Janssen Vaccines & Prevention B.V.

Clinical Protocol

A Randomized, Controlled, Observer-blind, Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26.RSV.preF in RSV-seronegative Toddlers 12 to 24 Months of Age

Protocol VAC18194RSV2002; Phase 1/2a

Amendment 6

VAC18194 (Ad26.RSV.preF)

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	21 December 2017
Amendment 1	06 April 2018
Amendment 2	13 July 2018
Amendment 3	07 November 2018
Amendment 4	08 April 2019
Amendment 5	05 July 2019
Amendment 6	25 May 2020

Amendment 6 (Issued date: 25 May 2020)

The overall reason for the amendment:
This protocol amendment is made primarily to reduce the overall number of RSV-seronegative toddlers in the study from 48 to 36. The reduction is made because of difficulties in recruiting seronegative toddlers due to a higher than expected seropositivity rate in the 12-24 month age group.

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

Rationale: To reduce the overall number of RSV-seronegative toddlers in the study from 48 to 36.

Synopsis: Overview of Study Design
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Rationale: Clarification that all concomitant medications utilized during an RTI or OM case will be collected, including outside of the 28-day post-vaccination period.

Synopsis: Safety Evaluations
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Rationale: Clarification that any RTI or OM case should be assessed and reported to the sponsor as an AE between the time of study vaccination through the following 28 days even if the event was not medically-attended and happened outside of the RSV season.

9.2.2 RTI Procedures (Figure 2)

Rationale: To add guidance on study conduct during the COVID-19 pandemic

Time and Events Schedule
Attachment 3: Guidance on Study Conduct during the COVID-19 Pandemic

Amendment 5 (Issued date: 05 July 2019)

The overall reason for the amendment:
This amendment is made to align the global protocol with changes made following requests from the German Health Authority:

- Clarification is added that the consent of both parents/legal guardians will be required in countries where this is specified by local regulation;
- Clarification is added on the reporting of any RTI or case of otitis media fulfilling the criterion of an SAE: all RTIs and cases of otitis media meeting seriousness criteria will be reported as SAEs; any RTI or case of otitis media reported as an (S)AE that is found to be positive for RSV will be excluded from the analyses of (S)AEs. However, the case will remain in the clinical database and will be tabulated separately in the clinical study report;
- Update of the monitoring rule for severe RSV-LRTI to reduce the numbers of events required to start an analysis from 3 to 2.

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

Rationale: To clarify that in countries where local regulation requires that both parents/legal guardians give consent, this will be applicable.

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Rationale: To clarify the reporting of any RTI or case of otitis media fulfilling the criterion of an SAE.

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Rationale: Update of the monitoring rule for severe RSV-LRTI to reduce the numbers of events required to start an analysis from 3 to 2.

Synopsis: Statistical Methods
11.3.1.3 Monitoring Rule for Severe RSV-LRTI

Rationale: In addition, other minor changes, clarifications, and corrections were made throughout the protocol.

Amendment 4 (Issued date: 08 April 2019)

The overall reason for the amendment: To introduce more active follow-up of ongoing RTIs/otitis media cases to capture the potential worsening of RTI/otitis media cases that are reported as not severe during the initial RTI visit and to clarify the responsibilities of the CEC in terms of evaluation of RTI cases and severity grading of RTIs.

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: To introduce active follow-up of ongoing RTIs/otitis media cases to capture the potential worsening of RTI/otitis media cases that are reported as not severe during the initial RTI visit.

Synopsis: RTI Procedures
Time and Events Schedule
9.2.2 RTI Procedures

Rationale: To clarify the responsibilities of the CEC in terms of evaluation of RTI cases and severity grading of RTIs in line with their responsibilities in the ongoing pediatric RSV study VAC18194RSV2001. Following items will be removed from the responsibility of the CEC: (i) the assessment of RSV positivity if a test result for RSV is missing, as an RTI will not be considered RSV-related in that case, and (ii) severity evaluation of all RTI and otitis media cases, as the severity evaluation of all cases will be performed by the PI(s).The CEC will confirm RTIs considered severe by the PI(s) by reviewing all available clinical information related to the cases.

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11.3.3 Definitions of RSV RTI and LRTI
11.9.1 Clinical Endpoint Committee (CEC)

Rationale: To clarify that EIA cut-off criterion for seronegativity is a titer <1 EIA unit and that a cut-off for seropositivity is not applicable in this study. Only subjects with a titer <1 that meet the in- and exclusion criteria will be enrolled in the study.

Synopsis: Overview of Study Design
3.1 Overview of Study Design
9.1.3.1 Screening Phase: Days -42 to 1

Rationale: Clarification that vaccination with Nimenrix on Day 57 (replacing the third placebo dose) for subjects in the control group is optional. For these subjects, placebo (0.9% saline) will be replaced with Nimenrix as the Day 57 vaccination, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision).

Synopsis: Overview of Study Design; Dosage and Administration
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Rationale: To introduce the Participant Experience Survey that parents/legal guardians or caregivers of each study subject will be invited to complete at the final study visit.

Synopsis: Other Evaluations
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Rationale: To introduce the rationale for incorporating vaccination with Nimenrix® as an alternative for the Day 57 vaccination with placebo (0.9% saline) for subjects in the control group.

1.2 Nimenrix
3.2 Study Design Rationale

Rationale: Clarification that eCRF entry is the primary pathway for reporting SAEs in this study.

12.3.2 Serious Adverse Events

Rationale: 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 as adequate follow-up of RTI cases is ensured by introducing follow-up phone calls every 2 days and requesting subjects to notify sites in the event of worsening symptoms. This will enable closer follow-up of cases and prospective capture of medical seeking behaviors.

3.3.5 Overall Benefit/Risk Assessment
9.2.2 RTI Procedures

Rationale: Specification that for severe RTI events, expedited handling (ie, shipment on day of collection) of nasal swabs and expedited data entry (ie, on the day of knowledge of the event) is required.

Synopsis: RTI Procedures
9.2.2 RTI Procedures

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

Amendment 3 (Issued date: 07 November 2018)

The overall reason for the amendment: To incorporate vaccination with Nimenrix® as an alternative for the Day 57 vaccination with placebo (0.9% saline) for subjects in the control group (in accordance with the local label and local regulations, and unless contra-indicated). The incorporation of a licensed vaccine as a control offers a more accepted approach to this pediatric vaccine study. Nimenrix has been selected for incorporation in the design of this study as it has an adverse events (AE) profile similar to the anticipated study vaccine AE profile, and the recommended one-dose vaccination in the targeted age group matches the existing study design, which is essential to preserve the blind in the current study.

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: To incorporate Nimenrix as the Day 57 vaccination for subjects in the control group (in accordance with the local label and local regulations, and unless contra-indicated).

Synopsis: Overview of Study Design; Dosage and Administration
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3.3.2 Potential Benefits
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6 Dosage and Administration
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Rationale: Clarification that the exclusion criterion for urticaria, eczema and atopic dermatitis relates to a moderate to severe history of these illnesses.

4.2 Exclusion Criteria

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
3.3.5 Overall Benefit/Risk Assessment
9.1.3.2.1 Vaccination (Days 1, 29, and 57)
10.3 Contraindications to Vaccination

Rationale: Clarification that for cases of otitis media that occur during the study, the procedures are similar as for RTIs that occur during the study.

Synopsis: Overview of Study Design; RTI Procedures
Time and Events Schedule
3.1 Overview of Study Design
9.2.2 RTI Procedures

Rationale: Specification that injections may also be administered in the deltoid muscle, only if required by local health authority guidance.

Synopsis: Dosage and Administration
6 Dosage and Administration
14.3 Storage and Handling

Rationale: Clarification that an interim analysis will be performed when all subjects have data of 1 RSV season post-Dose 1.

Synopsis: Statistical Methods
11.8 Planned Analyses

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

Amendment 2 (Issued date: 13 July 2018)

The overall reason for the amendment: The protocol amendment is made to reduce the dose of Ad26.RSV.preF from 5×10^{10} vp to 2.5×10^{10} vp. In study VAC18194RSV2001 in RSV-seropositive toddlers, transient fevers were observed following initial dosing with 5×10^{10} vp of Ad26.RSV.preF in some subjects. Although the IDMC reviewed the interim analysis when 12 toddlers had reached Day 8 post-dose 1, with the recommendation that VAC18194RSV2001 should continue unmodified, the sponsor decided to implement a dose reduction in the current study in RSV-seronegative toddlers. An expanded rationale is presented in Section 3.2.

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

Rationale: To reduce the dose of Ad26.RSV.preF from 5×10^{10} vp to 2.5×10^{10} vp.

Synopsis: Primary Objectives; Overview of Study Design; Dosage and Administration
1.2 Overall Rationale for the Study
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3.2 Study Design Rationale
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6 Dosage and Administration
14.1 Physical Description of Study Vaccine

Rationale: Update of preclinical information.

1.1 Background

Rationale: Update of IDMC review criteria and data availability from VAC18194RSV2001 prior to dosing in the current study.

1.1 Background

Rationale: Correction of inconsistencies in the description of Formulation Buffer 2.

1.1 Background

Rationale: Update of study VAC18193RSV2003 status.

1.1 Background

Rationale: Clarification that exclusion criterion for known allergies at screening refers to vaccines or vaccine components, but not to egg allergies.

4.2 Exclusion Criteria

Rationale: Clarification that telephone calls to subjects for RTI monitoring after the first dose will be made during both the vaccination and safety follow-up phases.

Synopsis: Overview of Study Design
Time and Events Schedule
3.1 Overview of Study Design
9.1.3.3 Safety Follow-up Phase

Rationale: Clarification that a mid-turbinate swab for RSV RT-PCR testing will also be collected from any subject with otitis media during the study, independent of other RTI symptoms.

Synopsis: Overview of Study Design; RTI Procedures
3.1 Overview of Study Design
9.2.2 RTI Procedures

Rationale: Clarification that the primary analysis at 28 days post-final dose and the interim analysis after 1 RSV season post-first dose will be in all subjects.

11.8 Planned Analyses

Amendment 1 (Issued date: 06 April 2018)

The overall reason for the amendment: The protocol amendment is made to remove seropositive subjects from the study so that seronegative toddlers can be evaluated independent of any findings that might occur in seropositive toddlers at the $1x10^{11}$ vp dose level. Also, the number of blood draws for immunogenicity is reduced from five to four for each subject. In addition, a 7-day safety review post-first dose by the principal investigator/study responsible physician/scientist in the first 8 subjects has been added.

In order to be able to administer two vaccine doses to subjects before the start of the RSV season, the subset of subjects in study VAC18194RSV2001 for whom safety data will be reviewed by the IDMC prior to dosing in the current study is reduced from 24 to 12. This reduction is supported by additional safety data that have been collected. Humoral immunogenicity data in RSV-experienced adults aged ≥60 years indicate Th1-skewed responses with no safety concerns. No differences in immunogenicity or safety are expected between RSV-seropositive 1-year old-toddlers and seropositive adults; no differences in safety (solicited/unsolicited AEs) are expected between 1-year-old RSV-seropositive toddlers and RSV-seronegative toddlers. Additionally, preclinical data in RSV naïve animals indicate Th1-skewed responses, and show that Ad26.RSV.preF does not predispose to enhanced respiratory disease (ERD) after RSV challenge in cotton rats and mice.

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

Rationale: Removal of the cohort of seropositive toddlers.

Synopsis: Primary Objectives; Hypothesis; Overview of Study Design; Subject Population; Dosage and Administration; Statistical Methods
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5 Study Vaccine Allocation and Blinding
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11.3.1.3 Monitoring Rule for Severe RSV-LRTI
11.10 Study Vaccination Pausing Rules
14.1 Physical Description of Study Vaccine
14.3 Storage and Handling
17.9.1 Study Completion/End of Study

Rationale: Removal of blood draws for immunogenicity at Days 29, 57 and 239; addition of study visit to include blood draw for immunogenicity at the end of the first RSV season after the first dose; addition of blood for cellular immunogenicity to the existing draw for humoral immunogenicity at Day 85.

Synopsis: Overview of Study Design; Statistical Methods
Time and Events Schedule
3.1 Overview of Study Design
9.1.1 Overview
9.1.2 Visit Windows
9.1.3.2.3 End of RSV Season Visit
11.8 Planned Analyses

Rationale: In order to be able to dose subjects before the start of the RSV season, the subset of subjects in study VAC18194RSV2001 for whom safety data will be reviewed by the IDMC prior to dosing in the current study is reduced from 24 to 12.

1.1 Background
3.2 Study Design Rationale

Rationale: A 7-day safety review by the principal investigator/study responsible physician/scientist in the first 8 subjects has been added to increase monitoring after the first dose. It is also clarified that the 7-day IDMC review in the first 12 subjects will be done without a pause in enrollment.

Synopsis
3.1 Overview of Study Design
3.3.5 Overall Benefit/Risk Assessment

Rationale: Added clarification that serostatus can be assessed via the RSV EIA if available from a different study.

Synopsis
Time and Events Schedule
3.1 Overview of Study Design
4.1 Inclusion Criteria
9.1.3.1 Screening Phase

Rationale: Added requirement to assess oxygen saturation (SpO_2) at each visit.

Time and Events Schedule
9.1.3.1 Screening Phase
9.2.3.1 Vital Signs

Rationale: Added requirement to assess whether subjects are breastfeeding, with breastfeeding history, and whether family members smoke in the home environment, with smoking history.

9.1.3.1 Screening Phase

Rationale: Clarification that subjects will not be automatically withdrawn from the study if consent is withdrawn only for blood draws; subjects may remain and continue to receive study vaccine and undergo safety follow-up.

9.1.3.2.4 Early Withdrawal: Early Exit Visit
10.2 Discontinuation of Study Vaccine/Withdrawal from the Study

Rationale: Other minor corrections to remove inconsistencies.

1.1 Background
4.2 Exclusion Criteria

SYNOPSIS

A Randomized, Controlled, Observer-blind, Phase 1/2a Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of Ad26.RSV.preF in RSV-seronegative 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 Objective

- To assess the safety and reactogenicity of an intramuscular regimen of 3 doses of 2.5×10^{10} viral particles (vp) of Ad26.RSV.preF in RSV-seronegative toddlers aged 12 to 24 months.

Secondary Objectives

- To assess the humoral and cellular immune responses elicited by Ad26.RSV.preF as measured by virus neutralizing antibodies (VNAs), F protein binding antibodies (pre-F and/or post-F), and T-helper (Th)1/Th2 subtyping.
- To monitor for severe RSV-lower respiratory tract infection (LRTI) as a preliminary indication of enhanced respiratory disease (ERD).

Exploratory Objectives

- To further assess the humoral and cellular immune responses elicited by Ad26.RSV.preF. The assays to be used can include, but may not be limited to, RSV strain cross-neutralization, RSV F protein antibody specificity characterization, RSV G and/or N protein binding antibodies, adenovirus neutralization assay, functional and molecular antibody characterization (eg, avidity and antibody isotyping) and antibody sequencing if feasible, and evaluation of cellular immune response (interferon gamma [IFN-γ] enzyme-linked immunospot [ELISpot] assay, intracellular cytokine staining [ICS], cytokine analysis).
- To assess RSV infection rates (symptomatic and asymptomic) in Ad26.RSV.preF and control subjects.
- To assess symptomatic RSV infection rates in Ad26.RSV.preF and control subjects.
- To assess symptoms of respiratory illness via the Respiratory Tract Infection (RTI) Symptoms Form.

Primary Endpoints – Safety and Reactogenicity

- Solicited local and systemic adverse events (AEs) for 7 days after each vaccination.
- Unsolicited AEs for 28 days after each vaccination.
- Serious adverse events (SAEs) from first dose administration to the end of the study.

Secondary Endpoints – Immune Responses

The analysis of the immunogenicity of the vaccine regimens will include the characterization of both humoral and cellular responses. The focus of the immunogenicity analysis will be on 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 neutralizing antibodies to an A strain.
- F protein antibodies (enzyme-linked immunosorbent assay [ELISA]; pre- and/or post-F)

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

Cell-mediated Immune Response

- Flow cytometry (ICS)*

  Analysis of T-cell responses to RSV F protein peptides for Th1/Th2 subtyping.

  ** Cytokine analysis for Th1/Th2 profiling will be done if no ICS can be generated due to an insufficient number of peripheral blood mononuclear cells (PBMCs) for ICS assay (see the Exploratory Endpoints below).*

Secondary Endpoints – RSV Infection

- Severe RSV-LRTI

  Severe RSV-LRTI will be defined as the presence of severe LRTI as assessed by the Clinical Endpoint Committee (CEC), and confirmation of RSV infection from a nasal (mid-turbinate or nasopharyngeal) sample using independent reverse transcriptase polymerase chain reaction (RT-PCR) by a central laboratory. If no central laboratory RT-PCR result is available, a positive test result for RSV from a local laboratory (if available) could be used to confirm RSV infection upon evaluation by the CEC.

