**Janssen Vaccines & Prevention B.V.***

**Clinical Protocol**

# A Randomized, Double-blind Phase 3 Study to Assess the Immunogenicity and Safety of an Ad26.RSV.PreF-based Regimen at the End of Shelf-life in Adults Aged 60 to 75 Years

**Protocol VAC18193RSV3003; Phase 3**
**Amendment 2**

**VAC18193 (Ad26.RSV.preF [JNJ-64400141]/RSV preF Protein [JNJ-64213175])**

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

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

**EudraCT NUMBER:** 2021-002388-23

| | |
|---|---|
| **Status:** | Approved |
| **Date:** | 26 November 2021 |
| **Prepared by:** | Janssen Vaccines & Prevention B.V. |
| **EDMS number:** | EDMS-RIM-330911, 3.0 |

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

## PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 2 | This document |
| Amendment 1 | 23 September 2021 |
| Original Protocol | 17 May 2021 |

**Amendment 2 (This document)**

**Overall Rationale for the Amendment:** In view of the slow rate of enrollment in the current study, the following changes were made to the inclusion and exclusion criteria to facilitate enrollment: the upper age limit for inclusion was adapted from less than 65 years to 75 years inclusive; a prior vaccination with a viral-vectored SARS-CoV-2 vaccine is allowed if administered at least 6 months prior to randomization; and it was clarified that co-participation in the observational phase of interventional studies can be allowed upon sponsor approval.

Emerging data from other ongoing clinical studies with the Ad26/protein preF RSV vaccine in participants in the age range of 60 to 75 years show that there is no substantial impact of age on vaccine-induced humoral immune responses, primary analysis pre-F ELISA antibody titers, and vaccine safety between older adults of 60 to 75 years of age. Based on these data, the sponsor considers an upper age limit of 75 years (inclusive) acceptable for this study.

Clinical studies with Janssen's Ad26-vectored SARS-CoV-2 vaccine have not shown a clear impact of baseline pre-existing Ad26 neutralizing antibodies on vaccine-induced responses. Based on these data, the sponsor considers a prior vaccination with a viral-vectored SARS-CoV-2 vaccine acceptable if administered at least 6 months prior to randomization. A minimal window of 6 months has been chosen since humoral immune response data evaluating a potential interference of the anti-vector responses with the vaccine-induced responses in consecutive dosing with viral-vectored vaccines with different inserts are not available to date. During further development of viral-vectored vaccines, data on potential interference will become available; at that point, the time window may be adjusted for future immunogenicity trials. The standard dosing window for viral-vectored SARS-CoV-2 vaccines in other Ad26.RSV.preF-based vaccine efficacy studies is 28 days and does not foresee an impact on safety.

Participants who participate in the observational phase of an interventional study at screening may also be eligible for the current study since participation in the observational phase without product administration will not adversely impact safety of the participants or have an impact on the vaccine-induced immune response.

Furthermore, additional language referring to laboratory diagnostic tests for the follow-up and assessment of potential adverse events of special interest (AESIs) was added. Clarifications were made with regards to some exclusion criteria, the recording of medical history, and the solicited and unsolicited AE assessments to be performed during phone call visits. Additionally, an

inconsistency concerning the timing of the primary analysis was corrected and a few minor updates were made in alignment with the latest Janssen protocol template.

The changes made to the clinical protocol VAC18193RSV3003 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.7 Appendix 7: Protocol Amendment History.

| **Section Number and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Title page<br>1.1 Synopsis<br>4.1 Overall Design<br>5.1 Inclusion Criteria | Inclusion Criterion 3 was amended to expand the eligible age range from 60 to less than 65 years, to 60 to 75 years inclusive. | To facilitate enrollment |
| 5.2 Exclusion Criteria | Exclusion Criterion 10 was amended to allow the use of viral-vectored SARS-CoV-2 vaccines if administered at least 6 months prior to randomization. | To facilitate enrollment |
| 5.2 Exclusion Criteria | Footnote for Exclusion Criterion 13 was updated to allow participants who participate in the observational phase of interventional studies to be enrolled in the study, if approved by the sponsor or its delegate. | To facilitate enrollment |
| 5.2 Exclusion Criteria | A textual change was made to Exclusion Criterion 1 to clarify that participants with a history of malignancy within 5 years before screening, which is considered to have minimal risk of recurrence per investigator's judgement, can be enrolled. | Clarification |
| 5.2 Exclusion Criteria | Exclusion Criterion 7 was amended to restrict the exclusion of participants on treatment with immunoglobulins to those immunoglobulins expected to impact the vaccine-induced immune response. | Clarification |
| 1.3 Schedule of Activities | It was clarified that risk factors for blood clotting events and thrombocytopenia are to be collected and documented as part of the medical history at screening. | Clarification |
| 1.3 Schedule of Activities | It was clarified that the severity of solicited and unsolicited AEs and the occurrence of special reporting situations are to be assessed also during the phone call visits at 7 and 28 days post-vaccination, following the recording period specified for these events. | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3 Schedule of Activities<br>8.3.6.1 Thrombosis with Thrombocytopenia Syndrome | Additional language referring to laboratory diagnostic tests for the assessment of potential AESIs was added. | To facilitate and simplify the local site management of follow-up testings in the event of potential AESIs. |
| 9.4.1 General Considerations | It was clarified that the primary analysis will be performed when all participants have completed the visit 28 days post-vaccination or discontinued earlier. | Correction of an inconsistency |
| 4.4 End of Study Definition<br>8.3.1 Time Period and Frequency for Collecting AE, SAE, and AESI Information<br>8.3.3 Follow-up of AEs, SAEs and AESIs<br>10.2.4 Special Reporting Situations<br>10.2.6 PQC Handling<br>10.3.14 Study and Site Start and Closure<br>10.5 Appendix 5: Study Conduct During a Natural Disaster | A few minor updates were made in alignment with the latest Janssen protocol template | To align with the most recent Janssen protocol template. |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. | Minor errors were noted |

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## LIST OF IN-TEXT TABLES AND FIGURES

### TABLES



### FIGURES

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**A Randomized, Double-blind Phase 3 Study to Assess the Immunogenicity and Safety of an Ad26.RSV.PreF-based Regimen at the End of Shelf-life in Adults Aged 60 to 75 Years**

The respiratory syncytial virus (RSV) vaccine that will be investigated in this study, the Ad26/protein preF RSV vaccine (VAC18193), is a combination of 2 vaccine components, administered as a single intramuscular (IM) injection:

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

The aim of this study is to demonstrate the non-inferiority in terms of humoral immune responses of Ad26/protein preF RSV vaccine lots representing key stability indicating critical quality attributes (eg, potency of Ad26.RSV.preF, purity of RSV preF protein) halfway ("intermediate shelf-life") and at the end of the intended shelf-life ("end of shelf-life") in comparison to a non-aged Ad26/protein preF RSV vaccine lot. Demonstrating non-inferior humoral immune responses of material at "intermediate shelf-life" and at "end of shelf-life" to near release material will allow to infer efficacy throughout the vaccine shelf-life.

