tenderness	Mild discomfort to Touch	Discomfort with Movement	Significant discomfort at rest	Emergency room 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	Emergency room visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	Emergency room visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	>155	Emergency room visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	>100	Emergency room visit or hospitalization for malignant hypertension
Hypotension (systolic) - mm Hg	85 – 89	80 – 84	< 80	Emergency room visit or hospitalization for hypotensive shock
Respiratory Rate - breaths per minute	17 – 20	21 – 25	>25	Intubation

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

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

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

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	Emergency room 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 >800gms/24 hours or requires outpatient IV hydration	Emergency room 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	Emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Systemic Illness	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Emergency room visit or hospitalization

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 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 subject 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/mm3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC Decrease - cell/mm3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm3	650 – 1500	1501 – 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm3	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.

Attachment 2: Toxicity Tables for Cohort 1

The abbreviations used in the following tables are:

CNS: central nervous system; CK: creatine kinase; ULN: upper limit of normal

CLINICAL ADVERSE EVENTS
Grading scale used for clinical AEs is adapted from the Division of Microbiology and Infectious Diseases (DMID) "Pediatric Toxicity Tables for Children Greater Than 3 Months of Age (2007)". For AEs not included in the tables below, severity criteria guidelines will be provided in the full protocol.

Gastrointestinal	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	Minimal symptoms; caused minimal or no interference with, school or self-care activities. Child vomits once per day (24h).	Notable symptoms; required modification in activity or use of medications; did not result in cancellation of social activities. Child vomits 2-3 times per day (24h).	Incapacitating symptoms; required bed rest and/or resulted in cancellation of social activities. Child vomits 4-6 times per day (24h).	Unable to ingest food or fluid for more than 24 hours/≥ 7 episodes of vomiting per day or intractable vomiting. Emergency room visit or hospitalization and significant medical intervention/therapy required.
Diarrhea	Consistency of stools changes OR increase of 1-3 stools compared to normal frequency over a 24 hour period.	Liquid stools OR increase of 4-6 stools compared to normal frequency over a 24 hour period.	Increase of ≥7 stools compared to normal frequency over a 24 hour period OR child might need an infusion with fluid without hospitalization.	Emergency room visit or hospitalization and significant medical intervention/therapy required.
Appetite	Some loss of appetite but no decrease in oral intake.	Loss of appetite associated with decreased oral intake.	Almost no appetite, does not eat and/or weight loss.	Emergency room visit or hospitalization and significant medical intervention/therapy required.
Abdominal Pain	Mild.	Moderate; no treatment needed.	Moderate; treatment needed without hospitalization.	Emergency room visit or hospitalization and significant medical intervention/therapy required.
Constipation	Slight change in consistency/frequency of stool.	Hard, dry stools with a change in frequency.	Abdominal pain. Significant medical intervention/therapy required without hospitalization.	Distention and vomiting. Emergency room visit or hospitalization and significant medical intervention/therapy required.

Reactogenicity	Grade 1	Grade 2	Grade 3	Grade 4
Local reactions				
Pain/tenderness at injection site	Mild discomfort when the injection site is touched; child does not limit use of his/her arm or leg where the injection was done.	Notable discomfort when the injection site is touched; child limits use of his/her arm or leg where the injection was done.	Severe discomfort when the injection site is touched; child avoids use of his/her arm or leg where the injection was done.	Emergency room visit or hospitalization and significant medical intervention/therapy required.
Erythema/redness	≥10 and <25 mm diameter.	≥25 and <50 mm diameter.	≥50mm diameter.	Emergency room visit or hospitalization; necrosis or exfoliative dermatitis.
Induration/swelling	≥10 and <25 mm diameter.	≥25 and <50 mm diameter.	≥50mm diameter.	Emergency room visit or hospitalization; necrosis or exfoliative dermatitis.
Itching at the injection site	Infrequent, brief episode of scratching, easily distracted from scratching.	Frequent, longer episodes of scratching, difficult to distract.	Near constant scratching, or scratching during sleep; excoriation of skin.	Itching over entire body. Emergency room visit or hospitalization.
Edema	≥10 and <25 mm diameter.	≥25 and <50 mm diameter.	≥50mm diameter.	Emergency room visit or hospitalization; necrosis or exfoliative dermatitis.
Rash at the injection site	≥10 and <25 mm diameter.	≥25 and <50 mm diameter.	≥50mm diameter.	Emergency room visit or hospitalization; necrosis or exfoliative dermatitis.

Reactogenicity	Grade 1	Grade 2	Grade 3	Grade 4
Systemic reactions				
Allergic reaction	Pruritus without rash.	Pruritic rash.	Mild urticaria.	Severe urticaria anaphylaxis, angioedema. Emergency room visit or hospitalization and significant medical intervention/therapy required.
Irritable/Fussy/Crying/ Screaming	Easily consoled and returns to play easily. He/she has periods of crying fewer than 60 minutes.	Not easily consoled and is not easily interested in playing. He/she has periods of crying lasting between 60-120 minutes.	Very irritable, cannot be consoled and does not play. He/she has periods of continuous crying lasting more than 2 hours.	Inconsolable. Emergency room visit or hospitalization and significant medical intervention/therapy required.
Headache	Easily consoled and returns to play easily. Minimal symptoms; caused minimal or no interference with school or activities.	Not easily consoled and is not easily interested in playing. Notable symptoms; required modification in activity or use of medications; did not result in loss of school or cancellation of social activities.	Very irritable, cannot be consoled and does not play. Incapacitating symptoms; required bed rest and/or resulted in school or cancellation of social activities.	Intractable. Emergency room visit or hospitalization and significant medical intervention/therapy required.
Lethargy	Minimal symptoms; caused minimal or no interference with school or activities.	Notable symptoms; required modification in activity or use of medications; did not result in loss school or cancellation of social activities.	Incapacitating symptoms; required bed rest and/or resulted in loss of school or cancellation of social activities.	Emergency room visit or hospitalization and significant medical intervention/therapy required.
Chills	Minimal symptoms; caused minimal or no interference with school or activities.	Notable symptoms; required modification in activity or use of medications; did not result in loss of school or cancellation of social activities.	Incapacitating symptoms; required bed rest and/or resulted in loss of school or cancellation of social activities.	Emergency room visit or hospitalization and significant medical intervention/therapy required.

Other	Grade 1	Grade 2	Grade 3	Grade 4
Fever	38.0-38.4 °C or 100.4-101.1 °F.	38.5-40 °C or 101.2-104.0 °F.	Greater than 40 °C or 104.0 °F.	Sustained Fever: equal or greater than 40C (104.0F) for longer than 5 days.
Cutaneous	Localized rash.	Diffuse maculopapular rash.	Generalized urticaria.	Stevens-Johnson Syndrome or erythema multiforme.
Stomatitis	Mild discomfort.	Painful, difficulty swallowing, but able to eat and drink.	Painful: unable to swallow solids.	Painful: unable to swallow liquids; requires IV fluids.
Clinical symptom not otherwise specified in this table	No therapy; monitor condition.	May require minimal intervention and monitoring.	Requires medical care and possible hospitalization.	Requires active medical intervention, hospitalization, or hospice care.

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 Research and Development

Signature: electronic signature appended at the end of the protocol 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.

LAST PAGE

SIGNATURES

Signed by	Date	Justification
PPD	18Apr2019, 10:33:33 AM, UTC	Document Approval