Exploratory Endpoints – Immune Responses

Exploratory analyses may be performed to evaluate the vaccine-elicited immune responses further. These can include, but may not be limited to, the following assays (as available and applicable):

Humoral Immune Response

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

  Assessment of the strain cross-neutralizing capacity of the vaccine-induced immune response.
- F protein antibody specificity characterization

  Assessment of pre-F and post-F specificity by binding or functional assays as ELISA, and/or competition ELISA, epitope mapping, and functional VNAs.
- Nasal immunoglobulin antibodies to RSV F protein

  Analysis of immunoglobulin IgA or IgG antibodies to RSV pre-F and/or post-F.
- G and/or N protein antibodies (ELISA)

  Assessment of antibodies binding to RSV G and/or N protein to estimate the RSV infection rate (symptomatic and asymptomatic) in the study.
- Adenovirus neutralization assay

  Assessment of neutralizing antibody responses against the adenoviral vector.

- Functional and molecular antibody characterization

  Functional characterization of antibodies may be performed: antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). A molecular characterization of vaccine-elicited antibodies will include antibody avidity, other respiratory viral neutralizing or binding assays, immunoglobin isotype, functional VNAs to other respiratory viruses, and antibody assessments.

Cell-mediated Immune Response

- ICS

  Analysis of T-cell responses to RSV F protein peptide-stimulated PBMC (including, but not limited to, CD4+/CD8+, interleukin-2 [IL-2], IFN-γ, tumor necrosis factor alpha (TNF-α), activation markers and memory)

- Cytokine analysis

  Cytokine profiles of (*in vitro*) stimulated PBMC supernatant will be analyzed to assess the quantity and quality of elicited immune responses, including Th1/Th2 balance. The analysis can include, but may not be limited to, IFN-γ, IL-2, IL-4, IL-5, IL-13, and TNF-α.

- IFN-γ ELISpot assay

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

- Sequencing of the antibody repertoire will be done if feasible.

Exploratory Endpoints – RSV Infection

- RSV-RTI and RSV-LRTI confirmed by RT-PCR.
- Serology for, but not limited to, RSV protein G and/or N (and/or F) may be used to confirm exposure to RSV at the end of the season.

  To detect RSV infections by serology, a fold increase will be applied to determine if a subject is a seroconverter based on G and/or N ELISA. Fold increases for RSV infection will be determined based on 2 consecutive blood samples as planned in the Time and Events Schedule.
- RSV medically-attended respiratory tract infection (MA-RTI): includes all subjects with RSV-RTI that is medically-attended, ie, when the subject's parent/legal guardian or caregiver seeks medical attention outside normal study procedures, including healthcare professional visits to the home, clinic visits, emergency room attendance, hospital admission.

Hypothesis

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

OVERVIEW OF STUDY DESIGN

This is a multi-center, randomized, observer-blind, Phase 1/2a study, to be conducted in 36 male and female RSV-seronegative toddlers aged ≥12 to ≤24 months.

Each subject's RSV serostatus will be assessed by RSV enzyme immunoassay (EIA) at screening[a]. *Note*: serostatus may be assessed via this assay if available from a different study of the sponsor

[a] The cut-off for seronegativity is a titer <1 EIA unit.

(VAC18194RSV2001). If done within 42 days of first dose, this assessment would not have to be repeated in the absence of a history of respiratory infection during that period. Additionally, the seronegative status will be confirmed by the absence of an anamnestic humoral immune response (which is usually observed 7-10 days post antigen re-exposure in RSV seropositive subjects) from blood samples taken 7 days after the first dose.

Subjects will be randomized 1:1 to receive either Ad26/Ad26/Ad26 (at 2.5×10^{10} vp) or placebo/placebo/Nimenrix®[b,c] (or placebo/placebo/placebo) (Table 1).

Table 1: Study Design VAC18194RSV2002

Group	N[a]	Day 1	Day 29/Week 4	Day 57/Week 8
RSV-seronegative toddlers 12 to 24 months				
Group 1	18	Ad26.RSV.preF (2.5×10^{10} vp)	Ad26.RSV.preF (2.5×10^{10} vp)	Ad26.RSV.preF (2.5×10^{10} vp)
Group 2	18	Placebo (saline)	Placebo (saline)	Nimenrix [b] or Placebo (saline)

N = number of subjects; vp = viral particles

a: At the time of Amendment 6, 37 subjects have been enrolled.

b: In countries where the commercial vaccine Nimenrix is licensed, placebo (0.9% saline) can be replaced with Nimenrix as the Day 57 vaccination for the study subjects in the control group, in accordance with the local label and local regulations, and unless contra-indicated. Nimenrix will be administered, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision). In the US, Nimenrix will not be used unless it has been licensed for use or an Investigational New Drug (IND) has been submitted.

An Independent Data Monitoring Committee (IDMC) will evaluate safety and reactogenicity data on a regular basis.

An independent, blinded CEC has been established for ongoing study VAC18194RSV2001 in RSV-seropositive toddlers and all subsequent studies with Ad26.RSV.preF in children (including the current study), to assess suspected cases of severe LRTI and the occurrence of RSV infection.

The study will have 3 phases: a **screening phase**, a **vaccination phase**, and a **safety follow-up phase** through 2 RSV seasons after the first dose. The durations of the respective phases are as follows:

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[b] In countries where the commercial vaccine Nimenrix is licensed, placebo (0.9% saline) can be replaced with Nimenrix as the Day 57 vaccination for the study subjects in the control group, in accordance with the local label and local regulations, and unless contra-indicated. Nimenrix will be administered, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision). In the US, Nimenrix will not be used unless it has been licensed for use or an IND has been submitted. It should be recorded in the eCRF by the unblinded pharmacist whether the subject was vaccinated with either Nimenrix or placebo on Day 57.

[c] Nimenrix is a vaccine used to protect adults, adolescents, and children from the age of 6 weeks against invasive meningococcal disease caused by 4 groups of the bacterium *Neisseria meningitidis* (group A, C, W-135, and Y).[12]

Phase	
Screening:	up to 6 weeks before the first dose
Vaccination:	34 weeks • dosing on Days 1, 29 and 57 • safety follow-up through 6 months post-final dose • immunogenicity at: ➢ pre-Dose 1 (Day 1) ➢ 7 days post-Dose 1 (Day 8) ➢ 28 days post-Dose 3 (Day 85) ➢ end of the first RSV season after the first dose
Safety follow-up:	through 2 RSV seasons after the first dose

The end of the vaccination 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

No sentinel approach is taken for the 2.5×10^{10} vp dose, as this dose is lower than the 5×10^{10} vp dose currently being evaluated in several other studies, including study VAC18193RSV1003 in adults aged ≥60 years in stable health and study VAC18194RSV2001 in RSV-seropositive toddlers aged 12 to 24 months.

- The first 8 subjects will be enrolled and receive the first dose (Ad26.RSV.preF 2.5×10^{10} vp or placebo).
- 7-day safety in these first 8 subjects will be monitored by the principal investigator (PI[s]) or designee and the sponsor's study responsible physician/scientist (SRP/S). In the event of a significant safety finding, the IDMC will be consulted.
- 4 more subjects will be enrolled and receive the first dose (Ad26.RSV.preF 2.5×10^{10} vp or placebo).
- The IDMC will assess post-first dose reactogenicity by review of 7-day safety data for these first 12 subjects (6 subjects receiving Ad26.RSV.preF 2.5×10^{10} vp and 6 subjects receiving placebo).

Any safety finding will be closely monitored, although enrollment will not be paused for either the PI(s)/ SRP/S review of the first 8 subjects or the IDMC review of the first 12 subjects.

If the IDMC review does not take place before the first subject receives the scheduled second or third dose (due to potential slow recruitment), the PI(s) or designee and SRP/S will review the available data prior to the second or third dose being given as scheduled, respectively. In the event of a significant safety finding, the IDMC will be consulted.

In all post-first dose 7-day safety reviews, safety data for review will include solicited and unsolicited AEs and SAEs.

Second-dose Safety

Safety assessments will also be made 7 days after the second dose in the first 12 toddlers before administering the second dose to the remaining toddlers. Post-second dose 7-day safety will be monitored by the PI(s) or designee and SRP/S. Safety data for review will include solicited and unsolicited AEs and SAEs. Any safety finding will be closely monitored, although dosing will not be paused for this PI(s) or designee and SRP/S review.

Third-dose Safety

Safety assessments will also be made 7 days after the third dose in the first 12 toddlers before administering the third dose to the remaining toddlers. Post-third dose 7-day safety will be monitored by the PI(s) or designee and SRP/S. Safety data for review will include solicited and unsolicited AEs and SAEs. Any safety finding will be closely monitored, although dosing will not be paused for this PI(s) or designee and SRP/S review.

Safety Follow-up

During the entire study after the first dose, including during the vaccination phase and safety follow-up phase, the subject's parent/legal guardian or caregiver will be contacted periodically by telephone (or other communication, or by clinic visit) through 2 RSV seasons after the first dose (every 14 days ±3 days within the RSV season and every 30 days ±7 days outside of the season, unless the timing coincides with a visit). During the RSV season, these calls will remind the subject's parent/legal guardian or caregiver to record signs and symptoms of RTI and otitis media on a specific RTI Symptoms Form (see below under 'RTI PROCEDURES'), and to contact the site at the time of symptom onset [d]. During and outside the RSV season, these calls will check for SAEs and associated concomitant medications, MA-RTIs, medically-attended otitis media cases, and any subsequent medical care that may have been sought, since the previous visit or telephone contact (this includes contacts with subjects who received at least one dose of study vaccine but withdrew from further dosing). The sponsor will provide the site with a checklist for these follow-up phone calls.

SUBJECT POPULATION

Healthy (on the basis of physical examination, medical history and vital signs measurement performed at screening) male or female subjects, aged ≥12 to ≤24 months on the day of informed consent form (ICF) signature, who are seronegative for RSV within 42 days prior to dosing.

DOSAGE AND ADMINISTRATION

Every effort will be made to administer the first 2 doses before the start of the RSV season. The start and end of the RSV season will be determined based on the information from the national surveillance system (if available) or the local surveillance at the site (standard of care assessments, if available). The site will communicate to the sponsor when RSV starts to circulate in their region; the decision to stop screening of subjects at affected sites will be taken together with the sponsor.

Ad26.RSV.preF (JNJ-64400141) will be supplied in single-use vials. The 2.5×10^{10} vp dose will be administered in a volume of 0.25 mL by intramuscular injection.

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

Nimenrix [e] will be supplied as Nimenrix powder and solvent for solution for injection in pre-filled syringe or ampoule and administered as 0.5 mL solution for intramuscular injection.

The study vaccine will be prepared and may also be administered by the unblinded pharmacist, or other qualified individual, who will have no other study function following dosing.

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[d] *Note*: The RTI procedures also apply to all otitis media cases.

[e] In countries where the commercial vaccine Nimenrix is licensed, placebo (0.9% saline) can be replaced with Nimenrix as the Day 57 vaccination for the study subjects in the control group, in accordance with the local label and local regulations, and unless contra-indicated. Nimenrix will be administered, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision). In the US, Nimenrix will not be used unless it has been licensed for use or an IND has been submitted. It should be recorded in the eCRF by the unblinded pharmacist whether the subject was vaccinated with either Nimenrix or placebo on Day 57.

To ensure that the site staff or qualified professional staff who will do the observation as well as the subjects (and their parents/legal guardians) will be blinded, the necessary precautions will be taken as documented by the clinical sites and agreed upon by the sponsor.

Injections should be administered in the anterolateral aspect of the thigh. Only if required by local health authority guidance, injections may be administered in the deltoid muscle. Alternating injection sites will be used for all study vaccinations unless there is a medically justifiable reason in the judgment of the PI(s).

IMMUNOGENICITY EVALUATIONS

The humoral and cellular immunogenicity assays that may be used in this study (as available and applicable) are summarized in Table 2 and Table 3 below. Sample collection and processing will be performed by the staff at clinical sites according to current and approved Standard Operating Procedures.

In addition to RT-PCR performed on RTI nasal samples, any immunogenicity blood sample collected from all subjects may also be assayed by serology (eg, ELISA specific to RSV protein G and/or N as available and applicable) to confirm exposure to RSV at the end of the season if the sample volumes allow.

Table 2: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Secondary endpoints	
RSV neutralization A strain	Analysis of neutralizing antibodies to an A strain
F protein antibodies (ELISA; pre-F and/or post-F)	Analysis of antibodies binding to RSV F protein in pre-fusion and/or post-fusion form
Exploratory endpoints	
RSV strain cross-neutralization	Analysis of cross-neutralizing antibodies to B and/or a different A strain(s)
F protein antibody specificity characterization	Pre-F and post-F specificity by binding or functional assays as ELISA, and/or competition ELISA, epitope mapping, and functional VNAs
Nasal Ig antibodies to RSV F protein	Analysis includes, but not limited to, IgA or IgG antibodies to RSV pre-F and/or post-F
G and/or N protein antibodies (ELISA)	Analysis of antibodies binding to RSV G and/or N protein
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to, ADCC, ADCP, avidity, other respiratory viral neutralizing or binding assays, Ig isotype, functional VNAs to other respiratory viruses, and antibody assessments

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 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	
ICS	Analysis of T-cell responses to RSV F protein peptide-stimulated PBMC (including, but not limited to, $CD4^+/CD8^+$, IL-2, IFN-γ, TNF-α, activation markers and memory)
Cytokine analysis	Analysis of secreted cytokines (eg, IFN-γ, IL-2, IL-4, IL-5, IL-13, and TNF-α) in RSV F peptide-stimulated PBMC supernatant, including, but not limited to, measurement of Th1/Th2 cytokine balance
IFN-γ ELISpot	T-cell IFN-γ responses to RSV F protein peptides

ELISpot = enzyme-linked immunospot; F = fusion; ICS = intracellular cytokine staining; IFN-γ = interferon gamma; IL = interleukin; PBMC = peripheral blood mononuclear cell; Th = T-helper (cell); RSV = respiratory syncytial virus; TNF-α = tumor necrosis factor alpha
Note: Cytokine analysis for Th1/Th2 profiling will be done if no ICS data can be generated due to insufficient PBMCs for ICS assay.

RTI PROCEDURES

All RTIs and otitis media cases will be collected during the RSV season [f]. Outside the RSV season, only MA-RTIs, including severe LRTIs, and medically-attended otitis media cases will be collected.

During the RSV season, the subject's parent/legal guardian or caregiver should record any signs and symptoms of RTI (eg, runny nose, fever, severe cough, wheezing, rapid breathing, difficulty breathing) or otitis media on a daily basis using a specific RTI Symptoms Form, starting on the first day their child experiences symptoms, including the day on which the symptoms resolve. Outside the RSV season, parents/guardians or caregivers should likewise record signs and symptoms of RTI or otitis media on a daily basis using the RTI Symptoms Form as soon as possible for any MA-RTI or medically-attended otitis media case until resolution of symptoms.

In the event of an RTI, MA-RTI, or (medically-attended) otitis media, parents/legal guardians or caregivers should contact the site. Parents/legal guardians or caregivers will themselves be contacted periodically during the study. During the RSV season, these calls are to remind them to complete the RTI Symptoms Form in the event of any signs or symptoms of RTI or otitis media, and to contact the site at the time of symptom onset; during and outside the RSV season, these calls will check for SAEs and associated concomitant medications, MA-RTIs, medically-attended otitis media cases, and any subsequent medical care that may have been sought, since the previous visit or telephone contact.

During the season, and where possible outside the season (for MA-RTIs, including severe LRTIs or for medically-attended otitis media cases), site staff will conduct a physical examination (with vital signs, including oxygen saturation), and collect nasal samples, preferably within 72 hours after onset of symptoms. For suspected severe RTI cases, nasal swabs should be shipped on the day of collection to enable timely assessment of samples for the presence of RSV infection by central laboratory RT-PCR. (Nasal samples will not be collected if less than 7 days after the previous sample collection.) *Note*: A nasal swab for RSV RT-PCR testing will also be collected from any subject with otitis media (as recorded on the RTI Symptoms Form) during the study, independent of other RTI symptoms.

In all RTI or otitis media cases where results from the physical examination during the RTI site visit conclude that the RTI is not severe, and the RTI episode is still ongoing, a follow-up phone call (or other communication) to the parents/legal guardians or caregivers will be made once every 2 working days (±1 day) until symptom resolution. In the event of a worsening RTI, a follow-up RTI visit will be scheduled. (*Note*: In the event of a worsening RTI, a repeat nasal sample may be collected if less than 7 days after the previous sample collection at the discretion of the investigator.) Further follow-up visits to assess additional reported worsening of an RTI episode may be scheduled at the discretion of the investigator.

Note: RTI procedures (completion of the RTI symptoms form at home, and an RTI visit to the site with associated procedures, including nasal sampling) are not applicable for a non-medically-attended RTI that occurs outside the season, including those that started before the RSV season and continue into the season without worsening of symptoms.