**OBJECTIVES AND ENDPOINTS**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To demonstrate non-inferiority in terms of humoral immune responses induced by Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes around the intermediate shelf-life to Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes near release. | • pre-F enzyme-linked immunosorbent assay (ELISA) antibody titers at 14 days after vaccination. |
| • If non-inferiority is demonstrated for the Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes around the intermediate shelf-life:<br>To demonstrate non-inferiority in terms of humoral immune responses induced by Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes near the presumed end of shelf-life to Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes near release. | • pre-F ELISA antibody titers at 14 days after vaccination. |
| **Secondary** | |
| • To assess neutralizing antibody responses following vaccination | • Neutralizing antibody titers against RSV A2 strain at 14 days after vaccination |

| Objectives | Endpoints |
|---|---|
| • To assess the safety and reactogenicity of vaccination with different lots representing critical quality attributes around release, around the intermediate shelf-life, and near the presumed end of shelf-life. | • Solicited local (injection site) and systemic adverse events (AEs) for 7 days after vaccination<br>• Unsolicited AEs for 28 days after vaccination<br>• Serious adverse events (SAEs) and adverse events of special interest (AESIs) until 6 months after vaccination |
| **Exploratory** | |
| • To assess the vaccine-induced immune responses at 6 months post-vaccination | • pre-F ELISA antibody titers at 6 months after vaccination<br>• Neutralizing antibody titers against RSV A2 strain at 6 months after vaccination |

**HYPOTHESES**

To demonstrate the primary objectives, the following hypotheses will be tested sequentially:

**Null Hypothesis 1:**

Ad26/protein preF RSV vaccine lots representing the critical quality attributes around the intermediate shelf-life induces inferior geometric mean titers (GMTs) of the pre-F ELISA titers on Day 15, compared to Ad26/protein preF RSV vaccine lots representing the critical quality attributes near release.

**Alternative Hypothesis 1:**

Ad26/protein preF RSV vaccine lots representing the critical quality attributes around the intermediate shelf-life induces non-inferior GMTs of the pre-F ELISA titers on Day 15, compared to Ad26/protein preF RSV vaccine lots representing the critical quality attributes near release.

Non-inferiority will be shown if the lower limit of the 2-sided 95% confidence interval (CI) around the estimated geometric mean titer ratio (GMR) of the intermediate shelf-life lots versus the release lots lies entirely above 0.67.

If non-inferiority is shown for the intermediate shelf-life lots then the following hypotheses will be tested:

**Null Hypothesis 2:**

Ad26/protein preF RSV vaccine lots representing the critical quality attributes near the presumed end of shelf-life induces inferior GMTs of the pre-F ELISA titers on Day 15, compared to Ad26/protein preF RSV vaccine lots representing the critical quality attributes near release.

**Alternative Hypothesis 2:**

Ad26/protein preF RSV vaccine lots representing the critical quality attributes near the presumed end of shelf-life induces non-inferior GMTs of the pre-F ELISA titers on Day 15, compared to Ad26/protein preF RSV vaccine lots representing the critical quality attributes near release.

Non-inferiority will be shown if the lower limit of the 2-sided 95% CI around the estimated GMR (end of shelf-life lots versus release lots) lies entirely above 0.67.

## OVERALL DESIGN

This is a randomized, double-blind, multicenter, interventional Phase 3 study in adult participants aged ≥60 to ≤75 years. A target of 750 participants will be randomized in parallel in a 1:1:1 ratio to 1 of 3 groups (see Table 1). Study vaccine will be given by the IM route.

**Table 1: Study Design**

| Group | N | Vaccination on Day 1 |
|---|---|---|
| 1 | 250 | Ad26.RSV.preF $1.0\times10^{11}$ vp + RSV preF protein 150 µg (representing critical quality attributes around release) |
| 2 | 250 | Ad26.RSV.preF $2.5\times10^{10}$ vp + RSV preF protein 150 µg (representing critical quality attributes around the intermediate shelf-life) |
| 3 | 250 | Ad26.RSV.preF $1.0\times10^{10}$ vp + RSV preF protein 150 µg (representing critical quality attributes near the end of shelf-life) |

N = number of participants; vp = viral particles

After vaccination, participants will remain under observation at the study site for at least 15 minutes for presence of any acute reactions and solicited events. Any unsolicited AEs, solicited local (injection site) or systemic AEs, and vital signs (systolic and diastolic blood pressure [sitting], heart rate, respiratory rate, and body temperature) will be documented by study-site personnel following this observation period. In addition, participants will record solicited signs and symptoms in a participant diary beginning in the evening of the day of vaccination and on a daily basis for 7 days post-vaccination.

Blood will be collected from all participants pre-vaccination and at 14 days and 6 months post-vaccination to assess humoral immune responses.

Safety issues that might arise from this study may be escalated to an independent Data Monitoring Committee (DMC), as needed.

The end of the study is defined as the last participant's last visit.

## NUMBER OF PARTICIPANTS

A target of 750 participants will be randomized in parallel in a 1:1:1 ratio to 1 of 3 groups.

## VACCINATION GROUPS AND DURATION

The study comprises a screening period (Day -28 to Day 1), vaccination for each participant on Day 1, and a 6-month safety and immunogenicity follow-up period.

### Study Vaccine Administration

The investigational medicinal products (IMPs) to be administered to participants in this study are Ad26.RSV.preF and RSV preF protein.

The Ad26/protein preF RSV vaccine to be used in this study is composed of Ad26.RSV.preF and RSV preF protein, to be administered as a single injection (1.0 mL) in the deltoid muscle:

- Ad26.RSV.preF (JNJ-64400141) will be used at a dose level of $1.0\times10^{11}$ viral particles (vp) in Group 1, $2.5\times10^{10}$ vp in Group 2, and $1.0\times10^{10}$ vp in Group 3.
- RSV preF protein (JNJ-64213175) will be used at a dose level of 150 µg in all groups (Groups 1 to 3). Three different lots will be used (a release lot; an aged lot representing the presumed end of shelf-life; and an aged lot representing the intermediate shelf-life).

## IMMUNOGENICITY EVALUATIONS

Venous blood samples of approximately 10 mL will be collected for the determination of humoral immune responses. Humoral immunogenicity evaluations are summarized in the table below.

| Assay | Purpose |
|---|---|
| ***Primary and exploratory endpoints*** | |
| F-protein antibodies (RSV-A pre-F ELISA) | Analysis of antibodies binding to RSV-A F-protein in pre-fusion form |
| ***Secondary and exploratory endpoints*** | |
| RSV A neutralization assay (VNA A2) | Analysis of neutralizing antibodies against the RSV A2 strain |

ELISA = enzyme-linked immunosorbent assay; VNA = virus neutralization assay

## SAFETY EVALUATIONS

Safety assessments will include the monitoring of AEs and vital signs.

AEs and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated informed consent form (ICF) is obtained until the end of the study/early withdrawal. Solicited AEs, collected through a participant diary will be recorded from the time of vaccination until 7 days post-vaccination. All other unsolicited AEs and special reporting situations, whether serious or non-serious, will be reported from the time of vaccination until 28 days post-vaccination. All SAEs, AESIs, and AEs leading to discontinuation from the study (regardless of the causal relationship) are to be reported from the moment of vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up. All AEs will be followed until resolution or until clinically stable.

## STATISTICAL METHODS

### Sample Size Determination

Sample size calculations are performed under the following assumptions:

- a 10% decrease in GMT of the groups with aged lots (Group 2 and Group 3) versus the group with the non-aged lot (Group 1) (ie, assuming a true GMR of Day 15 pre-F ELISA titers equal to 0.9)
- a standard deviation of 1.3 at the $\log_2$ scale for pre-F ELISA on Day 15[a]
- a non-inferiority margin of 0.67 (2/3)
- a 2-sided $\alpha$ of 5%
- hierarchical testing (ie, first Group 2 versus Group 1; if non-inferiority is demonstrated, then Group 3 versus Group 1)

A total of 236 evaluable participants per group are needed to have 95% power to demonstrate non-inferiority for each comparison separately. With this sample size, the overall power to demonstrate non-inferiority of Group 3 versus Group 1 as the second comparison in the hierarchy is at least 90%.