Any RTI or otitis media case that is not due to RSV infection will be reported as an AE if it occurs between the time of any study vaccination through the following 28 days. During the study, any RTI or case of otitis media fulfilling the criterion of an SAE will be reported to the sponsor (and, when appropriate, extended to Regulatory Agencies). Any RTI or case of otitis media reported as an (S)AE that

[f] *Note*: The RTI procedures also apply to all otitis media cases.

is found to be positive for RSV will be excluded from the analyses of (S)AEs. However, the case will remain in the clinical database and will be tabulated separately in the clinical study report.

Any MA-RTI (including any severe LRTI) or (medically-attended) otitis media case which occurs between screening and Day 1 will be recorded on the Medical History page of the eCRF (RTI visit and RTI Symptoms Form completion is not required for these events prior to the first vaccination).

SAFETY EVALUATIONS

After each dose, subjects will be closely observed for a minimum of 30 minutes (or 60 minutes, depending on local or study-site requirements) post-vaccination, to monitor for 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 after this observation period. The subject's parent/legal guardian or caregiver will be given a thermometer, ruler and daily assessment (subject) diary with instructions for the proper recording of events. Each subject's parent/legal guardian or caregiver 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 next 7 days. Temperatures should be taken at approximately the same time each day, preferably in the evening and additionally whenever the child feels warm. All diary assessments, including body temperature 7 days post-vaccination, may be collected earlier in the day to coincide with the Day 8 clinic visit. Study-site personnel will collect and review subject diary information and confirm the entries at subsequent site visits.

All AEs, SAEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards. Unsolicited AEs will be collected for 28 days after each vaccination (ie, from the time of each vaccination through the following 28 days). SAEs will be collected from first dose administration 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 these periods when associated with any SAE, RTI or OM case.

OTHER EVALUATIONS

At Visit 12 (6 months post-Dose 3), parents/legal guardians or caregivers (where allowed by local regulations) will be invited to complete an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved Participant Experience Survey.

STATISTICAL METHODS

Sample Size Determination

The number of subjects for this study will provide a preliminary safety and immunogenicity assessment. Control 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.

Monitoring Rule for Severe RSV-LRTI

A monitoring rule with respect to severe RSV-LRTI will be installed for this study. If 1 event (regardless of the group) of severe RSV-LRTI is observed, no analysis will be done. If 2 or more events (regardless of the group) of severe RSV-LRTI have been observed, confidence limits for the difference in proportions (using Wilson score method) between the Ad26.RSV.preF group and control group (pooling placebo/placebo/Nimenrix and placebo/placebo/placebo) will be constructed by the external statistician who is supporting the IDMC:

- If the upper (one-sided) 95% confidence limit for the difference is <10%: continue the study; if study enrollment is still ongoing, continue enrollment.
- If the upper (one-sided) 95% confidence limit is ≥10% and the lower (one-sided) 80% confidence limit is >0: more frequent active monitoring of subjects, including weekly calls within the RSV season and more frequent medical review will be initiated.
- If the upper (one-sided) 95% confidence limit is ≥10% and the lower (one-sided) 95% confidence limit is >0: halt enrollment in this study or the next study; more frequent active monitoring of subjects, including weekly calls within the RSV season and more frequent medical review for all enrolled subjects should be initiated.

For example: assuming complete enrollment, if 2 or 3 severe RSV-LRTI events are observed and all occurred in the Ad26.RSV.preF group, the lower (one-sided) 80% (but not the 95%) confidence limit will be >0 and monitoring will be increased. If 4 severe RSV-LRTI events are observed and all occurred in the Ad26.RSV.preF group, the lower (one-sided) 95% confidence limit will be >0 and enrollment in all pediatric studies with Ad26.RSV.preF will be halted and monitoring of all enrolled subjects will be increased.

The IDMC will review unblinded data and give a recommendation to the sponsor. More details on this monitoring rule are specified in the IDMC charter.

Planned Analyses

The following analyses will be performed:

- Primary analysis 28 days post-final dose includes safety and immunogenicity; unblinded
- Interim analysis performed when all subjects have data of 1 RSV season post-Dose 1, includes safety and immunogenicity; unblinded
- Final analysis at the end of the study; unblinded

The primary analysis and interim analysis may be combined into one analysis. These analyses will also be shared with the IDMC.

Additional interim analyses (blinded or unblinded) 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 and clinical immunology laboratory personnel.

Immunogenicity Analyses

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% confidence interval 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.

RSV Infection

The incidence of any RSV infection, as described above under ‘RTI PROCEDURES’, in Ad26.RSV.preF and control subjects will be summarized by descriptive statistics.

Safety Analyses

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

TIME AND EVENTS SCHEDULE

Phase	Scree-ning	Vaccination Phase												Safety FU [a]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12 [a]	EoS	Exit [c]	*FU outside RSV season at 30-day intervals; FU within RSV season at 14-day intervals*
Visit Timing		Vac 1	Vac 1 + 3 d	Vac 1 + 7 d	Vac 2 (Vac 1 + 28 d)	Vac 2 + 3 d	Vac 2 + 7 d	Vac 3 (Vac 2 + 28 d)	Vac 3 + 3 d	Vac 3 + 7 d	Vac 3 + 28 d	Vac 3 + 6 mo	End of Season [b]		
Visit Week		0		1	4		5	8		9	12	34			
Target Visit Day ± Window (days)	-42 to 1	1	4±1	8 -1/+3 [d]	29±3	32±1 [e]	36±2 [d,e]	57±3 [e]	60±1 [e]	64±2 [e,f]	85±3 [e]	239±14 [e]	+28		
Visit Type	Screening	VACCINE 1	Safety (Telephone)	Safety and Immuno.	VACCINE 2	Safety (Telephone)	Safety	VACCINE 3	Safety (Telephone)	Safety	Safety and Immuno.	Safety	Safety and Immuno.	Early Exit	Safety FU (Telephone)
Written informed consent [g]	●														
Inclusion/exclusion criteria	●														
Demographics	●														
Medical history/pre-study medications	●														
Body length and weight	●	❶			❶			❶			●	●	●	●	
Physical examination	●	❶❷		❷	❶❷		❷	❶❷		❷	❷	❷	❷	❷	
Vital signs [h] incl. body temperature	●	❸		●	❸		●	❸		●	❽	❽	❽	❺	
RSV serostatus testing [i,j]	● 0.5 mL														
Randomization		❶													
Verification of selected eligibility criteria and contraindications to vaccination [k]		❶			❶			❶							
Pre-vaccination symptoms [m]		❶			❶			❶							
Cellular immunity [n]	❹ 4 mL										● 4 mL			❾ 4 mL	
Humoral immunity [l]	❹ 1 mL			● 1 mL							● 1 mL		● 2 mL	❾ 1 mL	
Nasal sample [w]	❹										●			●	
Vaccination		●			●			●							
30 min post-vaccination observation [o]		●			●			●							
Solicited AE recording		*Continuous*			*Continuous*			*Continuous*						❺	
Unsolicited AE recording [p]		*Continuous*												❻	
Concomitant medications [q]		*Continuous*													
SAE recording [s,t]		*Continuous*													
RTIs [u]		*Only if the RTI occurs during an RSV season*													
MA-RTIs; severe LRTIs [v]	❿	*Continuous*													
RTI Symptoms Form distribution [u]		●			●			●							
Subject diary distribution [x]		●			●			●							
Subject diary review			❼	●		❼	●		❼	●					

TIME AND EVENTS SCHEDULE

Phase	Scree-ning	Vaccination Phase												Safety FU [a]
Visit #	1	2	3	4	5	6	7	8	9	10	11	12 [a]	EoS	Exit [c]	*FU outside RSV season at 30-day intervals; FU within RSV season at 14-day intervals*
Visit Timing		Vac 1	Vac 1 + 3 d	Vac 1 + 7 d	Vac 2 (Vac 1 + 28 d)	Vac 2 + 3 d	Vac 2 + 7 d	Vac 3 (Vac 2 + 28 d)	Vac 3 + 3 d	Vac 3 + 7 d	Vac 3 + 28 d	Vac 3 + 6 mo	End of Season [b]		
Visit Week		0		1	4		5	8		9	12	34			
Target Visit Day ± Window (days)	-42 to 1	1	4±1	8 -1/+3 [d]	29±3	32±1 [e]	36±2 [d,e]	57±3 [e]	60±1 [e]	64±2 [e,f]	85±3 [e]	239±14 [e]	+28		
Visit Type	Screening	VACCINE 1	Safety (Telephone)	Safety and Immuno.	VACCINE 2	Safety (Telephone)	Safety	VACCINE 3	Safety (Telephone)	Safety	Safety and Immuno.	Safety	Safety and Immuno.	Early Exit	Safety FU (Telephone)
Participant Experience Survey												●		●	
Approx. daily blood draw, mL	5.5		–	1.0	–	–	–	–	–	–	5.0	–	2.0	5.0	–
Approx. cumulative blood draw, mL	5.5		5.5	6.5	6.5	6.5	6.5	6.5	6.5	6 5	11.5	11.5	**13.5**	–	–

PROCEDURES[y] IN THE EVENT OF AN RTI OR OTITIS MEDIA CASE

	Parent/Guardian	*Study Site*
Contact Site	●	
RTI Symptoms Form [u]	●	
Physical examination [z]		●
Vital signs [h] incl. body temperature		●
Oxygen saturation (SpO_2)		●
Nasal sample [w]		●
Concomitant medications [r]		●
(S)AE recording [s,t]		if applicable

❶ pre-dose; ❷ abbreviated physical examination only at the discretion of the investigator (based on health status of the subject); ❸ pre- and post-dose; ❹ baseline immunogenicity blood draw and collection of a baseline nasal sample can take place *either* at screening *or* prior to vaccination on Day 1, at the discretion of the investigator, however both samples should be collected on the same day; ❺ if within 7 days of the previous vaccination; ❻ if within 28 days of the last vaccination; ❼ check of diary during the telephone call; ❽ at the discretion of the investigator (based on health status of the subject); ❾ if before Day 85 collect 4 mL cellular + 1 mL humoral; if after, collect 2 mL humoral only; ❿ MA-RTIs (including severe LRTIs) that occur between screening and Day 1 will be recorded on the Medical History page of the eCRF.

Note: All blood samples (venous blood and fingerstick) collected during the study, including samples from subjects who have been screened but not enrolled into the study, will be stored and used for future research if the subject's parent(s)/legal guardian(s) consent.

Note: Guidance on study conduct during the COVID-19 pandemic is available in Attachment 3.

a. Safety follow-up during both the vaccination and safety follow-up phases through 2 RSV seasons after the first dose: telephone call (or other communication, or clinic visit) to the parent/legal guardian or caregiver of subjects every 30 days ±7 days outside the RSV season, but every 14 days ±3 days in season (unless the timing coincides with a visit). If criteria specified in the monitoring rule are met, calls during the RSV season will be made on a weekly basis.
b. End of first RSV season after the first dose. *Note*: Subjects' parents/legal guardians will be informed of the timing of the start and end of the RSV season in accordance with the country/region-specific RSV local surveillance system (if available) or the local surveillance at the site (standard of care assessments, if available).
c. For those subjects who are unable to continue participation in the study up to the visit at the end of the RSV season, but for whom consent is not withdrawn, an exit visit will be conducted as soon as possible.
d. If any subject comes in earlier than Day 8 for Visit 4 or Day 36 for Visit 7 (allowed windows are -1/+3 and ±2 days, respectively), 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 (or Day 36).
e. The timings of visits after the second/third vaccinations will be determined relative to the actual day of that vaccination.
f. If any subject comes in earlier than Day 64 for Visit 10 (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 64.
g. Signing of the ICF should be done before any study-related activity.
h. Respiratory rate, heart rate, body temperature, oxygen saturation (SpO_2). Note that body temperatures are recommended to be measured axillary (actual routes to be recorded in the eCRF).
i. 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.
j. *Note*: serostatus may be assessed via the RSV EIA if available from a different study of the sponsor (VAC18194RSV2001). If done within 42 days of first dose, this assessment would not have to be repeated in the absence of a history of respiratory infection during that period.
k. To include exclusion criteria 1, 2, 3, 4, 6, 7, 9, 10, 11, 13, 14, 15, 16, 17, and 18.
l. Blood for cellular immunity will also provide plasma for humoral assessments.
m. 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 or third 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.
n. PBMC samples to assess cellular immune responses will be collected at sites that have the capability to process the cells within the time frame specified in the laboratory manual.
o. Subjects will be closely observed for a minimum of 30 minutes (or 60 minutes, depending on local or study-site requirements) post-vaccination. Any unsolicited, solicited local and systemic AEs, and vital signs will be documented by study-site personnel following this observation period.
p. All AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards. All other AEs (unsolicited) and special reporting situations will be reported from each vaccination through the following 28 days.
q. 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, RTI or OM case. Pre-study therapies administered up to 30 days before first dose of study vaccine will be recorded during screening.
r. Collection of any concomitant medication given in response to an RTI or OM case.

s. All SAEs related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards. All other SAEs will be reported from the first vaccination onwards.
t. Any RTI or otitis media case fulfilling the criteria of an SAE will be reported as such during the entire study period.
u. The subject's parent/legal guardian or caregiver should record any signs and symptoms of RTI (eg, runny nose, fever, severe cough, wheezing, rapid breathing, or difficulty breathing) on a daily basis, starting on the first day their child experiences symptoms, including the day on which symptoms resolve. They will be contacted periodically during the study (every 14 days ±3 days within the RSV season and every 30 days ±7 days outside of the RSV season, unless the timing coincides with a visit): during the RSV season, these calls are to remind them to complete the RTI Symptoms Form in the event of symptoms and to contact the site at the time of symptom onset, preferably within 72 hours after onset of symptoms. During and outside the RSV season, these calls will be to check for any SAEs and associated concomitant medications and any MA-RTIs. Details of the RTI procedures are provided in Section 9.2.2.
v. Severe LRTIs are a subset of MA-RTIs. The CEC will assess suspected cases of severe LRTI, and whether these have arisen from RSV infection.
w. Nasal samples (mid-turbinate or nasopharyngeal samples) will not be collected if less than 7 days after the previous sample collection.
x. Rulers and thermometers will be distributed to the subject's parent/legal guardian or caregiver on each dosing day.
y. At any time from screening throughout the study.
z. In all RTI or otitis media cases where results from the physical examination during the RTI site visit conclude that the RTI is not severe, and the RTI episode is still ongoing, a follow-up phone call (or other communication) to the parents/legal guardians or caregivers will be made once every 2 working days (±1 day) until symptom resolution. In the event of a worsening RTI, a follow-up RTI visit will be scheduled.

AE = adverse event; CEC = Clinical Endpoint Committee; d = day; eCRF = electronic case report form; EoS = End of Season; FU = follow-up; ICF = informed consent form; LRTI = lower respiratory tract infection; mo = month; MA-RTI = medically-attended respiratory tract infection; PBMC = peripheral blood mononuclear cell; 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
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
CEC	Clinical Endpoint Committee
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
F	fusion
FA	Full Analysis (set)
FI	formalin-inactivated
FIH	first-in-human
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	intracellular cytokine staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IgA/IgG	immunoglobulin A/immunoglobulin G
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	interactive web response system
LRTI	lower respiratory tract infection
MA-RTI	medically-attended respiratory tract infection
mITT	modified Intent-to-treat
PBMC	peripheral blood mononuclear cell
PI	principal investigator
post-F	post-fusion
PPI	Per-protocol Immunogenicity (set)
PQC	Product Quality Complaint
pre-F	pre-fusion
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SpO_2	peripheral capillary oxygen saturation
SRP/S	study responsible physician/scientist
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th	T-helper (cell)
TNF-α	tumor necrosis factor alpha
URTI	upper respiratory tract infection
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.