To account for exclusions from the Per-protocol Immunogenicity (PPI) Set (see below for the definitions of analysis sets), dropouts, and missing samples, approximately 250 participants per group should be enrolled.

[a] Based on the standard deviation of pre-F ELISA at 14 days after vaccine administration observed in Group 14 of study VAC18193RSV1004.

**Populations for Analysis Sets**

The Full Analysis (FA) Set will include all participants who received study vaccine, regardless of the occurrence of protocol deviations. All safety and participant information analyses will be based on the FA Set.

The PPI Set will include all randomized participants who received study vaccine and for whom immunogenicity data are available. Samples taken after a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPI analysis.

The list of major protocol deviations that would lead to elimination from the immunogenicity analysis will be specified in the statistical analysis plan (SAP) or major protocol violation criteria document, which will be finalized before database lock and unblinding.

The primary analysis set for analyses related to RSV immunogenicity is the PPI Set. As a sensitivity analysis, key tables may also be based on the FA Set.

**Immunogenicity Analyses**

The primary immunogenicity objective will be assessed by calculating the 2-sided 95% CIs for the difference in log-transformed Day 15 pre-F ELISA titers for each of the comparisons (ie, Group 2 versus Group 1, and Group 3 versus Group 1).

The CIs will be calculated via an analysis of variance (ANOVA) including all groups (ie, Groups 1 to 3) with the log-transformed Day 15 pre-F ELISA titers as dependent variable and group as independent variable. The CIs around the difference will be back-transformed (by exponentiation) to CIs around a GMR ($GMT_{Group\ x}/GMT_{Group\ 1}$ where x is 2 or 3) and compared to the non-inferiority margin of 0.67 (2/3).

Non-inferiority of Group 2 versus Group 1 is demonstrated if the 2-sided 95% CI for the GMR ($GMT_{Group\ 2}/GMT_{Group\ 1}$) of the Day 15 pre-F ELISA titers lies entirely above 0.67. If non-inferiority of Group 2 versus Group 1 is not demonstrated, the study fails. If non-inferiority of Group 2 versus Group 1 is demonstrated, then non-inferiority of Group 3 versus Group 1 can be tested: similarly, non-inferiority of Group 3 versus Group 1 is demonstrated if the 2-sided 95% CI for the GMR ($GMT_{Group\ 3}/GMT_{Group\ 1}$) of the Day 15 pre-F ELISA titers lies entirely above 0.67.

As a sensitivity analysis to assess the impact of baseline titers, the primary endpoint will also be evaluated adjusting for the respective baseline titers. For immunogenicity, baseline is considered as the last assessment pre-vaccination. In a second sensitivity analysis, different variances between the study groups will be allowed. Therefore, the CIs will be calculated via Welch's ANOVA.

No formal statistical testing of the secondary and exploratory immunogenicity endpoints is planned.

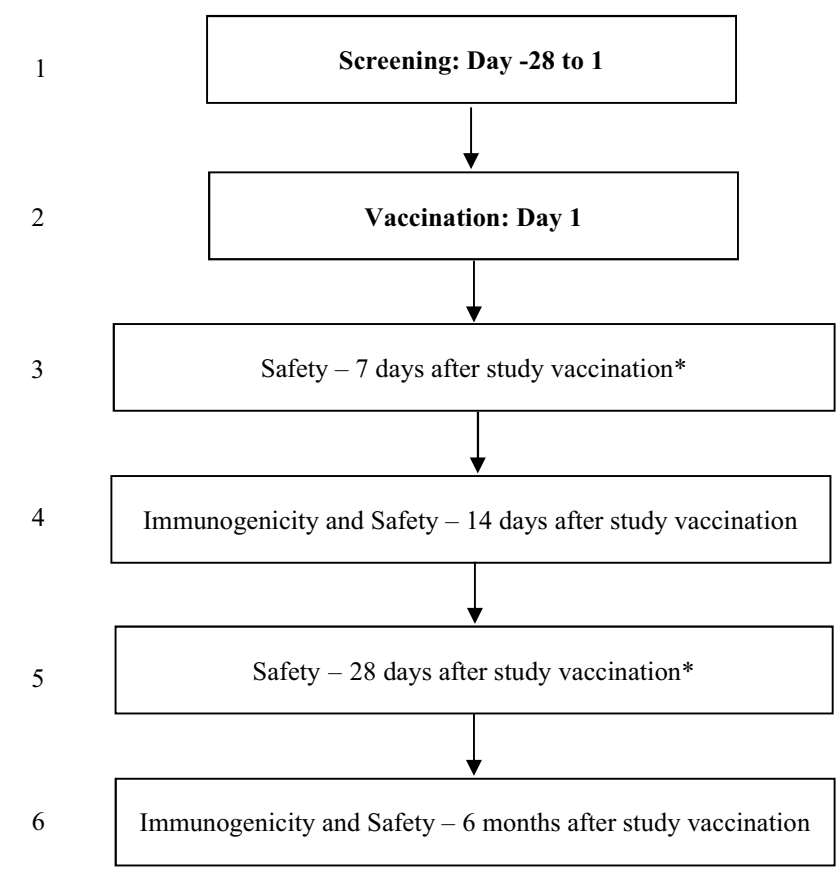
Immunogenicity data will be summarized descriptively by group. Descriptive statistics of the actual values (eg, geometric mean and 95% CI) will be calculated for continuous parameters at all timepoints. Geometric mean fold rises from baseline and corresponding 95% CIs will also be calculated. Baseline is considered the last available assessment prior to vaccination. Graphical representations will be prepared, as applicable. GMRs ($GMT_{Group\ 2}/GMT_{Group\ 1}$ and $GMT_{Group\ 3}/GMT_{Group\ 1}$) will also be calculated for VNA A2 in a similar manner as for pre-F ELISA. Frequency tabulations will be calculated for discrete (qualitative) parameters, as applicable.

**Safety Analyses**

No formal statistical testing of safety data is planned. All safety data will be analyzed descriptively by group. All safety analyses will be based on the FA Set.

## 1.2. Schema

**Figure 1: Schematic Overview of the Study**




* By telephone

## 1.3. Schedule of Activities

| Clinic Visit # | 1[a] | 2 | 3[b]☎ | 4 | 5[b]☎ | 6 | Exit[b,c]☎ |
|---|---|---|---|---|---|---|---|
| Visit Timing | | Vac | Vac + 7 d | Vac + 14 d | Vac + 28 d | Vac + 6 mo | |
| Visit Day | -28 to 1 | 1 | 8 | 15 | 29 | 183 | |
| Visit Window | | | ±2 d | -3 d / +7 d | ±7 d | ±14 d | |
| Visit Type | SCREENING | VACCINATION | Safety | Immunogenicity and Safety | Safety | Immunogenicity and Safety | Early exit |
| Written informed consent[d] | ● | | | | | | |
| Inclusion/exclusion criteria | ● | ❶ | | | | | |
| Demographics | ● | | | | | | |
| Medical history[e]/prestudy therapies[f] | ● | | | | | | |
| Vital signs[g] including body temperature | ● | ❷ | | | | | |
| Height and weight | ● | | | | | | |
| Randomization | | ❶ | | | | | |
| Pre-vaccination symptoms[h] | | ❶ | | | | | |
| Humoral immunity, mL | | ❶[o] 10 | | ●[o] 10 | | ●[o] 10 | |
| Vaccination | | ● | | | | | |
| 15-minute post-vaccination observation[i] | | ● | | | | | |
| Solicited AE recording[p] | | ------❸------ | | | | | ❹ |
| Unsolicited AE recording[q] | | ---------*continuous*---------- | | | | | ❺ |
| SAE recording | | ----------*continuous*---------- | | | | | ● |
| AESI recording[j] | | ----------*continuous*---------- | | | | | ● |
| Concomitant therapies[k] | | ----------*continuous*---------- | | | | | ● |
| History of SARS-CoV-2 vaccination[l] | | ----------*continuous*---------- | | | | | |
| Participant diary distribution[m,n] | | ● | | | | | |
| Participant diary (collection and) review by site staff[n] | | | | ● | | | |
| Approximate daily blood draw, mL | | 10 | – | 10 | – | 10 | – |
| Approximate cumulative blood draw, mL | | 10 | 10 | 20 | 20 | **30** | – |

❶ pre-vaccination; ❷ pre- and post-vaccination; ❸ solicited local (injection site) and solicited systemic AEs will be collected via participant diaries from vaccination until 7 days post-vaccination; ❹ if within 7 days of vaccination; ❺ if the early exit visit is within 28 days of vaccination.

Note: At any clinic visit, an abbreviated, symptom-directed physical examination may be performed if deemed necessary by the investigator based on any clinically relevant issues, clinically relevant symptoms, and medical history.

**Footnotes:**

a. Screening will be performed within 28 days prior to the study vaccination or on the day of vaccination. If screening is performed on the day of vaccination (recommended), Visit 1 and Visit 2 will coincide on Day 1. In that case, assessments should only be done once. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.
b. Safety visits and early exit visit will be by telephone.
c. An early exit visit will be conducted as soon as possible for those participants who are unable to continue participation in the study and withdraw from the study before Day 183, but who do not withdraw consent. Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent).
d. Signing of the ICF should be done before any study-related activity.
e. Medical history of all participants will be recorded in the eCRF, including whether each condition places the participant at increased risk for severe RSV disease. The conditions placing a participant at increased risk of severe RSV disease include: congestive heart failure, coronary artery disease (such as angina pectoris, ischemic cardiomyopathy, history of myocardial infarct, or history of coronary artery bypass graft or coronary artery stent), and chronic lung disease (such as asthma and chronic obstructive pulmonary disease.
   As part of the medical history, the investigator must also collect and document risk factors for blood clotting events and thrombocytopenia at screening. As done for any other medical history events, the information must be entered on the relevant eCRF pages such as Medical History page or Concomitant Medication page.
f. Prestudy therapies administered up to 30 days pre-vaccination must be recorded on Day 1.
g. Sitting systolic and diastolic blood pressure, heart rate, and respiratory rate after at least 5 minutes rest on Day 1. At non-vaccination visits, vital signs will be measured if deemed necessary by the investigator.
h. The investigator must check for clinically significant acute illness at the time of vaccination or body temperature ≥38.0°C (≥100.4°F) within 24 hours prior to the planned time of vaccination. In such cases, the participant may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator.
i. After vaccination, participants will remain under observation at the study site for at least 15 minutes for presence of any acute reactions and solicited events. Any unsolicited AEs, solicited local (injection site) or systemic AEs, and vital signs (systolic and diastolic blood pressure [sitting], heart rate, respiratory rate, and body temperature) will be documented by study-site personnel following this observation period.
j. AESIs, including potential AESIs, are to be reported to the sponsor from the moment of vaccination until 6 months after the vaccination. See Section 8.3.6.
k. Concomitant therapies will be collected from the time of study vaccination through 28 days post-vaccination when associated with an AE, and from ICF signature until 6 months post-vaccination when associated with an SAE or AESI.
l. Any history of SARS-CoV-2 vaccination (name/manufacturer of the vaccine and date of administration, whenever possible) prior to and during the study will be collected in the eCRF.
m. Rulers and thermometers will be distributed at Visit 2.
n. Participants will be contacted by telephone 2 to 4 days post-vaccination to remind them to fill in the participant diaries and to check that they are entering information correctly.
o. Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request. Please refer to Table 4 for a non-exhaustive list of tests that may be requested to be performed on these samples in case of potential AESI reporting.
p. Includes the assessment of the severity of solicited AEs during the Visit 3 phone call.

q. Includes the assessment of the severity of unsolicited AEs and the occurrence of special reporting situations during all visits up to 28 days post-vaccination, including the Visit 3 and Visit 5 phone calls.

AE = adverse event; AESI = adverse event of special interest; d = days; ICF = informed consent form; mo = months; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus-2; vac = vaccination

# 2. INTRODUCTION

The respiratory syncytial virus (RSV) vaccine that will be evaluated in this study, the Ad26/protein preF RSV vaccine (VAC18193), is a combination of 2 vaccine components, administered as single intramuscular (IM) injection:

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

For the most comprehensive nonclinical and clinical information regarding the Ad26/protein preF RSV vaccine, refer to the latest version of the Investigator's Brochure (IB) for Ad26/protein preF RSV vaccine (IB Ad26/protein preF RSV vaccine 2021).

The term "study vaccine" used throughout the protocol refers to the Ad26/protein preF RSV vaccine as defined in Section 6.1.

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.

## 2.1. Study Rationale

The aim of this study is to demonstrate the non-inferiority in terms of humoral immune responses of Ad26/protein preF RSV vaccine lots representing key stability indicating critical quality attributes (eg, potency of Ad26.RSV.preF, purity of RSV preF protein) halfway ("intermediate shelf-life") and at the end of the intended shelf-life ("end of shelf-life") in comparison to a non-aged Ad26/protein preF RSV vaccine lot. Demonstrating non-inferior humoral immune responses of material at "intermediate shelf-life" and at "end of shelf-life" to near release material will allow to infer efficacy throughout the vaccine shelf-life.

## 2.2. Background

RSV is an important cause of serious respiratory infections in adults aged 60 years and older, immunocompromised individuals, and those with underlying chronic cardiopulmonary conditions (Falsey 2005). Exact numbers on the burden of RSV disease in adults aged 60 years and older are limited. In long-term care facilities, RSV is estimated to infect 5% to 10% of the residents per year with significant rates of pneumonia (10%-20%) and death (2%-5%) as a consequence (Falsey 2000). In the United States (US), approximately 177,000 hospital admissions and approximately 10,000 to 14,000 deaths per year are due to severe RSV infections in adults aged 65 years and older (Falsey 2005). These data support the importance of developing a safe and effective vaccine for certain adult populations, such as older adults. Currently, no vaccines or specific treatments are available for RSV.

Several studies have indicated that high levels of serum neutralizing antibodies are associated with a reduced risk of severe RSV infection in older adults (Falsey 1998; Walsh 2004). There is some indication that decreased protection against RSV in older adults could be attributed to an age-related decline in RSV-specific T-cell function (de Bree 2005; Looney 2002). The Ad26.RSV.preF vaccine component evaluated in this study is based on the AdVac® platform, which has been shown to promote strong humoral and cellular responses (Barouch 2013; Barouch 2018; Data on file; Milligan 2016).

### Nonclinical Studies

For the most comprehensive nonclinical information regarding the Ad26/protein preF RSV vaccine, refer to the latest version of the IB for Ad26/protein preF RSV vaccine (IB Ad26/protein preF RSV vaccine 2021).

### Clinical Studies

For the most comprehensive clinical information regarding the Ad26/protein preF RSV vaccine, refer to the latest version of the IB for Ad26/protein preF RSV vaccine (IB Ad26/protein preF RSV vaccine 2021).