Study Naming Conventions

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

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

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

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

Study Identifier	Clinical Phase	Vaccine	Study Population
VAC18192RSV1001	1	Ad26.RSV.FA2	Adult subjects aged 18 to 50 years
VAC18192RSV1003	1	Ad26.RSV.FA2	Adult subjects aged 18 to 50 years
VAC18193RSV1003	1	Ad26.RSV.preF vaccine	Adults aged 60 years and older
VAC18193RSV2002	2a	Ad26.RSV.preF vaccine	Adult subjects aged 18 to 50 years
VAC18193RSV2003	2a	Ad26.RSV.preF vaccine	Adults aged 60 years and older
VAC18194RSV2001	1/2a	Ad26.RSV.preF vaccine	Adult subjects aged 18 to 50 years RSV-seropositive toddlers aged 12 to 24 months
Current study: VAC18194RSV2002	1/2a	Ad26.RSV.preF vaccine	RSV-seronegative toddlers aged 12 to 24 months
VAC18194RSV2003	1/2	Ad26.RSV.preF vaccine	RSV-seronegative infants aged 6 to 12 months

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.[18,43,47] 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 the deaths occurred in developing countries.[36] Nevertheless, the RSV disease burden in developed countries is substantial, with RSV infection during childhood linked to the development of wheezing, airway hyperreactivity, and asthma.[40,42,44,45,46] In the United States, 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 United States, RSV infection in children under 5 years of age is the cause of approximately 57,000 to 175,000 hospitalizations, 500,000 emergency room visits, and 500 deaths each year.[39,43,47] In children under 1 year of age, RSV is the most important cause of bronchiolitis, and RSV hospitalization is the highest among children under 6 months of age.[6,18]

Despite the high RSV disease burden, no licensed vaccine is available for RSV. The first vaccine candidate for use in young children, which consisted of formalin-inactivated RSV (FI-RSV), was associated with enhanced respiratory disease (ERD) upon infection with RSV.[26] 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.[35]

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 following the immunization of adults with an Ad26-vectored human immunodeficiency virus (HIV) vaccine (Ad26.ENVA.01), and immunization of adults and infants with an adenovirus serotype 35 (Ad35)-vectored tuberculosis (TB) vaccine (Ad35.TB-S). These data demonstrate predominantly interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) production in $CD4^+$ and $CD8^+$ T-cells.[2,5,38] Furthermore, in mice, Ad26- and Ad35-vectored vaccines with circumsporozoite (CS) transgene inserts (Ad26.CS.01 and Ad35.CS.01), when given as single immunizations or in combination as a heterologous prime-boost regimen at dose levels ranging from 1×10^8 viral particles (vp) to 1×10^{10} vp, induce predominantly $CD8^+$ T-cell responses, as well as mainly immunoglobulin IgG2a antibody responses, indicative of a Th1-biased response.[41]

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

The results indicate that there have been no safety concerns following vaccination in either study. After vaccination with Ad26.RSV.FA2, local reactogenicity comprised almost exclusively mild to moderate pain of median duration 1 to 3 days. The most commonly experienced solicited systemic adverse events (AEs) (headache, fatigue, chills, myalgia) were also mostly mild to moderate in severity, with a median duration of 1 to 3 days; most unsolicited AEs and most laboratory toxicities were mild to moderate in severity. No serious adverse events (SAEs) were reported and no AEs led to withdrawal from study vaccine.[24,25]

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

FA2 and preF RSV Vaccines

The candidate vaccine assessed in the current study is Ad26.RSV.preF, a replication-incompetent Ad26 containing a DNA transgene that encodes for the pre-fusion (pre-F) conformation-stabilized F protein derived from the RSV A2 strain.

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

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

The F protein of RSV undergoes a conformational transition from a metastable pre-fusion conformation to a stable post-fusion conformation. Neutralizing sensitive epitopes reside on both proteins, but recent evidence indicates that those epitopes specific to the pre-F protein seem to be more potent than those previously identified and present on the post-F protein.[15,17] This evidence

resulted 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 configuration encoded by this vector differs by only 5 amino acids from the wild-type used in the FA2 construct.[30] This change in the transgene confers more stability to the pre-fusion form of the molecule before it undergoes its natural transition to the post-fusion form.[30] This change also induces higher immune responses against pre-fusion epitopes because the majority of neutralizing antibodies target the pre-fusion protein conformation.[31,37] 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.[23]

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 RSV A2 (in cotton rats and mice) and RSV B strains (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.[23]

Ad26.RSV.preF Clinical Data

Ad26.RSV.preF is currently under evaluation in 4 randomized, controlled, double-blind studies: the FIH Phase 1 study VAC18193RSV1003 in subjects aged ≥60 years in stable health; the Phase 1/2a study VAC18194RSV2001 in adults aged ≥18 to ≤50 years and RSV-seropositive toddlers aged 12 to 24 months; the exploratory Phase 2a study VAC18193RSV2002 in adults aged ≥18 to ≤50 years to evaluate Ad26.RSV.preF in a virus challenge model; and the Phase 2a study VAC18193RSV2003 in subjects aged ≥60 years in stable health to evaluate seasonal influenza vaccine and Ad26.RSV.preF, with and without co-administration.

In the VAC18193RSV1003 study, 72 male and female subjects were randomized to 1 of 5 groups and have received the first (Day 1) of 2 intramuscular injections as follows:

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

Safety and immunogenicity data from the unblinded interim 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 the immunogenicity of the vaccine; the 1×10^{11} vp dose of Ad26.RSV.preF was more immunogenic than the 5×10^{10} vp dose. No safety concerns were revealed; the reactogenicity of both doses was comparable.

In the VAC18194RSV2001 study, first 12 male and female adult subjects and then at least 36 male and female RSV-seropositive toddlers are randomized to receive 2 intramuscular injections as follows:

Adults (aged ≥18 to ≤50 years):

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

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

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

At the start of June 2018, the Independent Data Monitoring Committee (IDMC) evaluated Day 8 safety data from the first 12 toddlers and Day 29 safety data from 8 toddlers. Prior to initiating dosing in the current study (VAC18194RSV2002), the IDMC will convene to review additional safety data (unblinded at the study group level) from VAC18194RSV2001 collected up to this point (ie, from at least the first 12 toddlers), including solicited AEs, unsolicited AEs and SAEs through 28 days after the first dose of 5×10^{10} vp of Ad26.RSV.preF; immune response data (RSV F protein binding antibodies [pre-F and/or post-F], RSV virus neutralization assay, Th1/Th2 subtyping) through 28 days after the first dose are also expected to be available for additional toddlers.

The formulation buffer that is used in study VAC18194RSV2001 and in all other ongoing studies (Formulation Buffer2)[g] will be used in the current study. In study VAC18193RSV1003, Ad26.RSV.preF is provided in a different formulation buffer (Formulation Buffer)1[h].

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

[g] Formulation Buffer 2: 15 mM citrate, 5% (w/w) hydroxypropyl-β-cyclodextrin, 0.4% (v/v) ethanol, 0.03% (w/w) polysorbate-80, 75 mM sodium chloride, pH 6.2.

[h] Formulation Buffer 1: 20 mM histidine, 5% (w/v) sucrose, 0.1 mM ethylenediaminetetraacetic acid, 0.5% (v/v) ethanol, 0.02% (w/w) polysorbate-80, 75 mM sodium chloride, pH 6.5.

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

Safety Data Supporting the Dose Selection

The dose level for Ad26.RSV.preF used in the current study is supported by experience in adults with other Ad26-based vaccines encoding for different antigens (including EnvA [in Ad26.ENVA.01 against HIV];[4,5] CS protein [in Ad26.CS.01 against malaria];[48] and Ebola glycoprotein [in Ad26.ZEBOV against Ebola virus][33]).

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

In addition, 17 clinical studies with Ad26 vaccines (Ad26.RSV.preF, Ad26.Mos[4].HIV, and Ad26.ZEBOV) are ongoing. At least 4,579 subjects (including approximately 96 subjects 4-11 years of age in VAC52150EBL3001) have been enrolled in these ongoing studies, of whom approximately 456 received at least 1 vaccination with an Ad26-based vaccine (mainly 5×10^{10} vp) up to 31 August 2017. For the remainder of subjects, study vaccine assignment is not yet known. To date, all Ad26-based vaccines were found to be well-tolerated, no safety concerns have been identified. Note that, in general, at a given dose level, no significant differences in safety profiles of Ad26-based vaccines have been observed based upon the transgene used.[21,22]

Apart from the ongoing VAC18193RSV1003, VAC18193RSV2003 and VAC18194RSV2001 studies outlined in the previous section and VAC52150EBL3001, Ad26-vectored vaccines have only been tested in adults (ie, subjects 18 to 50 years of age). Ad35-vectored vaccines have been tested in 904 subjects, including 555 adults and 349 infants. Data from Bacillus Calmette-Guérin-primed infants immunized with Ad35 encoding for TB antigens (AERAS-402) indicated that the highest immune responses were obtained following administration of 1×10^{11} vp. The safety of this Ad35-based TB vaccine was acceptable when tested in infants aged 14 weeks and older at doses from 1×10^{8} vp to 1×10^{11} vp.

1.2. Nimenrix

Nimenrix® is a vaccine indicated to protect adults, adolescents, and children from the age of 6 weeks against invasive meningococcal disease caused by 4 groups of the bacterium *Neisseria meningitidis* (group A, C, W-135, and Y). Nimenrix is administered intramuscularly by injection into the thigh or deltoid muscle.

The rationale for the selection of Nimenrix is provided in Section 3.2.

1.3. Overall Rationale for the Study

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

This current study will evaluate the safety, reactogenicity, and immunogenicity of Ad26.RSV.preF at a dose of 2.5×10^{10} vp in RSV-seronegative toddlers aged 12 to 24 months.

The dose selection rationale is provided in Section 3.2.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective is:

- To assess the safety and reactogenicity of an intramuscular regimen of 3 doses of 2.5×10^{10} vp of Ad26.RSV.preF in RSV-seronegative toddlers aged 12 to 24 months.

Secondary Objectives

The secondary objectives are:

- To assess the humoral and cellular immune responses elicited by Ad26.RSV.preF as measured by virus neutralizing antibodies (VNAs), F protein binding antibodies (pre-F and/or post-F), and Th1/Th2 subtyping.
- To monitor for severe RSV-LRTI as a preliminary indication of ERD.

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 can include, but may not be limited to, RSV strain cross-neutralization, RSV F protein antibody specificity characterization, RSV G and/or N protein binding antibodies, adenovirus neutralization assay, functional and molecular antibody characterization (eg, avidity and antibody isotyping) and antibody sequencing if feasible, and evaluation of cellular immune response (IFN-γ enzyme-linked immunospot [ELISpot] assay, intracellular cytokine staining [ICS], cytokine analysis).
- To assess RSV infection rates (symptomatic and asymptomic) in Ad26.RSV.preF and control subjects.
- To assess symptomatic RSV infection rates in Ad26.RSV.preF and control subjects.
- To assess symptoms of respiratory illness via the Respiratory Tract Infection (RTI) Symptoms Form.

2.1.2. Endpoints

Primary Endpoints – Safety and Reactogenicity

- Solicited local and systemic AEs for 7 days after each vaccination.
- Unsolicited AEs for 28 days after each vaccination.
- SAEs from first dose administration to the end of the study.

Secondary Endpoints – Immune Responses

The analysis of the immunogenicity of the vaccine regimens will include the characterization of both humoral and cellular responses. The focus of the immunogenicity analysis will be on 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 neutralizing antibodies to an A strain.

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

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

Cell-mediated Immune Response

- Flow cytometry (ICS)*

  Analysis of T-cell responses to RSV F protein peptides for Th1/Th2 subtyping.

  ** Cytokine analysis for Th1/Th2 profiling will be done if no ICS can be generated due to an insufficient number of peripheral blood mononuclear cells (PBMCs) for ICS assay (see the Exploratory Endpoints below).*

Secondary Endpoints – RSV Infection

- Severe RSV-LRTI

  Severe RSV-LRTI will be defined as the presence of severe LRTI as assessed by the Clinical Endpoint Committee (CEC; See Section 11.3.1.2), and confirmation of RSV infection from a nasal (mid-turbinate or nasopharyngeal) sample using independent reverse transcriptase polymerase chain reaction (RT-PCR) by a central laboratory. If no central laboratory RT-PCR result is available, a positive test result for RSV from a local laboratory (if available) could be used to confirm RSV infection upon evaluation by the CEC.

Exploratory Endpoints – Immune Responses

Exploratory analyses may be performed to evaluate the vaccine-elicited immune responses further. These can include, but may not be limited to, the following assays (as available and applicable):

Humoral Immune Response

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

  Assessment of the strain cross-neutralizing capacity of the vaccine-induced immune response.

- F protein antibody specificity characterization

  Assessment of pre-F and post-F specificity by binding or functional assays as ELISA, and/or competition ELISA, epitope mapping, and functional VNAs.

- Nasal immunoglobulin antibodies to RSV F protein

  Analysis of IgA or IgG antibodies to RSV pre-F and/or post-F

- G and/or N protein antibodies (ELISA)

  Assessment of antibodies binding to RSV G and/or N protein to estimate the RSV infection rate (symptomatic and asymptomatic) in the study.

- Adenovirus neutralization assay

  Assessment of neutralizing antibody responses against the adenoviral vector.

- Functional and molecular antibody characterization

  Functional characterization of antibodies may be performed: antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).[9] A molecular characterization of vaccine-elicited antibodies will include antibody avidity, other respiratory viral neutralizing or binding assays, immunoglobulin isotype, functional VNAs to other respiratory viruses, and antibody assessments.

Cell-mediated Immune Response

- ICS

  Analysis of T-cell responses to RSV F protein peptide-stimulated PBMC (including, but not limited to, $CD4^+/CD8^+$, interleukin [IL]-2, IFN-γ, TNF-α, activation markers and memory)

- Cytokine analysis

  Cytokine profiles of (*in vitro*) stimulated PBMC supernatant will be analyzed to assess the quantity and quality of elicited immune responses, including Th1/Th2 balance. The analysis can include, but may not be limited to, IFN-γ, IL-2, IL-4, IL-5, IL-13, and TNF-α.

- IFN-γ ELISpot assay

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

- Sequencing of the antibody repertoire will be done if feasible.

Exploratory Endpoints – RSV Infection

- RSV-RTI and RSV-LRTI confirmed by RT-PCR.
- Serology for, but not limited to, RSV protein G and/or N (and/or F) may be used to confirm exposure to RSV at the end of the season.

  To detect RSV infections by serology, a fold increase will be applied to determine if a subject is a seroconverter based on G and/or N ELISA. Fold increases for RSV infection will be determined based on 2 consecutive blood samples as planned in the Time and Events Schedule.
- RSV medically-attended respiratory tract infection (MA-RTI): includes all subjects with RSV-RTI that is medically-attended, ie, when the subject's parent/legal guardian or caregiver seeks medical attention outside normal study procedures, including healthcare professional visits to the home, clinic visits, emergency room attendance, hospital admission.

See Section 9.2, Study Evaluations, 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 RSV-seronegative toddlers.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multi-center, randomized, observer-blind[i], Phase 1/2a study, to be conducted in 36 male and female RSV-seronegative toddlers aged ≥12 to ≤24 months.

Each subject's RSV serostatus will be assessed by RSV enzyme immunoassay (EIA) at screening[j] (see Section 9.1.3.1). *Note*: serostatus may be assessed via this assay if available from a different study of the sponsor (VAC18194RSV2001). If done within 42 days of first dose, this assessment would not have to be repeated in the absence of a history of respiratory infection during that period. Additionally, the seronegative status will be confirmed by the absence of an anamnestic humoral immune response (which is usually observed 7-10 days post antigen re-exposure in RSV seropositive subjects) from blood samples taken 7 days after the first dose.

[i] *Note*: The vaccine administrator will be unblinded but will have no other study function following dosing. The site staff or qualified professional staff who will do the observation and the subjects will be blinded.

[j] The cut-off for seronegativity is a titer <1 EIA unit.

Subjects will be randomized 1:1 to receive either Ad26/Ad26/Ad26 (at 2.5×10^{10} vp) or placebo/placebo/Nimenrix [k,l] (or placebo/placebo/placebo) (Table 4).

Table 4: Study Design VAC18194RSV2002

Group	N[a]	Day 1	Day 29/Week 4	Day 57/Week 8
RSV-seronegative toddlers 12 to 24 months				
Group 1	18	Ad26.RSV.preF (2.5×10^{10} vp)	Ad26.RSV.preF (2.5×10^{10} vp)	Ad26.RSV.preF (2.5×10^{10} vp)
Group 2	18	Placebo (saline)	Placebo (saline)	Nimenrix [b] or Placebo (saline)

N = number of subjects; vp = viral particles

a: At the time of Amendment 6, 37 subjects have been enrolled.

b: In countries where the commercial vaccine Nimenrix is licensed, placebo (0.9% saline) can be replaced with Nimenrix as the Day 57 vaccination for the study subjects in the control group, in accordance with the local label and local regulations, and unless contra-indicated. Nimenrix will be administered, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision). In the US, Nimenrix will not be used unless it has been licensed for use or an Investigational New Drug (IND) has been submitted.

An IDMC has been established for the ongoing study VAC18194RSV2001 in RSV-seropositive toddlers and all subsequent studies with Ad26.RSV.preF in children (including the current study), to evaluate safety and reactogenicity data on a regular basis. See Section 11.9.2 for details.

An independent, blinded CEC has been established for ongoing study VAC18194RSV2001 in RSV-seropositive toddlers and all subsequent studies with Ad26.RSV.preF in children (including the current study), to assess suspected cases of severe LRTI and the occurrence of RSV infection. See Section 11.9.1 for details.

The study will have 3 phases: a **screening phase**, a **vaccination phase**, and a **safety follow-up phase** through 2 RSV seasons after the first dose. The durations of the respective phases are as follows:

k In countries where the commercial vaccine Nimenrix is licensed, placebo (0.9% saline) can be replaced with Nimenrix as the Day 57 vaccination for the study subjects in the control group, in accordance with the local label and local regulations, and unless contra-indicated. Nimenrix will be administered, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision). In the US, Nimenrix will not be used unless it has been licensed for use or an IND has been submitted. It should be recorded in the eCRF by the unblinded pharmacist whether the subject was vaccinated with either Nimenrix or placebo on Day 57.

l Nimenrix is a vaccine used to protect adults, adolescents, and children from the age of 6 weeks against invasive meningococcal disease caused by 4 groups of the bacterium *Neisseria meningitidis* (group A, C, W-135, and Y).[12]

Phase	
Screening:	up to 6 weeks before the first dose
Vaccination:	34 weeks • dosing on Days 1, 29 and 57 • safety follow-up through 6 months post-final dose • immunogenicity at: ➢ pre-Dose 1 (Day 1) ➢ 7 days post-Dose 1 (Day 8) ➢ 28 days post-Dose 3 (Day 85) ➢ end of the first RSV season post-first dose
Safety follow-up:	through 2 RSV seasons after the first dose

The start and end of the RSV season will be determined based on the information from the national surveillance system (if available) or the local surveillance at the site (standard of care assessments, if available). The site will communicate to the sponsor when RSV starts to circulate in their region; the decision to stop screening of subjects at affected sites will be taken together with the sponsor.

The end of the vaccination 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

No sentinel approach is taken for the 2.5×10^{10} vp dose, as this dose is lower than the 5×10^{10} vp dose currently being evaluated in several other studies, including study VAC18193RSV1003 in adults aged ≥60 years in stable health and study VAC18194RSV2001 in RSV-seropositive toddlers aged 12 to 24 months (see Section 1.1).

- The first 8 subjects will be enrolled and receive the first dose (Ad26.RSV.preF 2.5×10^{10} vp or placebo).
- 7-day safety in these first 8 subjects will be monitored by the principal investigator (PI[s]) or designee and the sponsor's study responsible physician/scientist (SRP/S). In the event of a significant safety finding, the IDMC will be consulted.
- 4 more subjects will be enrolled and receive the first dose (Ad26.RSV.preF 2.5×10^{10} vp or placebo).
- The IDMC will assess post-first dose reactogenicity by review of 7-day safety data for these first 12 subjects (6 subjects receiving Ad26.RSV.preF 2.5×10^{10} vp and 6 subjects receiving placebo).

Any safety finding will be closely monitored, although enrollment will not be paused for either the PI(s) or designee and SRP/S review of the first 8 subjects or the IDMC review of the first 12 subjects.

If the IDMC review does not take place before the first subject receives the scheduled second or third dose (due to potential slow recruitment), the PI(s) or designee and SRP/S will review the available data prior to the second or third dose being given as scheduled, respectively. In the event of a significant safety finding, the IDMC will be consulted.

In all post-first dose 7-day safety reviews, safety data for review will include solicited and unsolicited AEs and SAEs.

Second-dose Safety

Safety assessments will also be made 7 days after the second dose in the first 12 toddlers before administering the second dose to the remaining toddlers. Post-second dose 7-day safety will be monitored by the PI(s) or designee and SRP/S. Safety data for review will include solicited and unsolicited AEs and SAEs. Any safety finding will be closely monitored, although dosing will not be paused for this PI(s) or designee and SRP/S review.

Third-dose Safety

Safety assessments will also be made 7 days after the third dose in the first 12 toddlers before administering the third dose to the remaining toddlers. Post-third dose 7-day safety will be monitored by the PI(s) or designee and SRP/S. Safety data for review will include solicited and unsolicited AEs and SAEs. Any safety finding will be closely monitored, although dosing will not be paused for this PI(s) or designee and SRP/S review.

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

After each dose, subjects will be closely observed for a minimum of 30 minutes (or 60 minutes, depending on local or study-site requirements) post-vaccination, 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 after this observation period. The subject's parent/legal guardian or caregiver will be given a thermometer, ruler and daily assessment (subject) diary with instructions for the proper recording of events. Each subject's parent/legal guardian or caregiver 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 next 7 days. Temperatures[m] should be taken at approximately the same time each day, preferably in the evening[n] and additionally whenever the child feels warm. Study-site personnel will collect and review subject diary information and confirm the entries at subsequent site visits.

[m] Recommended to be measured axillary (actual routes to be recorded in the eCRF).

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

Unsolicited AEs will be collected for 28 days after each vaccination (ie, from the time of each vaccination through the following 28 days). SAEs will be collected from first dose administration 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 these periods when associated with any SAE, RTI or OM case.

Blood will be collected for immunogenicity assessments as follows:

- pre-vaccination and 7 days after the first dose, at 28 days after the third dose and at the end of the RSV season.

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

All blood samples (venous blood and fingerstick) collected during the study, including samples from subjects who have been screened but not enrolled into the study, will be stored and used for future research if the subject's parent(s)/legal guardian(s) consent (see also Section 16.2.5).

RTIs and otitis media cases will be collected during the RSV season [p]. Outside the RSV season, only MA-RTIs, including severe LRTIs, and medically-attended otitis media cases will be collected. During the RSV season, the subject's parent/legal guardian or caregiver should record any signs and symptoms of RTI (eg, runny nose, fever, severe cough, wheezing, rapid breathing, or difficulty breathing) or otitis media on a daily basis using a study-specific RTI Symptoms Form, starting on the first day their child experiences symptoms, including the day on which the symptoms resolve. Outside the RSV season, parents/guardians or caregivers should likewise record signs and symptoms of RTI on a daily basis using the RTI Symptoms Form as soon as possible for any MA-RTI until resolution of symptoms. For details of RTI procedures, see Section 9.2.2.

During the entire study after the first dose, including during the vaccination phase and safety follow-up phase, the subject's parent/legal guardian or caregiver will be contacted periodically by telephone (or other communication, or by clinic visit) through 2 RSV seasons after the first dose (every 14 days ±3 days within the RSV season, every 30 days ±7 days outside of the season, unless the timing coincides with a visit). During the RSV season, these calls will remind the subject's parent/legal guardian or caregiver to record signs and symptoms of RTI, and to contact the site at the time of symptom onset. During and outside the RSV season, these calls will check for SAEs and associated concomitant medications, MA-RTIs, and any subsequent medical care that may have been sought, since the previous visit or telephone contact (this includes

[o] By venous blood sample or fingerstick, at the discretion of the investigator. If fingerstick is done at screening, baseline blood draw for immunogenicity should be on Day 1.

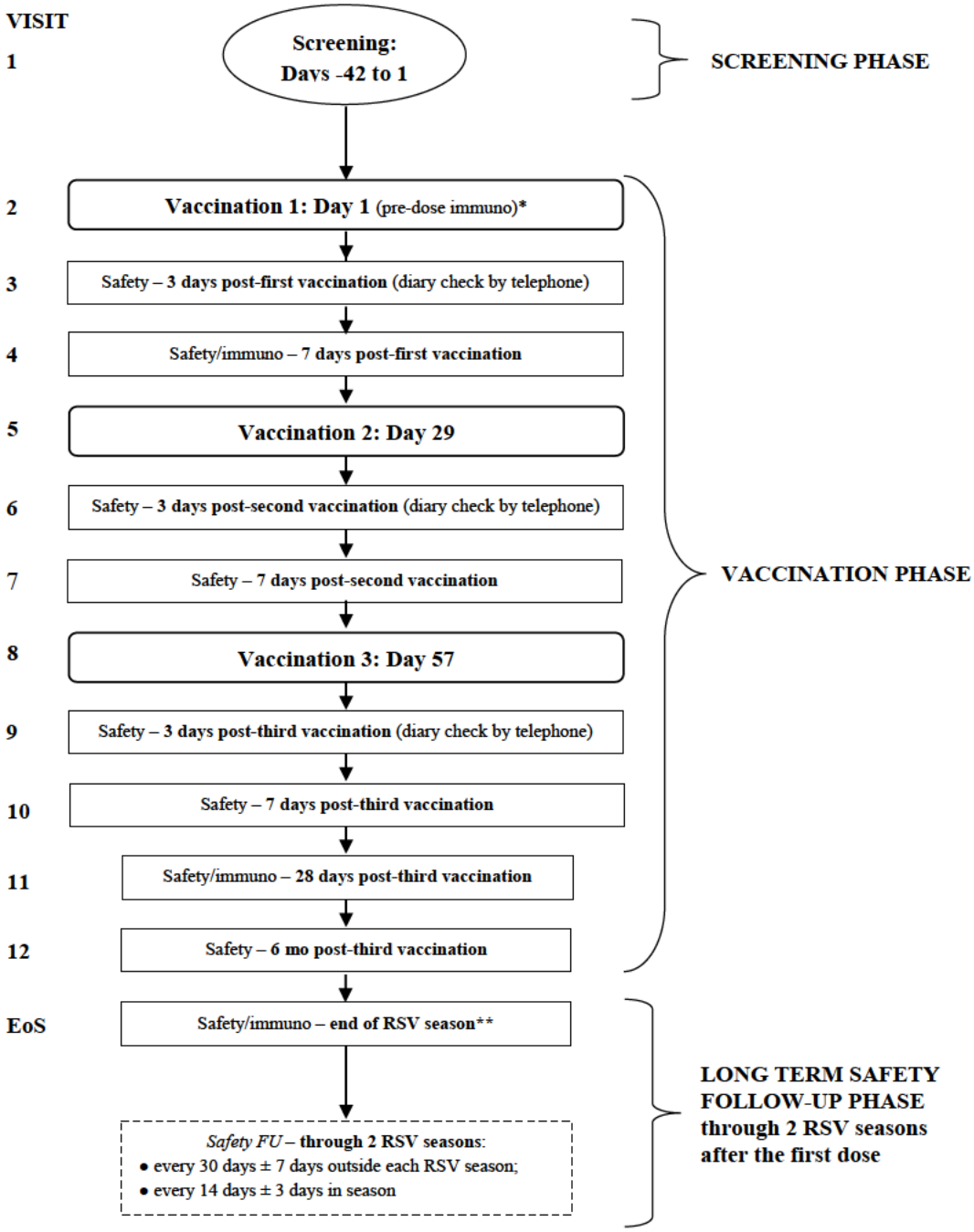
[p] *Note*: The RTI procedures (see Section 9.2.2) also apply to all otitis media cases.

contacts with subjects who received at least one dose of study vaccine but withdrew from further dosing). The sponsor will provide the site with a checklist for these follow-up phone calls.

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

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



* Baseline immunogenicity blood draw can take place either at screening or prior to vaccination on Day 1, at the discretion of the investigator.

** End of season visit may fall before Visit 12, depending on the timing.

3.2. Study Design Rationale

Vector Selection

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

Dose Selection

In study VAC18194RSV2001, ongoing in UK and Finland, the IDMC reviewed the interim analysis when 12 toddlers had reached Day 8 post-first dose (5×10^{10} vp of Ad26.RSV.preF or placebo). Their recommendation was that the study should continue unmodified. Transient fevers were observed in some subjects, comparable in intensity to those seen following measles, mumps and rubella (MMR) immunization in this age group. A recent study from Africa in 1- to 3-year-old infants revealed only 5 cases of fever in over 380 subjects in which 2/3 infants had received 5×10^{10} vp of an Ad26-vectored Ebola vaccine. Thus, the transient fevers observed in study VAC18194RSV2001 may be based on a regional effect. In addition, available immunogenicity data from study VAC18194RSV2001 in 8 toddlers after the first dose (5 after 5×10^{10} vp of Ad26.RSV.preF and 3 after placebo) showed that the vaccine was immunogenic, inducing a consistent increase in neutralizing antibody titers without affecting qualitative Th1/Th2 balances. Prior to dosing toddlers in the current study (VAC18194RSV2002), the IDMC will convene to review additional safety data (unblinded at the study group level) from VAC18194RSV2001 collected up to this point (from at least the first 12 toddlers), including solicited AEs, unsolicited AEs and SAEs through 28 days after the first dose of 5×10^{10} vp of Ad26.RSV.preF; immune response data (RSV F protein binding antibodies [pre-F and/or post-F], RSV virus neutralization assay, and Th1/Th2 subtyping) through 28 days after the first dose are also expected to be available for additional toddlers dosed in VAC18194RSV2001. The continued general safety and tolerability of the vaccine in VAC18194RSV2001 will further support the expectation that safety will be acceptable at the dose of $2.5x10^{10}$ vp in the current study.

The 2.5×10^{10} vp dose will be used in the current study because this dose has been highly immunogenic for the individual Ad26 vector components in the sponsor's HIV vaccine program where induction of Th1 responses in antigen-naïve individuals, similar to antigen-naïve RSV-seronegative toddlers, has been observed. It is hypothesised that an adenovirus-vectored vaccine with a Th1 profile against RSV will reduce the likelihood of disease enhancement in RSV-seronegative recipients. The 2.5×10^{10} vp dose is therefore thought to be an appropriate dose to start with for preliminary ERD assessment in RSV-seronegative toddlers before progressing to younger age groups, and performing dose-response assessments, in future studies.

Blinding, Control, Study Phase/Periods, Vaccine Groups

Controls (Nimenrix or placebo) will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of Ad26.RSV.preF vaccine. Randomization will be used to minimize bias in the assignment of subjects to vaccine groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across vaccine groups, and to enhance the validity of statistical comparisons

across vaccine groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

The incorporation of a licensed vaccine as an alternative to placebo offers a more accepted approach to this pediatric vaccine study. Nimenrix has been selected for incorporation in the design of this study as the recommended one-dose vaccination in the targeted age group matches the existing study design, which is essential to preserve the blind in the current study.

3.3. Risk/Benefit Section

3.3.1. Known Benefits

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

In countries where the commercial vaccine Nimenrix [q] is licensed, Nimenrix will be incorporated as the Day 57 vaccination for subjects in the control group, in accordance with the local label and local regulations, and unless contra-indicated. Nimenrix will be administered, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision). See Attachment 2 for further details.

Vaccination with Nimenrix may provide protection against invasive meningococcal disease caused by *N. meningitidis*.

3.3.2. 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.

3.3.3. Known Risks

Single doses of 5×10^{10} vp of Ad26.RSV.preF are under investigation in the ongoing FIH Phase 1 study VAC18193RSV1003 in elderly subjects. Safety data from the unblinded interim analyses at 28 days post-Dose 1 and at 6 months post-Dose 1 in all subjects did not reveal safety concerns. The unblinded interim analysis 6 months post-Dose 1 also confirmed the immunogenicity seen at 28 days post-Dose 1 over time.

The most common side effects from initial vaccination with Nimenrix (seen in more than 1 patient in 10) are loss of appetite, irritability, drowsiness, tiredness, headache, fever, swelling, and pain and redness at the site of injection.[12]

[q] Nimenrix is a vaccine used to protect adults, adolescents, and children from the age of 6 weeks against invasive meningococcal disease caused by 4 groups of the bacterium *Neisseria meningitidis* (group A, C, W-135, and Y).[12]

For further details, see the Nimenrix Summary of Product Characteristics.

3.3.4. Potential Risks

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

Risks Related to Vaccination

In general, intramuscular injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration/swelling, arm discomfort or bruising of the skin at vaccine injection sites.

Subjects may exhibit general signs and symptoms associated with administration of a vaccine, or vaccination with placebo, including (in pediatric subjects:) loss of appetite, vomiting, diarrhea, decreased activity/lethargy, irritability/crying. 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.

Risks Related to Adenoviral-vectored Vaccines

Safety data available from completed clinical studies in adults with other Ad26-vectored vaccine candidates, in which Ad26 with different inserts has been evaluated at dose levels ranging from 1×10^{9} vp to 1×10^{11} vp, indicate that no safety concerns would be anticipated from vaccination with Ad26.RSV.preF at doses of 2.5×10^{10} vp, 5×10^{10} vp or 1×10^{11} vp.[21,22]

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, refer to 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 1×10^{8} vp to 1×10^{11} vp in infants aged 14 weeks and older.

Risks Related to RSV Vaccines

In the 1960s, an 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 to a control group.[8,13,26,27] Children aged between 2 months and 7 years 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 FI-RSV vaccinated children died.[27] 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 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; or 4) may have induced a Th2-skewed allergic type T-cell response.[35]

In general, adenoviral-vectored vaccines have been shown to promote a Th1-biased response.[41] 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 Samples

Collection of nasal samples may cause a nosebleed.

Risks from Blood Draws

As with all clinical studies requiring blood sampling, there are risks associated with venipuncture and multiple blood sample collection. Blood drawing may cause pain, tenderness, bruising, bleeding, dizziness, vasovagal response, syncope, and, rarely, infection at the site where the blood is taken. The total blood volume to be collected is considered to be an acceptable amount of blood over this time period from the population in this study (see Section 16.1, Study-Specific Design Considerations).

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 risks that are not known. If any significant new risks are identified, the PI(s) and parent(s)/legal guardian(s) of subjects will be informed.

3.3.5. 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 be closely observed by study staff for a minimum of 30 minutes (or 60 minutes, depending on local or study-site requirements) post-vaccination, or longer if deemed necessary by the investigator, to monitor the development of any acute reactions. Any unsolicited and solicited local or systemic AEs will be documented during this period. The subject's parent/legal guardian or caregiver 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. SAEs will be recorded from first dose administration through the end of the study.

- 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.