### Clinical Safety Experience with Ad26-based Vaccines

The Janssen Adenoviral Vaccine (AdVac) Safety Database Report (version 6.0; AdVac Safety Database 2021) contains pooled safety data of the following Ad26-based vaccine candidates: Ad26.ZEBOV (Ebola virus), Ad26.ENVA.01, Ad26.Mos.HIV, and Ad26.Mos4.HIV (HIV), Ad26.CS.01 (malaria), Ad26.RSV.FA2 and Ad26.RSV.preF (RSV), Ad26.Filo (filovirus), Ad26.ZIKV.001 (Zika virus), and Ad26.HPV16 and Ad26.HPV18 (HPV). Data from all studies for which the database had been locked for either the interim, primary, or final analysis for which the sponsor has been fully unblinded are included in the AdVac Safety Database Report, ie, 32 completed and ongoing unblinded clinical studies (cutoff date of 31 December 2020). In total, 8,826 participants were vaccinated with an Ad26-based vaccine. Of these 8,826 participants, 8,152 participants (in all 32 studies) were adults, and 674 participants (in 3 studies) were children.

The report also provides a high-level overview of all clinical study SAEs and vaccine exposure during pregnancy cases reported in the Janssen Global Safety Database that also includes all ongoing (open-label and blinded) studies, non-Janssen sponsored studies, and mass vaccination campaigns which are not integrated in the AdVac Safety Database Report. This data set includes also SAEs and pregnancy cases of Ad26.COV2.S (Janssen COVID-19 vaccine) vaccine clinical studies. About 200,000 participants were dosed with an Ad26-based vaccine at the cutoff date of 31 December 2020.

No significant safety issues have been identified from the data available in the current adenoviral vaccine safety database. Overall, the Ad26-based vaccines were well tolerated, without significant safety issues identified.

**Thrombosis With Thrombocytopenia Syndrome**

Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), in some cases accompanied by internal bleeding, has been observed very rarely following vaccination with the Janssen COVID-19 (Ad26.COV2.S) vaccine. Reports include severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis and arterial thrombosis, in combination with thrombocytopenia. The associated symptoms began approximately 1 to 2 weeks after vaccination, mostly in women under 60 years of age. Thrombosis in combination with thrombocytopenia can be fatal. The exact pathophysiology of TTS is unclear. This event has not been observed to date with any other Janssen Ad26-based vaccines. Participants should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision, skin bruising or petechiae beyond the site of vaccination.

## 2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of the Ad26/protein preF RSV vaccine may be found in the IB for Ad26/protein preF RSV vaccine (IB Ad26/protein preF RSV vaccine 2021).

### 2.3.1. Risks Related to Study Participation

The following potential risks for the Ad26/protein preF RSV vaccine will be monitored during the study:

**Risks Related to Ad26/protein preF RSV Vaccine**

The Ad26/protein preF RSV vaccine is currently being studied in 4 ongoing studies in more than 6,500 participants aged 60 years and older, including participants with comorbidities, to assess safety and immunogenicity and to investigate whether the vaccine prevents RSV disease. In these studies, the most commonly reported solicited local adverse events (AEs) were injection site pain/tenderness and swelling (mild to moderate). The most frequently reported solicited systemic AEs were fatigue, muscle pain, headache, chills, joint pain, and nausea, which were mild to moderate in severity. These solicited AEs were short-lived and resolved within a few days. Overall, available results from these studies show the vaccine to be well-tolerated with no safety concerns.

**General Risks Related to Vaccination**

In general, IM injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration, swelling, arm discomfort, or bruising of the skin. Participants may exhibit general signs and symptoms associated with IM injection of a vaccine, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue. These side effects will be monitored, but are generally short-term and do not require treatment.

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

participants should be observed until the symptoms resolve. Fear of injection might lead to fainting and fast breathing.

Participants may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, urticaria, or even anaphylaxis. Severe reactions are rare. Participants with a known or suspected allergy, or with a history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine), will be excluded from the study.

After vaccination, participants will remain at the study site for at least 15 minutes and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions.

**Pregnancy and Birth Control**

The effect of the Ad26/protein preF RSV vaccine on a fetus or nursing baby is unknown. Participants may therefore only participate if they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and not intending to conceive by any methods. Participants who are surgically sterile are also eligible for the study. Follow-up information regarding the outcome of the pregnancy will be required.

Because the effect on sperm is unknown, participants must inform the study-site personnel if their partner becomes pregnant during the study. Follow-up information regarding the outcome of the pregnancy will be requested upon the consent provided by the partner.

**Participants with Immunosuppression/Reduced Immune Response**

Participants with abnormal function of the immune system will be excluded from the study. Limited evidence indicates that inactivated vaccines (or nonreplicating 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.

**Risks from Blood Draws**

Blood draws may cause pain, tenderness, bruising, bleeding, dizziness, vasovagal response, syncope, and rarely, infection at the site where the blood is taken. Participants with contraindications to IM injections and blood draws (eg, bleeding disorders) will be excluded.

**Concomitant Vaccination**

Concomitant vaccination might have an influence on both the safety profile and immunogenicity of the Ad26/protein preF RSV vaccine. Likewise, the Ad26/protein preF RSV vaccine might have an influence on both the safety profile and immunogenicity of any concomitant vaccination. As a result, licensed live attenuated vaccines should be given at least 28 days before or after vaccination. Other licensed (not live) vaccines (eg, influenza, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before or after vaccination to avoid potential confusion of adverse

reactions and potential immune interference. If a vaccine is indicated in a postexposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

For Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) vaccines licensed or available under Emergency Use Authorization: live attenuated vaccines should be given at least 28 days before or after vaccination; non-live vaccines should be given at least 14 days before or after vaccination. A viral-vectored SARS-CoV-2 vaccine is not to be given at any time prior to randomization or during the study period until 28 days after study vaccination.

**Unknown Risks**

There may be other risks that are not known. If any significant new risks are identified, the investigators and participants will be informed.

### 2.3.2. Benefits of Study Participation

Participants may benefit from clinical testing.

The clinical benefits of the Ad26/protein preF RSV vaccine have yet to be confirmed.

The Ad26/protein preF RSV vaccine is under development for prophylaxis of RSV disease and vaccine efficacy is being evaluated in ongoing studies. Results from the primary analysis of study VAC18193RSV2001 with approximately 5,800 participants showed the potential for the vaccine to prevent lower respiratory tract disease caused by RSV in participants 65 years and older.

### 2.3.3. Benefit-Risk Assessment of Study Participation

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:

- The dose levels of Ad26.RSV.preF and RSV preF protein used in the current study were determined from the primary analysis of Cohort 2 in study VAC18193RSV1004 and are currently under further evaluation in studies VAC18193RSV1004 and VAC18193RSV2001. Lower dose levels of Ad26.RSV.preF were evaluated in studies VAC18193RSV1004 and VAC18193RSV2005. The available safety data from all studies show the vaccine to be well-tolerated with no safety concerns. For details on the justification for dose levels selected for this study, see Section 4.3. In the primary analysis of study VAC18193RSV2001, vaccine efficacy was demonstrated for these dose levels in adults aged 65 years and above, for the prevention of LRTD caused by RSV.
- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:

  In general, safety evaluations will be performed at scheduled visits during the study, as indicated in the Schedule of Activities.

After vaccination, participants will remain at the study site for at least 15 minutes and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use a participant diary to document solicited signs and symptoms. Details are provided in Section 8.2.

The investigator or the designee will document unsolicited AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs) as indicated in Sections 8.2 and 8.3 and Appendix 2.

Any clinically significant abnormalities will be followed by the investigator until resolution or until clinically stable.

After vaccination, participants will enter a 6-month safety follow-up period for collection of SAEs and AESIs.

All AEs, SAEs, and AESIs will be followed by the investigator until clinical resolution or until a clinically stable condition is reached, or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts. An early exit visit will be conducted for those participants who are unable to continue participation in the study and withdraw from the study before Day 183, but who do not withdraw consent. Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent) (Section 7.2).

- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:

  Safety issues that might arise from this study may be escalated to an independent Data Monitoring Committee (DMC), as needed.

  Study vaccinations will be discontinued in participants for the reasons described in Section 7.

  Temporary contraindications to study vaccination are described in Section 5.5.

## 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To demonstrate non-inferiority in terms of humoral immune responses induced by Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes around the intermediate shelf-life to Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes near release. | • pre-F enzyme-linked immunosorbent assay (ELISA) antibody titers at 14 days after vaccination. |
| • If non-inferiority is demonstrated for the Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes around the intermediate shelf-life: | • pre-F ELISA antibody titers at 14 days after vaccination. |

| Objectives | Endpoints |
|---|---|
| To demonstrate non-inferiority in terms of humoral immune responses induced by Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes near the presumed end of shelf-life to Ad26.RSV.preF-based study vaccine lots representing the critical quality attributes near release. | |
| **Secondary** | |
| • To assess neutralizing antibody responses following vaccination | • Neutralizing antibody titers against RSV A2 strain at 14 days after vaccination |
| • To assess the safety and reactogenicity of vaccination with different lots representing critical quality attributes around release, around the intermediate shelf-life, and near the presumed end of shelf-life. | • Solicited local (injection site) and systemic AEs for 7 days after vaccination.<br>• Unsolicited AEs for 28 days after vaccination.<br>• SAEs and AESIs until 6 months after vaccination. |
| **Exploratory** | |
| • To assess the vaccine-induced immune responses at 6 months post-vaccination | • pre-F ELISA antibody titers at 6 months after vaccination<br>• Neutralizing antibody titers against RSV A2 strain at 6 months after vaccination |

Refer to Section 8 for evaluations related to endpoints.

## HYPOTHESES

To demonstrate the primary objectives, the following hypotheses will be tested sequentially:

### Null Hypothesis 1:

Ad26/protein preF RSV vaccine lots representing the critical quality attributes around the intermediate shelf-life induces inferior geometric mean titers (GMTs) of the pre-F ELISA titers on Day 15, compared to Ad26/protein preF RSV vaccine lots representing the critical quality attributes near release.

### Alternative Hypothesis 1:

Ad26/protein preF RSV vaccine lots representing the critical quality attributes around the intermediate shelf-life induces non-inferior GMTs of the pre-F ELISA titers on Day 15, compared to Ad26/protein preF RSV vaccine lots representing the critical quality attributes near release.

Non-inferiority will be shown if the lower limit of the 2-sided 95% confidence interval (CI) around the estimated geometric mean titer ratio (GMR) of the intermediate shelf-life lots versus the release lots lies entirely above 0.67.

If non-inferiority is shown for the intermediate shelf-life lots then the following hypotheses will be tested:

**Null Hypothesis 2:**

Ad26/protein preF RSV vaccine lots representing the critical quality attributes near the presumed end of shelf-life induces inferior GMTs of the pre-F ELISA titers on Day 15, compared to Ad26/protein preF RSV vaccine lots representing the critical quality attributes near release.

**Alternative Hypothesis 2:**

Ad26/protein preF RSV vaccine lots representing the critical quality attributes near the presumed end of shelf-life induces non-inferior GMTs of the pre-F ELISA titers on Day 15, compared to Ad26/protein preF RSV vaccine lots representing the critical quality attributes near release.

Non-inferiority will be shown if the lower limit of the 2-sided 95% CI around the estimated GMR (end of shelf-life lots versus release lots) lies entirely above 0.67.

# 4. STUDY DESIGN

## 4.1. Overall Design

This is a randomized, double-blind, multicenter, interventional Phase 3 study in adult participants aged ≥60 to ≤75 years. A target of 750 participants will be randomized in parallel in a 1:1:1 ratio to 1 of 3 groups (see Table 2).

All participants will receive Ad26/protein preF RSV vaccine on Day 1 by the IM route.

**Table 2: Study Design**

| Group | N | Vaccination on Day 1 |
|---|---|---|
| 1 | 250 | Ad26.RSV.preF $1.0\times10^{11}$ vp + RSV preF protein 150 µg (representing critical quality attributes around release) |
| 2 | 250 | Ad26.RSV.preF $2.5\times10^{10}$ vp + RSV preF protein 150 µg (representing critical quality attributes around the intermediate shelf-life) |
| 3 | 250 | Ad26.RSV.preF $1.0\times10^{10}$ vp + RSV preF protein 150 µg (representing critical quality attributes near the end of shelf-life) |

N = number of participants; vp = viral particles

After vaccination, participants will remain under observation at the study site for at least 15 minutes for presence of any acute reactions and solicited events. Any unsolicited AEs, solicited local (injection site) or systemic AEs, and vital signs (systolic and diastolic blood pressure [sitting], heart rate, respiratory rate, and body temperature) will be documented by study-site personnel following this observation period. In addition, participants will record solicited signs and symptoms in a participant diary beginning in the evening of the day of vaccination and on a daily basis for 7 days post-vaccination (Section 8).

The reporting periods of AEs, SAEs, and AESIs are detailed in Section 8.3. The reporting periods for concomitant therapy are outlined in Section 6.8.

Blood will be collected from all participants pre-vaccination and at 14 days and 6 months post-vaccination to assess humoral immune responses.

Safety issues that might arise from this study may be escalated to an independent DMC, as needed.

The study comprises a screening period (Day -28 to Day 1), vaccination for each participant on Day 1, and a 6-month safety and immunogenicity follow-up period. The end of the study is defined as the last participant's last visit.

Over the entire study, the total blood volume to be collected from each participant will be approximately 30 mL.

Unscheduled study 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 Section 1.2 (Figure 1). Further details are provided in the Schedule of Activities.

## 4.2. Scientific Rationale for Study Design

For the rationale for performing this study, refer to Section 2.1.

### Blinding

Randomization will be used to minimize bias in the assignment of participants to vaccination groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across vaccination groups, and to enhance the validity of statistical comparisons across vaccination groups.

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

### Vaccination Groups

The groups will differ in the dose level (Ad26.RSV.preF) and lots (RSV preF protein) of the study vaccine (see Table 2). The Ad26/protein RSV preF lots in the different groups were set to represent vaccine critical quality attributes near release, around the intermediate shelf-life, and near the presumed end of shelf-life, respectively.

### Vaccine Component Selection

The rationale behind the selection of the Ad26/protein preF RSV vaccine is described in Section 2.2 and in the IB for Ad26/protein preF RSV vaccine (IB Ad26/protein preF RSV vaccine 2021).

### Dose Level Selection

The rationale behind the dose level selection for the Ad26/protein preF RSV vaccine is described in Section 4.3.

### 4.2.1. Study-Specific Ethical Design Considerations

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

The primary ethical concern is that this study will be performed in adult participants who will receive no benefit from participation in the study, except for compensation for the time and inconveniences that may arise from participation in the study.

See Section 2.3 for Benefit-Risk Assessment.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the US Department of Health and Human Services Office for Human Research Protections, and US FDA guidelines of 550 mL in any 8-week period (OHRP 1998; FDA 1998).

The results of this study may be made available to all participants through a plain language summary at the conclusion of the study according to local standards/restrictions.