- Several safety measures are included in this protocol to minimize the potential risk to subjects, including the following:
  - Safety review by the PI(s) or designee and SRP/S of 7-day safety data in the first 8 subjects after the first dose; safety review by the IDMC of 7-day safety data in the first 12 subjects after the first dose. These safety assessments at 7 days post-first dose are described in Section 3.1.
  - For all subjects, there are pre-specified rules that would result in pausing of further study vaccinations if predefined conditions occur, preventing exposure of new subjects to study vaccine until the PI(s) or designee/SRP/S and 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[r], 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 or third 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.
  - During the RSV season, careful monitoring will be in place to check for the occurrence of RTI/otitis media [s]. The subject's parent/legal guardian or caregiver will record any signs and symptoms of RTI (eg, runny nose, fever, severe cough, wheezing, rapid breathing, or difficulty breathing) on a daily basis using the study-specific RTI Symptoms Form, starting on the first day their child experiences symptoms, including the day on which symptoms resolve. Nasal samples will be collected by the site staff and analyzed for identification and confirmation of RSV infection. The presence of severe LRTI and RSV infection will be determined by the CEC. The IDMC will be informed of any case of severe RSV-LRTI as assessed by the CEC. For such cases, a monitoring rule is applied (see Section 11.3.1.3).

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

[s] *Note*: The RTI procedures (see Section 9.2.2) also apply to all otitis media cases.

– Assuming all subjects are recruited before the season, if 4 severe RSV-LRTI events are observed and all occur in the Ad26.RSV.preF group, enrollment in all pediatric studies with Ad26.RSV.preF will be halted and monitoring of all enrolled subjects will be increased (see Section 11.3.1.3).

Nimenrix has been shown to be at least as effective as comparable vaccines at stimulating an immune response to the 4 groups of the *N. meningitidis* bacterium in people of different age groups. Nimenrix offered the benefits of conjugated vaccines over conventional vaccines, including producing a strong immune response in young children. Nimenrix is well-tolerated and it can be safely given together with other routinely used vaccines in the different age groups.[12]

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 42 days before administration of the first dose of study vaccine.

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

Note: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including 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.

4.1. Inclusion Criteria

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

1. Criterion amended per Amendment 5:

   1.1 Each subject's parent(s)/legal guardian(s) must sign an informed consent form (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 2 RSV seasons 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. In countries where regulation requires that both parents/legal guardians give consent, this will be applicable.

2. Criterion amended per Amendment 4:

   2.1 Subject is male or female, whose age on the day of ICF signature is ≥12 months to ≤24 months and who is seronegative for RSV within 42 days prior to dosing.

   Note: Serostatus may be assessed via the RSV EIA if available from a different study of the sponsor (VAC18194RSV2001). If done within 42 days of first dose, this assessment would not have to be repeated in the absence of a history of respiratory infection during that period.

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

4. 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.

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

6. Each subject'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

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

1. Criterion amended per Amendment 4:

   1.1 Subject has moderate or severe illness (this does not include minor illnesses such as diarrhea) or temperature ≥38.0 ºC within 24 hours prior to the first dose of study vaccine; the subject may be enrolled at a later date[t], or be withdrawn at the discretion of the investigator and after consultation with the sponsor.

2. Any subject who has had an RTI between screening and randomization that the PI(s) feels would make them ineligible.

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

4. Subject has any clinically significant acute or chronic medical condition (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) that, in the opinion of

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

the investigator, would preclude participation.

5. Subject has major congenital anomalies (after discussion with the SRP/S) or known cytogenetic disorders (eg, Down's syndrome).

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

7. 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.

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

9. 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 this study.

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

10. Criterion amended per Amendment 2:

    10.1 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.

11. Criterion amended per Amendment 3:

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

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

13. 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 study.

14. Subject has a history of receipt of blood products or immunoglobulin within 3 months of randomization.

15. 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.

16. Subject has a contraindication to intramuscular injections and blood draws, eg, bleeding disorders.

17. 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.
18. Subject's parent(s)/legal guardian(s) cannot communicate reliably with the investigator.
19. Criterion amended per Amendment 4:
    19.1 Subject is a family member of either the investigator, 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, or employee of the sponsor.

4.3. Prohibitions and Restrictions

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

1. See Section 8, Pre-study and Concomitant Therapy, for details on 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.
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. 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,[10] 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. Subjects will be randomly assigned to a treatment group based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks. No stratification will be applied.

The randomization ratio is 1:1.

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.

Every effort will be made to determine the serostatus of subjects. During the study, any subject who was assessed as seronegative at screening and who subsequently shows an anamnestic response at Day 8 will be replaced if possible.

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 will occur at the time of the primary analysis. The results will only be available to a selected group of sponsor personnel, excluding personnel involved in data collection and data management and clinical immunology laboratory personnel. From the primary analysis onwards, group level results may be shared with the investigator or other blinded clinical staff, as needed, however, efforts will be made to preserve the blinding to the individual subject allocation.

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

The subjects, the subject's parent/legal guardian or caregiver, study-site personnel and investigator, as well as sponsor personnel involved in data collection and data management and clinical immunology laboratory 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 the preparation of study vaccines will be monitored by an independent study vaccine monitor (see also Section 17.8).

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

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's parent/legal guardian or caregiver).

6. DOSAGE AND ADMINISTRATION

Every effort will be made to administer the first 2 doses before the start of the RSV season.

Ad26.RSV.preF (JNJ-64400141) will be supplied in single-use vials. The dose of 2.5×10^{10} vp will be administered in a volume of 0.25 mL by intramuscular injection. Placebo will be supplied as sterile 0.9% saline for intramuscular injection. Nimenrix [u] will be supplied as Nimenrix powder and solvent for solution for injection in pre-filled syringe or ampoule and administered as 0.5 mL solution for intramuscular injection.

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

To ensure that the site staff or qualified professional staff who will do the observation as well as the subjects (and their parents/legal guardians) will be blinded, the necessary precautions will be taken as documented by the clinical sites and agreed upon by the sponsor.

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

[u] In countries where the commercial vaccine Nimenrix is licensed, placebo (0.9% saline) can be replaced with Nimenrix as the Day 57 vaccination for the study subjects in the control group, in accordance with the local label and local regulations, and unless contra-indicated. Nimenrix will be administered, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision). In the US, Nimenrix will not be used unless it has been licensed for use or an IND has been submitted.

Injections should be administered in the anterolateral aspect of the thigh. Only if required by local health authority guidance, injections may be administered in the deltoid muscle [v]. Alternating injection sites will be used for all study vaccinations unless there is a medically justifiable reason in the judgment of the PI(s).

A play assistant may be present to distract the infant/toddler while the subject's parent/legal guardian or caregiver holds the child to receive the vaccination.

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 healthcare professional. The unblinded pharmacist, or other qualified individual, may also perform vaccine administration, but will have no other study function following dosing. The date and time of each study vaccine administration will be recorded in the eCRF.

8. PRE-STUDY AND CONCOMITANT THERAPY

Pre-study therapies 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 SAE(s), RTI or OM case that meet the criteria outlined in Section 12.3.2.

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

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

Subjects can receive medications such as acetaminophen, non-steroidal anti-inflammatory drugs, 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.)

Chronic or recurrent use of immunomodulators/suppressors, eg, cancer chemotherapeutic agents, oral or parenteral corticosteroids for at least 5 days is prohibited within 42 days prior to randomization, or planned during the study.

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

[v] For each vaccination, a record should be made in the eCRF of which leg (or arm) was injected.

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.

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 safety and reactogenicity will include physical assessment by study-site personnel, and the subject's parent/legal guardian or caregiver reports on signs and symptoms post-vaccination. Additional visits may be required if in the investigator's opinion, further clinical or laboratory evaluation is needed.

Each 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 the injection site) and solicited systemic AEs.

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 study personnel at visits indicated on the Time and Events Schedule.

At each visit or telephone call during the RSV season, each subject's parent/legal guardian or caregiver should be informed that, if their child develops any symptoms of RTI (such as runny nose, fever, severe cough, wheezing, rapid breathing, or difficulty breathing) or otitis media, they should record signs and symptoms of RTI and contact the site as soon as possible [w].

The Time and Events Schedule summarizes frequency and timing of safety and immunogenicity measurements applicable to this study. Additionally, a summary of Procedures in the Event of an RTI is provided showing procedures applicable for both parents/guardians and for the study site.

The total blood volume to be collected from each subject over approximately 36 to 40 weeks from screening will be approximately 13.5 mL.

[w] *Note*: The RTI procedures (see Section 9.2.2) also apply to all otitis media cases.

9.1.2. Visit Windows

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

- Second vaccination: ±3 days
- Third vaccination: ±3 days
- 3 days post-vaccination safety only visit: ±1 day
- 7 days post-vaccination safety and immunogenicity visit: after first dose: –1/+3 days; after second and third doses: ±2 days
- 28 days post-final vaccination safety and immunogenicity visit: ±3 days
- 6 months post-final vaccination safety visit: ±14 days
- End of RSV season safety and immunogenicity visit: +28 days

9.1.3. Screening and Study Visits

Note: It is possible for any visit to be conducted in the subject's home if the site has an established Standard Operating Procedure as such.

9.1.3.1. 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 and Section 4.2, respectively, will be included into the study. The investigator will provide detailed information on the study to the subject's parent(s)/legal guardian(s) and will obtain his/her written informed consent prior to the 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. *Note*: In countries where regulation requires that both parents/legal guardians give consent, this will be applicable.

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, oxygen saturation [SpO_2]) and length and weight
- Demographic information
- Medical history
- Review of pre-study medications
- Review of inclusion/exclusion criteria
- Blood sample for immunogenicity testing*
- Nasal sample for immunogenicity testing*
- Blood sample for RSV serostatus testing**

* Collection of blood samples and nasal samples for baseline immunogenicity assessments can be either at screening or pre-dose on Day 1, at the discretion of the investigator, however both samples should be collected on the same day. *Note*: If blood is collected by fingerstick for RSV serostatus at screening, baseline blood draw for immunogenicity should be on Day 1.

** By venous blood sample or fingerstick, at the discretion of the investigator.

Note: At screening, information will also be collected whether the toddler is currently breastfed, with breastfeeding history, number and ages of siblings, and whether family members smoke in the home environment, with smoking history.

RSV seropositivity will be assessed by RSV EIA at screening. The cut-off for seronegativity is a titer <1 EIA unit. *Note*: Serostatus may be assessed via this assay if available from a different study of the sponsor (VAC18194RSV2001). If done within 42 days of first dose, this assessment would not have to be repeated in the absence of a history of respiratory infection during that period. Every effort will be made to determine the serostatus of subjects. Any subject who was assessed as seronegative at screening and who subsequently shows an anamnestic response at Day 8 will be replaced if possible.

The seronegative status will be confirmed by the absence of an anamnestic humoral immune response from blood samples taken 7 days after the first dose. An anamnestic response is defined as a >4-fold increase in pre-F ELISA within 7 days post Dose 1. The criteria for assessment of the anamnestic response will be specified in the SAP.

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.

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

Between screening and Day 1, only MA-RTIs (including severe LRTIs) will be collected. Any MA-RTI or severe LRTI which occurs during this period will be recorded on the Medical History page of the eCRF.

9.1.3.2. Vaccination Phase: Day 1 to Day 239

9.1.3.2.1. Vaccination (Days 1, 29, and 57)

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

After re-check of the inclusion and exclusion criteria,[x] abbreviated physical examination (at the discretion of the investigator) and measurement of vital signs, length 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[y], or be withdrawn at the discretion of the investigator and after consultation with the sponsor.

Collection of blood samples and nasal samples for baseline immunogenicity assessments can be either at screening or pre-dose on Day 1, at the discretion of the investigator, however both samples should be collected on the same day. If fingerstick sampling for RSV serology is done 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 (or 60 minutes, depending on local or study-site requirements) post-vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or solicited systemic AEs 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.

RTI Symptoms Forms will be distributed to each subject's parent/legal guardian or caregiver. See Section 9.2.2 for details on completion of the RTI Symptoms Form.

Visits 5 and 8: Day 29/Vaccination 2 and Day 57/Vaccination 3

After verification of selected eligibility criteria,[a] abbreviated physical examination (at the discretion of the investigator) and measurement of vital signs, length and weight will be performed for all subjects pre-vaccination. Before the second or third 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

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[x] Exclusion criterion 1, 2, 3, 4, 6, 7, 9, 10, 11, 13, 14, 15, 16, 17, and 18.

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

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 study vaccine.

Subjects will be closely observed for a minimum of 30 minutes (or 60 minutes, depending on local or study-site requirements) post-vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or solicited systemic AEs 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.

RTI Symptoms Forms will be distributed to each subject's parent/legal guardian or caregiver.

9.1.3.2.2. Post-vaccination Follow-Up

9.1.3.2.2.1. Post-first, Post-second and Post-third Vaccination Follow-Up

Visits 3 and 4 (3 and 7 Days Post-first Vaccination), Visits 6 and 7 (3 and 7 Days Post-second Vaccination) and Visits 9 and 10 (3 and 7 Days Post-third Vaccination)

Visits 3, 6 and 9 at 3 days post-vaccination will be a telephone call to check subject diaries and to collect safety information (solicited and unsolicited AEs, SAEs, concomitant medications, and RTIs).

Visits 4, 7 and 10 at 7 days post-vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, and recording of any (serious) AEs, concomitant medications and RTIs. The subject diary will be reviewed and collected. If Visit 4 occurs before the end of Day 8, Visit 7 occurs before the end of Day 36 or Visit 10 occurs before the end of Day 64 (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 the next visit (ie, Visit 5, Visit 8 or Visit 11, respectively).

A blood sample for immunogenicity assessments will be collected from all subjects 7 days post-first vaccination.

Note: If any subject comes in earlier than Day 8 for Visit 4, Day 36 for Visit 7 or Day 64 for Visit 10 (allowed windows are -1/+3, ±2 days, and ±2 days, respectively), 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 (ie, Day 8, Day 36 or Day 64, respectively).

9.1.3.2.2.2. Post-last Vaccination Follow-Up

Visits 11 and 12 (28 Days and 6 Months Post-third Vaccination)

Visits 11 and 12 will include an abbreviated physical examination including vital signs measurement (at the discretion of the investigator), measurement of length and weight, recording of unsolicited AEs (Visit 11 only), any RTIs, any SAEs, concomitant medications, and any MA-RTIs.

Samples for immunogenicity assessments will be collected at Visit 11.

A nasal sample will be collected 28 days post-final vaccination from all subjects at Visit 11.

Parents/legal guardians or caregivers (where allowed by local regulations) will be invited to complete an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved Participant Experience Survey at Visit 12 (See Section 9.2.4).

9.1.3.2.3. End of RSV Season Visit

The end of season visit will include an abbreviated physical examination including vital signs measurement (at the discretion of the investigator), measurement of length and weight, any RTIs, any SAEs, concomitant medications, and any MA-RTIs.

Samples for immunogenicity (humoral) assessments will be collected.

Subjects' parents/legal guardians will be informed of the timing of the start and end of the RSV season in accordance with the country/region-specific RSV local surveillance system (if available) or the local surveillance at the site (standard of care assessments, if available).

9.1.3.2.4. Early Withdrawal: Early Exit Visit

For those subjects who are unable to continue participation in the study up to the visit at the end of the RSV season, 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 12 will be performed (see Section 9.1.3.2.2.2). Samples for immunogenicity assessments will be collected at the early exit visit as follows: if the early exit visit is before Day 85, 4 mL for cellular assessments and 1 mL for humoral assessments will be collected; if the early exit visit is after Day 85, 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.

Note: Subjects for whom consent is withdrawn only for blood draws may remain in the study and continue to receive study vaccine and undergo safety follow-up.

9.1.3.3. Safety Follow-up

Each subject's parent/legal guardian or caregiver will be contacted by telephone (or other communication, or clinic visit) through 2 RSV seasons after the first dose, including during the vaccination phase and safety follow-up phase (every 30 days ±7 days outside of the RSV season, and every 14 days ±3 days within the RSV season, unless the timing coincides with a visit).

During the RSV season, these calls will remind the parents/legal guardians or caregivers to contact the site if their child develops any symptoms of RTI/otitis media; during and outside the RSV season, these calls will be to check for any SAEs and associated concomitant medications, any MA-RTIs/medically-attended otitis media cases, and any subsequent medical care that may have been sought, since the previous visit or telephone contact (this 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 according to the Time and Events Schedule. Sample collection and processing will be performed by the staff at clinical sites according to current and approved Standard Operating Procedures.

The humoral and cellular immunogenicity assays that may be used in this study (as available and applicable) are summarized in Table 5 and Table 6, respectively.

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

Table 5: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Secondary endpoints	
RSV neutralization A strain	Analysis of neutralizing antibodies to an A strain
F protein antibodies (ELISA; pre-F and/or post-F)	Analysis of antibodies binding to RSV F protein in pre-fusion and/or post-fusion form
Exploratory endpoints	
RSV strain cross-neutralization	Analysis of cross-neutralizing antibodies to B and/or a different A strain(s)
F protein antibody specificity characterization	Pre-F and post-F specificity by binding or functional assays as ELISA, and/or competition ELISA, epitope mapping, and functional VNAs
Nasal Ig antibodies to RSV F protein	Analysis includes, but not limited to, IgA or IgG antibodies to RSV pre-F and/or post-F
G and/or N protein antibodies (ELISA)	Analysis of antibodies binding to RSV G and/or N protein
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to, ADCC, ADCP, avidity, other respiratory viral neutralizing or binding assays, Ig isotype, functional VNAs to other respiratory viruses, and antibody assessments

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 6: 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	
ICS	Analysis of T-cell responses to RSV F protein peptide-stimulated PBMC (including, but not limited to, $CD4^+/CD8^+$, IL-2, IFN-γ, TNF-α, activation markers and memory)
Cytokine analysis	Analysis of secreted cytokines (eg, IFN-γ, IL-2, IL-4, IL-5, IL-13, and TNF-α) in RSV F peptide-stimulated PBMC supernatant, including, but not limited to, measurement of Th1/Th2 cytokine balance
IFN-γ ELISpot	T-cell IFN-γ responses to RSV F protein peptides

ELISpot = enzyme-linked immunospot; F = fusion; ICS = intracellular cytokine staining; IFN-γ = interferon gamma; IL = interleukin; PBMC = peripheral blood mononuclear cell; Th = T-helper (cell); RSV = respiratory syncytial virus; TNF-α = tumor necrosis factor alpha
Note: Cytokine analysis for Th1/Th2 profiling will be done if no ICS data can be generated due to insufficient PBMCs for ICS assay.

In addition to RT-PCR performed on RTI nasal samples, any immunogenicity blood sample collected from all subjects may also be assayed by serology (eg, ELISA specific to RSV protein G and/or N as available and applicable) to confirm exposure to RSV at the end of the season if the sample volumes allow.

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

9.2.2. RTI Procedures

All RTIs and otitis media cases will be collected during the RSV season[z]. Outside the RSV season, only MA-RTIs (including severe LRTIs; see Section 11.3.1.1) and medically-attended otitis media cases will be collected.

During the RSV season, the subject's parent/legal guardian or caregiver should record any signs and symptoms of RTI (eg, runny nose, fever, severe cough, wheezing, rapid breathing, difficulty breathing) or otitis media on a daily basis using a specific RTI Symptoms Form, starting on the first day their child experiences symptoms. Outside the RSV season, parents/guardians or caregivers should likewise record signs and symptoms of RTI or otitis media on a daily basis using the RTI Symptoms Form as soon as possible for any MA-RTI or medically-attended otitis media case until resolution of symptoms. A new form should be completed each day the subject has symptoms, including the day on which the symptoms resolve. RTI Symptoms Forms will be distributed at the timepoints as indicated in the Time and Events Schedule. Completed RTI forms can either be mailed to the site or brought to the site at the next visit.

[z] *Note*: The RTI procedures also apply to all otitis media cases.

In the event of an RTI, MA-RTI, or (medically-attended) otitis media, parents/legal guardians or caregivers should contact the site. Parents/legal guardians or caregivers will themselves be contacted periodically during the study. During the RSV season, these calls are to remind them to complete the RTI Symptoms Form in the event of any signs or symptoms of RTI or otitis media, and to contact the site at the time of symptom onset; during and outside the RSV season, these calls will check for SAEs and associated concomitant medications, MA-RTIs, medically-attended otitis media cases, and any subsequent medical care that may have been sought, since the previous visit or telephone contact (this includes contacts with subjects who received at least one dose of study vaccine but withdrew from further dosing).

During the season, and where possible outside the season (for MA-RTIs, including severe LRTIs or for medically-attended otitis media cases), site staff will conduct a physical examination (with vital signs, including oxygen saturation), and collect nasal samples, preferably within 72 hours after onset of symptoms. For suspected severe RTI cases, nasal swabs should be shipped on the day of collection to enable timely assessment of samples for the presence of RSV infection by central laboratory RT-PCR. To evaluate the safety of the Ad26.RSV.preF vaccine, nasal samples may also be assessed for the presence of other respiratory pathogens. The actual dates and times of sample collection and physical examination data must be recorded in the eCRF, preferably within 24 hours of sample collection. Any suspected case of severe RSV-LRTI should be recorded in the eCRF within 24 hours of knowledge of the event. (*Note*: Nasal samples will not be collected if less than 7 days after the previous sample collection.) *Note*: A nasal swab for RSV RT-PCR testing will also be collected from any subject with otitis media (as recorded on the RTI Symptoms Form) during the study, independent of other RTI symptoms.

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

In all RTI or otitis media cases where results from the physical examination during the RTI site visit conclude that the RTI is not severe, and the RTI episode is still ongoing, a follow-up phone call (or other communication) to the parents/legal guardians or caregivers will be made once every 2 working days (±1 day) until symptom resolution. In the event of a worsening RTI, a follow-up RTI visit will be scheduled. (*Note*: In the event of a worsening RTI, a repeat nasal sample may be collected if less than 7 days after the previous sample collection at the discretion of the investigator.) The data from this second RTI visit must be recorded in a separate eCRF page and will have a separate conclusion (severe/non-severe). Further follow-up visits to assess additional reported worsening of an RTI episode may be scheduled at the discretion of the investigator.

Signs and symptoms of RTI or otitis media recorded by the subject's parent/legal guardian on the RTI Symptoms Form will be transferred onto the applicable RTI symptoms page in the eCRF, preferably within 24 hours of receipt of the form.

Note: RTI procedures (completion of the RTI symptoms form at home, and an RTI visit to the site with associated procedures, including nasal sampling) are not applicable for a non-medically-attended RTI that occurs outside the season, including those that started before the RSV season and continue into the season without worsening of symptoms.

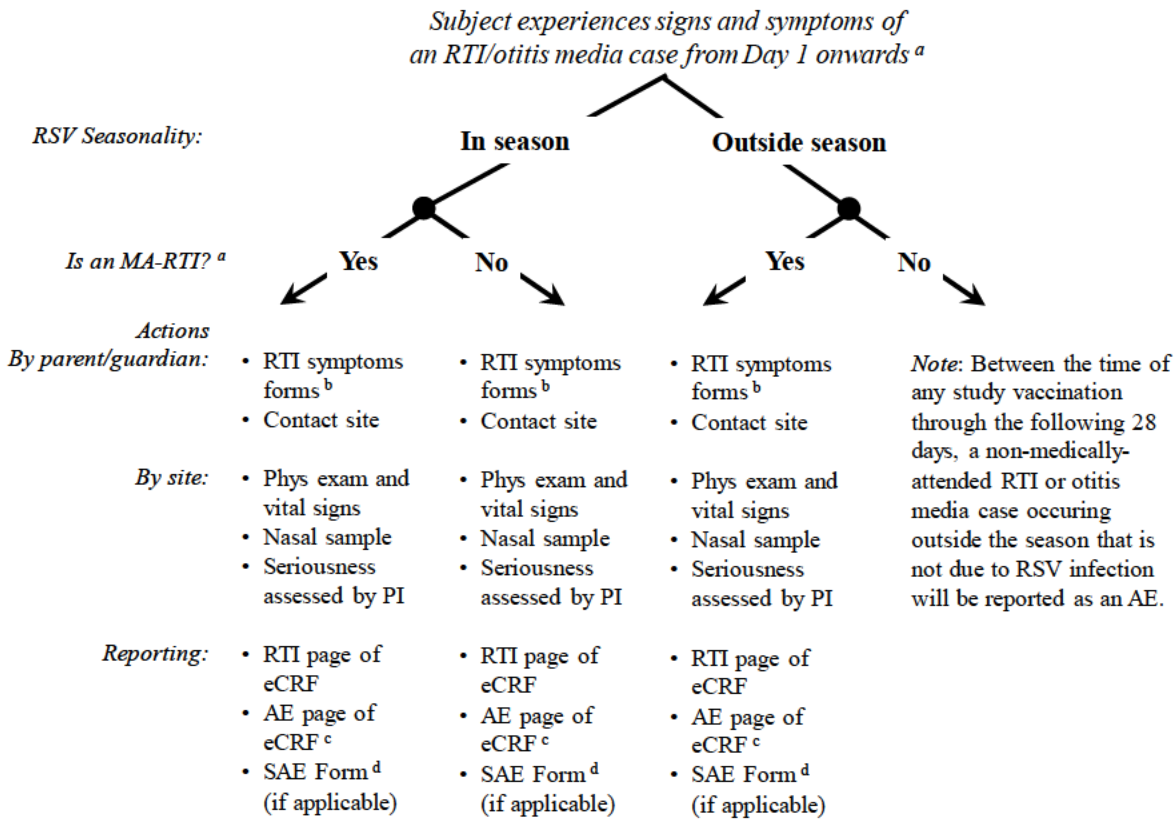
Any RTI or otitis media case that is not due to RSV infection will be reported as an AE if it occurs between the time of any study vaccination through the following 28 days. During the study, any RTI or case of otitis media fulfilling the criterion of an SAE will be reported to the sponsor (and, when appropriate, extended to Regulatory Agencies). Any RTI or case of otitis media reported as an (S)AE that is found to be positive for RSV will be excluded from the analyses of (S)AEs. However, the case will remain in the clinical database and will be tabulated separately in the clinical study report.

Any MA-RTI (including any severe LRTI) or (medically-attended) otitis media case which occurs between screening and Day 1 will be recorded on the Medical History page of the eCRF (RTI visit and RTI Symptoms Form completion is not required for these events prior to the first vaccination).

An overview of the RTI procedures is provided in Figure 2 below. *Note*: The RTI procedures also apply to all otitis media cases.

Any parent/legal guardian or caregiver who seeks medical attention for their child due to an RTI or otitis media should make the attending healthcare professional aware that their child is taking part in an RSV vaccine study. Each parent/legal guardian or caregiver will be given a wallet card with key study information and study-site contact details (see Section 12.3.1). These details should be shared with the attending healthcare professional.

Figure 2: Procedures in the Event of a Respiratory Tract Infection or Otitis Media Case



[a] Severe LRTIs are a subset of MA-RTIs. *Note*: Any MA-RTI (including any severe LRTI) which occurs between screening and Day 1 will be recorded on the Medical History page of the eCRF.

[b] During the RSV season, subjects' parents/guardians or caregivers should record signs and symptoms of RTI using the RTI Symptoms Form on a daily basis starting on the first day they experience symptoms, including the day on which symptoms resolve. Outside the RSV season, parents/guardians or caregivers should likewise record signs and symptoms of RTI on a daily basis using the RTI Symptoms Form as soon as possible for any MA-RTI until resolution of symptoms.

Subjects' parents/guardians or caregivers will be informed of the timing of the start and end of the RSV season in accordance with the country/region-specific RSV local surveillance system.

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

[d] During the study, any RTI or case of otitis media fulfilling the criterion of an SAE will be reported to the sponsor (and, when appropriate, extended to Regulatory Agencies). Any RTI or case of otitis media reported as an (S)AE that is found to be positive for RSV will be excluded from the analyses of (S)AEs. However, the case will remain in the clinical database and will be tabulated separately in the clinical study report.

9.2.3. Safety Evaluations

Any clinically relevant changes occurring 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 reactogenicity according to the timepoints provided in the Time and Events Schedule.

Adverse Events

All AEs will be reported as specified in Section 12.3.1, All Adverse Events.

Unsolicited AEs

Unsolicited AEs will be reported by the subject (ie, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time of each vaccination through the following 28 days, or early discontinuation. Relatedness of unsolicited AEs should be determined by the investigator. Additionally, AEs that are related to the study procedures or are related to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards.

Solicited AEs

Information related to solicited AEs as defined in Section 12.1.1, will be recorded by the subject's parent/legal guardian or caregiver in a diary for 7 days after each vaccination. Each subject's parent/legal guardian or caregiver 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 (or 60-minute, depending on local or study-site requirements) post-vaccination assessment of solicited events at the site. Diary information will be transcribed by the study personnel in the appropriate eCRF pages.

Injection Site (Local) Adverse Events

Each subject's parent/legal guardian or caregiver 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 healthcare 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 healthcare professional's assessment, both symptoms have been combined to allow self-assessment by the subject's parent/legal guardian or caregiver. 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.[28,29]

Systemic Adverse Events

The subject's parent/legal guardian or caregiver will be instructed on how to record daily temperature[aa] using a thermometer provided for home use. The subject's parent/legal guardian or caregiver 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[bb]. 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 ≥38.0 °C, as recorded in at least one measurement.[32]

The subject's parent/legal guardian or caregiver s will also be instructed on how to note daily in the diary for 7 days post-vaccination symptoms of the following events: loss of appetite, vomiting, diarrhea, decreased activity/lethargy, irritability/crying and fever (ie, body temperature ≥38.0 °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's parent/legal guardian or caregiver will be instructed to record the date of last symptoms and maximum severity in the diary after resolution.

[aa] Recommended to be measured axillary (actual routes to be recorded in the eCRF).

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

9.2.3.1. Vital Signs

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), and respiratory rate (breaths per minute)
- Body temperature (the axillary route is recommended)
- Oxygen saturation (SpO_2)

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.

9.2.3.2. Physical Examination

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

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

9.2.4. Other Evaluations

At Visit 12 (6 months post-Dose 3), parents/legal guardians or caregivers (where allowed by local regulations) of each study subject will be invited to complete an IEC/IRB approved Participant Experience Survey, to share to their experience in this study. The responses will be collected by an external party and anonymously provided to the sponsor.

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 three 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 he or she has to discontinue from study vaccination before the end of the study vaccine regimen.

Subjects will be discontinued from study vaccination 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
- Any related SAE
- Any related AE, worsening of health status or intercurrent illness that, in the opinion of the investigator, requires study vaccine discontinuation
- Repeated failure to comply with protocol requirements
- Decision by the sponsor, investigator, local regulatory authorities or IRB/IEC

Note: A subject will not be automatically withdrawn from the study if consent is withdrawn only for blood draws; they may remain in the study and continue to receive study vaccine and undergo safety follow-up.

Withdrawal From the Study

Parents/legal guardians have 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 parents/legal guardians are not obliged to give a reason for withdrawing prematurely, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the subject's rights.

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

- 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 the 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 9.1.3.2.4).

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

10.3. Contraindications to Vaccination

The following events constitute a contraindication to vaccination at that point in time:

- 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[cc] 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 or third 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. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine (see Section 4.3).

11. STATISTICAL METHODS

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

Planned analyses are described in Section 11.8.

11.1. Analysis Sets

Vaccination assignment will follow the as-treated principle.

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

The Full Analysis (FA) set includes all subjects who were randomized and received at least one dose of study vaccine, regardless of the occurrence of protocol deviations. 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 (PPI) analysis set 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. Any subject with an anamnestic response at Day 8 will not be included in the PPI analysis set.

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 will not be taken into account.

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

Additionally, a modified intent-to-treat (mITT) analysis set is defined as a subset of the FA set excluding subjects who are seronegative at screening but for whom there is an anamnestic response at Day 8. The criteria for assessment of the anamnestic response will be specified in the SAP. The mITT set will be the primary analysis set for assessment of RSV infection in seronegative subjects.

11.2. Sample Size Determination

The number of subjects chosen for this study will provide a preliminary safety and immunogenicity assessment. Control recipients (Nimenrix or placebo) 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.

Table 7 shows the probabilities of observing at least 1 AE at given true AE rates:

Table 7: Probability of Observing at Least One Adverse Event at a Given True Adverse Event Rate

True Adverse Event Rate	Probability of Observing at Least One Adverse Event in N Subjects N=18
0.5%	9%
1%	17%
2.5%	37%
5%	60%
10%	85%
25%	99%
50%	100%

A monitoring rule for severe RSV-LRTI is described in Section 11.3.1.3. Based on this rule and assuming an event rate in controls of 1%, there is at least 80% power to halt enrollment in this or the next study if the incidence in the Ad26.RSV.preF group is approximately 25% or more.

11.3. Criteria for Endpoints of RSV Infection

11.3.1. Definitions for Endpoints of RSV Infection

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

- Severe RSV-LRTI (secondary endpoint)
- RSV MA-RTI (exploratory endpoint)
- RSV-RTI (exploratory endpoint)
- RSV-LRTI (exploratory endpoint)

11.3.1.1. Definitions of Severe RSV-LRTI

Severe RSV-LRTI will be defined as the presence of severe LRTI as assessed by the CEC, and confirmation of RSV infection by nasal (mid-turbinate or nasopharyngeal) sample using independent RT-PCR by a central laboratory. See also Section 11.9.1. If no central laboratory RT-PCR result is available, a positive test result (including commercial test results) for RSV from a local laboratory (if available) could be used to confirm RSV infection upon evaluation by the CEC.