## 4.3. Justification for Dose

The dose level for the Ad26/protein preF RSV vaccine used in the current study was determined from the primary analysis of Cohort 2 in study VAC18193RSV1004. From this primary analysis, a significant increase in humoral immune responses including virus neutralizing antibodies (virus neutralization assay) and pre-F antibody titers were observed in groups combining Ad26.RSV.preF ($5\times10^{10}$ vp or $1\times10^{11}$ vp) and RSV preF protein (50 µg or 150 µg) compared to Ad26.RSV.preF $1\times10^{11}$ vp alone. No relevant differences between combination groups and Ad26.RSV.preF alone were noted for cellular immune responses. All regimens had acceptable safety and reactogenicity profiles, which were similar across groups. Additionally, in the primary analysis of study VAC18193RSV2001, vaccine efficacy was demonstrated for these dose levels. Based on these data, the dose levels of Ad26.RSV.preF and RSV preF protein selected for the present study are $1\times10^{11}$ vp and 150 µg, respectively.

The lower Ad26.RSV.preF dose levels in the current study (Group 2 and Group 3) have been evaluated in study VAC18193RSV2005. These dose levels were selected based on the primary and interim analyses of the study in combination with preliminary stability data of Ad26.RSV.preF drug product manufactured and filled using the intended commercial process. The potency (infectious units) of the dose level that will be assessed in Group 3 is estimated to be below the remaining drug product potency around the presumed end of shelf-life (>24 months storage at 2°C to 8°C).

Three differentially aged RSV preF protein lots will be used in the study. Participants in Group 1 will receive an RSV preF protein lot that has been recently manufactured (non-aged) representing the drug product specifications after release. Participants in Group 2 will receive a naturally aged RSV preF protein lot that has been stored 12 to 24 months at 2°C to 8°C representing the drug product purity around the intermediate shelf-life. Participants in Group 3 will receive a naturally aged RSV preF protein lot that has been stored >24 months at 2°C to 8°C representing the drug product purity around the presumed end of shelf-life.

## 4.4. End of Study Definition

**End of Study Definition**

The end of study is considered as the last visit (on Day 183) for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

**Participant Study Completion Definition**

A participant will be considered to have completed the study if the participant has completed assessments at the Day 183 visit.

# 5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days prior to the study vaccination or on the day of vaccination.[a] Refer to Section 5.4 for conditions under which the repeat of any screening procedures are allowed.

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

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

## 5.1. Inclusion Criteria

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

1. must sign an informed consent form (ICF) indicating that the participant understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study.

[a] If screening is performed on the day of vaccination (recommended), Visit 1 and Visit 2 will coincide on Day 1. In that case, assessments should only be done once. Screening must be completed and all eligibility criteria must be fulfilled prior to randomization and vaccination.

2. must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

3. Criterion modified per Amendment 2

   3.1 aged ≥60 to ≤75 years on the day of signing the ICF and expected to be available for the duration of the study.

4. before randomization, a participant must be:

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

   b. not intending to conceive by any methods.

   *Note: Surgically sterile participants are also eligible for the study.*

5. in the investigator's clinical judgment, a participant must be in stable health at the time of vaccination. Participants may have underlying illnesses such as hypertension, congestive heart failure, chronic obstructive pulmonary disease, Type 2 diabetes, hyperlipoproteinemia, or hypothyroidism, as long as their symptoms and signs are stable at the time of vaccination, and these conditions receive routine follow-up by the participant's healthcare provider. Participants will be included on the basis of medical history and vital signs[a] performed between ICF signature and vaccination.

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

7. must be able to read, understand, and complete questionnaires in the eDiary.

8. must be willing to provide verifiable identification, has means to be contacted and to contact the investigator during the study.

9. must be able to work with smartphones/tablets/computers.

## 5.2. Exclusion Criteria

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

1. Criterion modified per Amendment 2

   1.1 history of malignancy within 5 years before screening not in the following categories:

      a. Participants with squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix may be enrolled at the discretion of the investigator.

[a] Participants can be enrolled with Grade 1 or Grade 2 values for vital signs measurements (refer to Appendix 4: Toxicity Grading Scale).

b. Participants with a history of malignancy within 5 years before screening, with minimal risk of recurrence per investigator's judgement, can be enrolled.

2. known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine) (refer to IB Ad26/protein preF RSV vaccine 2021).

   *Note: Participants with egg allergies can be enrolled.*

3. abnormal function of the immune system resulting from:

   a. Clinical conditions (eg, autoimmune disease or immunodeficiency expected to have an impact on the immune response elicited by the study vaccine. Participants with autoimmune disease (eg, autoimmune-mediated thyroid disease, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis, and Type 1 diabetes) that is stable and inactive without the use of systemic immunomodulators and glucocorticoids may be enrolled at the discretion of the investigator.

   b. Use of systemic corticosteroids within 2 months before administration of study vaccine until 14 days after study vaccination.

   *Note: Ocular, topical, or inhaled steroids are allowed.*

   c. Administration of antineoplastic and immunomodulating agents, eg, cancer chemotherapeutic agents, or radiotherapy within 6 months before administration of study vaccine until 14 days after study vaccination.

4. per medical history, participant has chronic active hepatitis B or hepatitis C infection.

5. per medical history, participant has human immunodeficiency virus (HIV) type 1 or type 2 infection.

6. history of acute polyneuropathy (eg, Guillain-Barré syndrome) or chronic idiopathic demyelinating polyneuropathy.

7. Criterion modified per Amendment 2

   7.1 received hematopoietic stem cell transplant in medical history, treatment with immunoglobulins expected to impact the vaccine-induced immune response (including monoclonal antibodies for chronic underlying conditions) in the 2 months, immunoglobulins specific to RSV, human metapneumovirus, or parainfluenza viruses in the 12 months, apheresis therapies in the 4 months, or blood products in the 4 months before the planned administration of study vaccine or has any plans to receive such treatment during the study.

   *Note: The investigator is encouraged to contact the sponsor to discuss eligibility of participants on immunoglobulin treatment.*

8. history of TTS or heparin-induced thrombocytopenia and thrombosis (HITT).

9. received or plans to receive:

   a. licensed live attenuated vaccines within 28 days before or after the planned administration of study vaccine.

   b. other licensed (not live) vaccines within 14 days before or after the planned administration of study vaccine.

10. Criterion modified per Amendment 2

    10.1 received or plans to receive a SARS-CoV-2 vaccine:

       a. live attenuated SARS-CoV-2 vaccine within 28 days before or after planned administration of study vaccine.

       b. non-live SARS-CoV-2 vaccine within 14 days before or after planned administration of study vaccine.

       c. viral-vectored SARS-CoV-2 vaccine within 6 months prior to randomization or during the study period until 28 days after study vaccination.

11. received an RSV vaccine in a previous RSV vaccine study.

12. received or plans to receive an Ad26-vectored vaccine at any time prior to randomization until 28 days after study vaccination (this does not apply to SARS-CoV-2 vaccines: for exclusion criteria related to SARS-CoV-2 vaccines, please refer to Exclusion Criterion 10).

13. Criterion modified per Amendment 2

    13.1 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 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, without intervention) or in the observational phase of interventional studies is allowed upon approval of the sponsor or its delegate.*

14. has a serious chronic disorder, eg, severe chronic obstructive pulmonary disease or severe congestive heart failure, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, Alzheimer's disease, or has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

15. has had major surgery (per the investigator's judgment) within 4 weeks before administration of the study vaccine or will not have recovered from surgery per the investigator's judgment at time of vaccination.

16. contraindication to IM injections and blood draws (eg, bleeding disorders).

17. employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.
18. has had major psychiatric illness and/or drug or alcohol abuse which in the investigator's opinion would compromise the participant's safety and/or compliance with the study procedures.
19. cannot communicate reliably with the investigator.
20. who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or is unlikely to complete the full course of vaccination and observation.
21. who has significant scarring, tattoos, abrasions, cuts, or infections over the deltoid region of both arms that, in the investigator's opinion, could interfere with evaluation of injection site local reactions.