11.3.1.2. Presence of Severe RSV-LRTI as Assessed by the Clinical Endpoint Committee (CEC)

For subjects with an RTI that is considered severe by the PI(s) (based on below-mentioned WHO criteria)[34], the CEC will determine the presence or absence of severe LRTI by reviewing all available clinical information related to respiratory disease, with a special focus on the following characteristics ("WHO" criteria)[34]:

- Respiratory infection defined as cough or difficulty breathing

  AND

- LRTI defined as fast breathing or peripheral capillary oxygen saturation (SpO_2) <95%

  AND

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

Determination of RSV Infection

A subject is considered RSV positive if the subject has a positive RT-PCR for RSV on nasal (mid-turbinate or nasopharyngeal) samples (central laboratory; see Section 9.2.2). If no central laboratory RT-PCR result is available, a positive test result (including commercial test results) for RSV from a local laboratory (if available) could be used to confirm RSV infection upon evaluation by the CEC.

If a test result for RSV is missing (ie, not available or not conclusive), the RTI will not be considered RSV-related.

11.3.1.3. Monitoring Rule for Severe RSV-LRTI

In this section 'severe RSV-LRTI' refers to the assessment made by the CEC.

With respect to the secondary endpoint 'severe RSV-LRTI', a monitoring rule for severe RSV-LRTI is as follows.

- If 1 event (regardless of group) of 'severe RSV-LRTI' is observed, no analysis will be done. *Note:* However, the IDMC will be informed and may convene.
- As soon as 2 or more events (regardless of group) of 'severe RSV-LRTI' have been observed, confidence limits for the difference in proportions (using Wilson score method) between the Ad26.RSV.preF group and control group (pooling placebo/placebo/Nimenrix and placebo/placebo/placebo) will be constructed by the external statistician who is supporting the IDMC:
  - If the upper (one-sided) 95% confidence limit for the difference is <10%: continue the study; if study enrollment is still ongoing, continue enrollment.
  - If the upper (one-sided) 95% confidence limit is ≥10% and the lower (one-sided) 80% confidence limit is >0: more frequent active monitoring of subjects, including weekly calls within the RSV season and more frequent medical review will be initiated.
  - If the upper (one-sided) 95% confidence limit is ≥10% and the lower (one-sided) 95% confidence limit is >0: halt enrollment in this study or the next study; more frequent active monitoring of subjects, including weekly calls within the RSV season and more frequent medical review for all enrolled subjects should be initiated.

For example: assuming complete enrollment, if 2 or 3 severe RSV-LRTI events are observed and all occurred in the Ad26.RSV.preF group, the lower (one-sided) 80% (but not the 95%)

confidence limit will be >0 and monitoring will be increased. If 4 severe RSV-LRTI events are observed and all occurred in the Ad26.RSV.preF group, the lower (one-sided) 95% confidence limit will be >0 and enrollment in all pediatric studies with Ad26.RSV.preF will be halted and monitoring of all enrolled subjects will be increased.

More details on this monitoring rule are specified in the IDMC charter.

11.3.2. Definitions of RSV MA-RTI

RSV MA-RTI includes all subjects with RSV-RTI that is medically-attended, ie, when the subject's parent/legal guardian or caregiver seeks medical attention outside normal study procedures, including healthcare professional visits to the home, clinic visits, emergency room attendance, and hospital admission.

Determination of RSV Infection

A subject is considered RSV positive if the subject has a positive RT-PCR for RSV nasal (mid-turbinate or nasopharyngeal) samples (central laboratory; see Section 9.2.2). If no central laboratory RT-PCR result is available, a positive test result (including commercial test results) for RSV from a local laboratory (if available) could be used to confirm RSV infection upon evaluation by the CEC.

If a test result for RSV is missing (ie, not available or not conclusive), the RTI will not be considered RSV-related.

11.4. Subject Information

For all subjects, demographic characteristics (eg, age, weight and length percentiles according to WHO pediatric growth and weight charts,[49] race, and gender), and other baseline characteristics (eg, physical examination, medical history, concomitant diseases) will be tabulated and summarized with descriptive statistics.

11.5. Immunogenicity Analyses

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% confidence interval 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

The presence of RSV infection, as described in Section 9.2.2, will be assessed by RT-PCR. The presence of RSV infection will be summarized by descriptive statistics.

Any RTI or otitis media case recorded as an AE in the eCRF that is subsequently found to be RSV positive by RT-PCR (central laboratory or based on CEC assessment if available) will be excluded from the safety analysis and tabulated separately (refer to Section 11.7).

The mITT set is the primary analysis set for assessment of RSV infection in seronegative subjects.

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 SAEs from first dose administration onwards, will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 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 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 time frame (eg, 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. *Note*: Frequencies of post-dose 3 AEs in the control group will be presented separately for Nimenrix and placebo.

Any RTI or otitis media case recorded as an AE in the eCRF that is subsequently found to be RSV positive by RT-PCR (central laboratory or based on CEC assessment if available) will be excluded from the safety analysis and tabulated separately.

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. *Note*: Vital signs data post-dose 3 in the control group will be presented separately for Nimenrix and placebo.

Physical Examination

Physical examination abnormalities will be listed.

11.8. Planned Analyses

The following analyses will be performed:

- Primary analysis 28 days post-final dose in all subjects, includes safety and immunogenicity; unblinded
- Interim analysis performed when all subjects have data of 1 RSV season post-Dose 1, includes safety and immunogenicity; unblinded
- Final analysis at the end of the study; unblinded

The primary analysis and interim analysis may be combined into one analysis. These analyses will also be shared with the IDMC.

Additional interim analyses (blinded or unblinded) 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 and clinical immunology laboratory personnel.

11.9. Data Review Committees

11.9.1. 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, 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 CEC will assess suspected cases of severe LRTI and the occurrence of RSV infection. If the RTI is assessed to be a severe RSV-LRTI by the CEC (see Section 11.3.1.2), this will be shared with the IDMC which then might convene to run the monitoring rule.

11.9.2. 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 presence of severe LRTI and the occurrence of RSV infection will be determined by the CEC, a separate committee (see Section 11.9.1).

The IDMC will monitor severe RSV-LRTI as assessed by the CEC according to the rule described in Section 11.3.1.3 and further 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. An immunologist may be included on an ad hoc basis, as needed. 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 unblinded data.

Details on the intervals of the safety evaluations 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.

11.10. Study Vaccination Pausing Rules

The PI(s) or designee and the SRP/S 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 vaccination, and trigger a meeting of the IDMC to discuss study suspension, adaptation or discontinuation of further vaccination:

1. One or more subjects experience an SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine (ie, by the PI[s]); *OR*
2. One or more subjects experience anaphylaxis clearly not attributable to other causes than vaccination with study vaccine; *OR*
3. Two or more subjects 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 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. Death of any subject, considered related to study vaccine or if the causal relationship to the study vaccine cannot be excluded.

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

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.

Note: The study will also be paused if specific severe RSV-LRTI monitoring criteria are met as described in Section 11.3.1.3.

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 within 24 hours after the AE is reported. Any suspected case of severe RSV-LRTI should be recorded in the eCRF within 24 hours of knowledge of the event.

If any of the above specific pausing rules are met, the IDMC will make recommendations regarding continuation of the study or discontinuation to the sponsor. Study suspensions or terminations will occur within 5 working days after the decision is made, unless local regulations specify a shorter time frame. Local regulatory authorities including IECs/IRBs will be informed within appropriate regulatory-mandated time frames. The study may be resumed only upon the 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, IECs/IRBs and 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.[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 Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading 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 (ie, questioning of the subject's parent/legal guardian or caregiver).

Solicited Adverse Events

Solicited AEs are predefined local (at the injection site) and systemic events for which the subject's parent/legal guardian or caregiver is specifically questioned and which are noted by the subject's parent/legal guardian or caregiver in their diary (see Section 9.1.1, Overview).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the subject's parent/legal guardian or caregiver is 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 the 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 Council for Harmonisation [ICH])

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

Note: The sponsor collects AEs, whether serious or non-serious, related to the study procedures or non-investigational (concomitant) Janssen products from ICF signature onwards. All other

non-serious AEs and special reporting situations will be reported from each vaccination through the following 28 days on the Adverse Event eCRF page (refer to Section 12.3.1, All Adverse Events, for time of last AE recording). All other serious AEs will be reported from the first vaccination onwards. Clinically relevant medical events, occurring between ICF signature and time of first vaccination, are collected on the Medical History eCRF page as pre-existing conditions.

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

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The 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.

During the study, any RTI or case of otitis media fulfilling the criterion of an SAE will be reported to the sponsor (and, when appropriate, extended to Regulatory Agencies). Any RTI or

case of otitis media reported as an (S)AE that is found to be positive for RSV by RT-PCR will be excluded from the analyses of (S)AEs. However, the case will remain in the clinical database and will be tabulated separately in the clinical study report.

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 Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions.[1]

For Nimenrix, the expectedness of an AE will be determined by whether or not it is listed in the Summary of Product Characteristics.

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, Attribution Definitions.

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 will be coded for severity using the toxicity grading table in Attachment 1. 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).

The severity of solicited AEs will be graded in the diary by the subject's parent/legal guardian or caregiver based on the severity assessment provided in the diary and then verified by the investigator.

12.2. Special Reporting Situations

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

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

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

12.3. Procedures

12.3.1. All Adverse Events

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

All non-serious AEs and special reporting situations will be reported until 28 days (including relevant visit window, if applicable) after first dose of study vaccine and thereafter, pre-dose on the day of vaccination and 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), which are ongoing on the day of the subsequent vaccination, should be recorded on the eCRF AE page.

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

Solicited AEs will be recorded by each subject's parent/legal guardian or caregiver 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 relevant 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, 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 Independent Ethics Committee/Institutional Review Board (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.

The subject's parent/legal guardian or caregiver will be provided with a "wallet (study) card" and instructed that the subject will carry this card 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

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

SAEs must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event. Information regarding SAEs will be transmitted to the sponsor using the SAE Form and Safety Report Form of the CRF, which must be completed and reviewed 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 transmitted electronically or by facsimile (fax; only when the electronic system is not available).

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 healthcare practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during a 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.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and immunogenicity of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of 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 (see 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 frozen liquid to be thawed prior to use, and will be filled in stoppered and sealed 2 mL single-use glass vials. The dose of 2.5×10^{10} vp will be administered in a volume of 0.25 mL by intramuscular injection.

Refer to the Investigator's Brochure for details of the components of Ad26.RSV.preF and a list of excipients.[1]

Placebo

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

Nimenrix

Nimenrix will be supplied as Nimenrix powder and solvent for solution for injection in pre-filled syringe or ampoule and administered as 0.5 mL solution for intramuscular injection.

Nimenrix is a meningococcal group A, C, W-135 and Y conjugate vaccine for intramuscular injection (Pfizer) indicated to protect adults, adolescents, and children from the age of 6 weeks against invasive meningococcal disease caused by 4 groups of the bacterium *Neisseria meningitidis* (group A, C, W-135, and Y).

Nimenrix will be used in line with the licensed indication, and it will not be formally compared to either the study vaccine or placebo.

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. If 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.

Injections should be administered in the anterolateral aspect of the thigh. Only if required by local health authority guidance, injections may be administered in the deltoid muscle. Alternating injection sites will be used for all study vaccinations.

The study vaccine will be prepared and may also be administered by the unblinded site pharmacist, or other qualified individual, who will have no other study function following dosing.

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[1]
- Summary of Product Characteristics for Nimenrix
- Investigational Product Preparation Instructions/Investigational Product Procedures Manual
- Laboratory Manual (including procedures for collection of nasal samples)
- IWRS Manual

- Electronic Data Capture (eDC) Manual/eCRF completion guidelines and randomization instructions
- Sample ICF
- Subject diaries
- Rulers
- Thermometers
- RTI Symptoms Forms for subject's parents/legal guardian or caregiver
- Contact information page(s)
- Participant Experience Survey

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The parents/legal guardians 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 guardians 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/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. *Note*: In countries where regulation requires that both parents/legal guardians give consent, this will be applicable

The total blood volume drawn from each subject will not exceed the most stringent (European Medicines Agency) guidelines for pediatric subjects in clinical studies: blood loss should not exceed 3% of total blood volume over 4 weeks, and it should not exceed 1% of total blood volume at any single time.[11]

See Section 3.3 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.

GCP 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

Each subject's parent(s)/legal guardian(s) 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's parent/legal guardian 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. *Note*: In countries where regulation requires that both parents/legal guardians give consent, this will be applicable.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subject's parent/legal guardian the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the

study may entail. The subject's parent/legal guardian 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's parent/legal guardian is authorizing such access. It also denotes that the subject's parent/legal guardian 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's parent/legal guardian 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 parent(s)/legal guardian(s) personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject's parent/legal guardian.

All blood samples (venous blood and fingerstick) collected during the study, including samples from subjects who have been screened but not enrolled into the study, will be stored and used for future research if the subject's parent(s)/legal guardian(s) consent (see also Section 16.2.5).

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

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand Ad26.RSV.preF, 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. Included are samples from subjects who were screened but not randomized which may also be used to develop tests/assays related to Ad26.RSV.preF and RSV.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. The subject's parent(s)/legal guardian(s) may withdraw their consent for their samples to be stored for research (see Section 10.2).

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the 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(s)
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, 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(s), 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 sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

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

17.5. Case Report Form Completion

CRFs are prepared and provided by the sponsor for each 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 electronic 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 the 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 (See Section 9.2.2 and Section 12.3.2).

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 vaccination phase will be when the last subject completes the visit 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 through 2 RSV seasons 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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Attachment 1: Toxicity Tables

CLINICAL ADVERSE EVENTS

The grading scale used for clinical adverse events is adapted from the Division of Microbiology and Infectious Diseases (DMID) "Pediatric Toxicity Tables for Children Greater Than 3 Months of Age (2007)". For adverse events not included in the tables below, severity criteria guidelines are provided in Section 12.1.3.

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.	≥50 mm diameter.	Emergency room visit or hospitalization; necrosis or exfoliative dermatitis.
Induration/swelling	≥10 and <25 mm diameter; child does not limit use of his/her arm or leg where the injection was done.	≥25 and <50 mm diameter; child limits use of his/her arm or leg where the injection was done.	≥50 mm diameter; child avoids use of his/her arm or leg where the injection was done.	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.	≥50 mm 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.	≥50 mm 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 40 °C (104.0 °F) 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 intravenous fluids.
Clinical symptom not otherwise specified in this table	Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.	Sufficient discomfort is present to cause interference with normal activity.	Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability.

Attachment 2: Vaccination of Subjects From the Control Group With the Licensed Vaccine Nimenrix

In countries where the commercial vaccine Nimenrix (Meningococcal group A, C, W-135, and Y conjugate vaccine) is licensed, Nimenrix can be administered to all consented pediatric subjects to replace the Day 57 vaccination with placebo (0.9% saline) in the control group, in accordance with the local label and local regulations, and unless contra-indicated. Nimenrix will be administered, only if permitted by the subject's parent/legal guardian and following PI assessment on a case-by-case basis as vaccination with Nimenrix outside this study might be preferred (joint parent/legal guardian and PI decision). In the US, Nimenrix will not be used unless it has been licensed for use or an IND has been submitted.

Nimenrix would be used according to the terms of the marketing authorization and unless contra-indicated, taking into account the specific subject's age, and other childhood vaccines already received. *Note*: Required vaccination with Nimenrix depending on the judgment of the investigator or per national immunization schedule may be considered to be a contraindication for vaccination with Nimenrix in this study.

Attachment 3: Guidance on Study Conduct during the COVID-19 Pandemic

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

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

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

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

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

GUIDANCE SPECIFIC TO THIS PROTOCOL:

- End of RSV season visits (that include blood sampling for immunogenicity) may be delayed until the COVID-19 situation has resolved sufficiently for the subject to safely visit the site, in line with national/regional guidelines.
- Follow-up of RTIs is of importance for the study since monitoring for severe RSV-LRTI is used as a preliminary indicator of ERD. Therefore, although a nasal sample might not be taken, it is important for any RTI to be followed to be aware of a severe RTI occurring during the study.
- During the COVID-19 pandemic, in cases where a nasal swab is unable to be collected by site staff, and where local regulations allow, and with sponsor awareness, a trained parent/caregiver may obtain, store and transport the sample using instructions provided by the sponsor. Documentation of training completion and distribution of instructions should be noted in the subject's record. Whenever possible, collection by site staff is preferred.
- During the COVID-19 pandemic and at the impacted sites, clinical Site GCP audits with direct impact/engagement from the clinical investigator team will not be conducted, to comply with national, local and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study related documents may take place with limited impact/engagement, if possible.
- If on-site monitoring visits are not possible, the site monitor may contact the investigator to arrange monitoring visits and activities remotely. Additional on-site monitoring visits may be needed in the future to catch up on source data verification.
- Consent for remote visits (telephone or video consultation) of subjects will be performed as applicable for the measures taken and according to local guidance for informed consent applicable during the COVID-19 pandemic. Documentation of this consent should be noted in the subject's record.

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Vaccines & Prevention B.V.

Signature: 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.

Signature

User	Date	Reason
PPD	25-May-2020 19:19:09 (GMT)	Document Approval