**NOTE:** Investigators should ensure that all study enrollment criteria have been met prior to vaccination. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the study vaccine is given such that the participant no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4 describes options for rescreening. The required documentation to support meeting the enrollment criteria is described under Source Documents in Appendix 3.

## 5.3. Lifestyle Considerations

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

1. refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.
2. agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria.

## 5.4. Screen Failures

**Participant Identification, Enrollment, and Screening Logs**

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant

identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Rescreening is allowed only for resolution of an acute condition or meeting a time window (eg, for a prohibited medication). Only 1 rescreening per participant is permitted. Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.

### 5.5. Criteria for Temporarily Delaying Study Vaccine Administration

The following events constitute a temporary contraindication to study vaccination:

- Clinically significant acute illness at the time of vaccination. This does not include minor illnesses, such as diarrhea or mild upper respiratory tract infection.
- Fever (body temperature ≥38.0°C [≥100.4°F]) within 24 hours prior to the planned time of vaccination.

If any of these events occur at the scheduled time for vaccination, randomization at a later date within the screening window (allowed window up to 10 days) is permitted at the discretion of the investigator and after consultation with the sponsor. If randomization cannot occur within the screening window, rescreening is required.

If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

## 6. STUDY VACCINE(S) AND CONCOMITANT THERAPY

### 6.1. Study Vaccine Administration

The investigational medicinal products (IMPs) to be administered to participants in this study are Ad26.RSV.preF and RSV preF protein.

The Ad26/protein preF RSV vaccine to be used in this study is composed of Ad26.RSV.preF and RSV preF protein, to be administered as a single injection (1.0 mL) in the deltoid muscle:

- Ad26.RSV.preF (JNJ-64400141) will be used at a dose level of $1.0\times10^{11}$ viral particles (vp) in Group 1, $2.5\times10^{10}$ vp in Group 2, and $1.0\times10^{10}$ vp in Group 3.
- RSV preF protein (JNJ-64213175) will be used at a dose level of 150 µg in all groups (Groups 1 to 3). Three different lots will be used (a release lot; an aged lot representing the presumed end of shelf-life; and an aged lot representing the intermediate shelf-life).

Ad26.RSV.preF and RSV preF protein will be manufactured and provided under the responsibility of the sponsor. Labels will contain information to meet the applicable regulatory requirements. Note that RSV preF protein will be labelled as “RSV-F Vaccine”. Refer to the IB for Ad26/protein preF RSV vaccine for details on the components and a list of the excipients (IB Ad26/protein preF RSV vaccine 2021).

Participants will be vaccinated at the study site according to the schedule shown in Table 2. On Day 1, each participant will receive an IM injection of Ad26/protein preF RSV vaccine.

Study vaccine administration must be captured in the source documents and the electronic case report form (eCRF).

For a definition of study vaccine overdose, refer to Section 6.7.

## 6.2. Preparation/Handling/Storage/Accountability

**Preparation/Handling/Storage**

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

An unblinded study-site pharmacist, or other qualified individual will prepare the appropriate vials and syringes, labeled with the participant's identification number, and provide the syringes for Ad26/protein preF RSV vaccine in a blinded manner to the blinded study vaccine administrator who will perform the injection.

Refer to the Investigational Product Preparation Instructions and Study Site Investigational Product and Procedures Manual for additional guidance on study vaccine preparation, handling, and storage.

**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 participant 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 containing hazardous liquids, such as used ampules, needles, syringes, and vials, 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. Study vaccine will be supplied only to participants participating in the study. Study vaccine may not be relabeled or reassigned for use by other participants. 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.

Refer to the Investigational Product Preparation Instructions and Study Site Investigational Product and Procedures Manual for additional guidance on the final disposition of unused study vaccines.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

**Study Vaccine Allocation**

***Procedures for Randomization***

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 3 groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks. The interactive web response system (IWRS) will assign a unique study vaccine allocation code, which will dictate the study vaccine assignment and matching study vaccine kit for the participant. The requestor must use their own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

**Blinding**

The investigator will not be provided with randomization codes until database lock of the final analysis. The participants remain blinded until database lock of the final analysis. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

For the sponsor, unblinding (at the participant level) will occur at the time of the primary analysis (Section 9.5). From the primary analysis onwards, group level results may be shared as needed, however, efforts will be made to preserve the blinding to the individual participant allocation.

Data that may potentially unblind the randomization group assignment (eg, immunogenicity data, study vaccine preparation/accountability data, study vaccine allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

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

The study-site pharmacist or qualified individual with primary responsibility for study vaccine preparation and dispensing will be unblinded to study vaccine allocation.

Participants who have had their randomization group assignment unblinded should continue to return for scheduled evaluations.

Participants who withdraw will not be replaced.

## 6.4. Study Vaccination Compliance

Study vaccine will be administered IM by blinded qualified study-site personnel at the study site. Details of each administration will be recorded in the eCRF (including date and time of injection, and site of administration). For blinding procedures, see Section 6.3.

## 6.5. Dose Modification

Not applicable.

## 6.6. Continued Access to Study Vaccine After the End of the Study

Participants will be instructed that study vaccine will not be made available to them after they have completed/discontinued study vaccination.

## 6.7. Treatment of Overdose

For this study, any dose of the Ad26/protein preF RSV vaccine greater than the protocol-specified dose will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs/AESIs until resolution.
- Document the quantity of the excess dose in the eCRF.
- Report as a special reporting situation.

## 6.8. Concomitant Therapy

Prestudy therapies administered within the 30 days before administration of the study vaccine must be recorded on Day 1. Additionally, any history of SARS-CoV-2 vaccination (name/manufacturer of the vaccine and date of administration, whenever possible) prior to and during the study will be collected in the eCRF.

Concomitant therapies associated with solicited AEs will be collected by the participants in the participant diary from the time of study vaccination through 7 days after vaccination. Concomitant therapies associated with unsolicited AEs will be collected and recorded in the eCRF from the time of study vaccination through 28 days after vaccination. Concomitant therapies associated with SAEs or AESIs will be collected and recorded in the eCRF from ICF signature until 6 months after vaccination.

Analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs may be used post-vaccination only in cases of medical need (eg, fever or pain) and their use must be documented. Use of these medications as routine prophylaxis prior to study vaccination is discouraged.

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

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

Vaccination with licensed live attenuated vaccines within 28 days of a study vaccination (ie, before or after) is prohibited. Other licensed (not live) 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.

For SARS-CoV-2 vaccines licensed or available under Emergency Use Authorization: live attenuated vaccines should be given at least 28 days before or after vaccination; non-live vaccines should be given at least 14 days before or after vaccination. A viral-vectored SARS-CoV-2 vaccine is not to be given within 6 months prior to randomization or during the study period until 28 days after the last study vaccination.

Use of systemic corticosteroids[a] must be documented until 14 days after study vaccination. Antineoplastic and immunomodulating agents, eg, cancer chemotherapeutic agents or systemic corticosteroids, or radiotherapy are prohibited until 14 days after study vaccination. If the use of systemic corticosteroids, antineoplastic or immunomodulating agents or any therapy described in

[a] Note: Ocular, topical, or inhaled steroids are allowed.

exclusion criterion 7 becomes medically indicated during the study for any participant, the sponsor should be notified.

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

# 7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Vaccination

A participant's study vaccination must be discontinued if:

- The participant withdraws consent to receive study vaccination.
- The investigator believes that for safety reasons or reactogenicity reasons (eg, AE) it is in the best interest of the participant to discontinue study vaccination.

Study vaccine assigned to the participant who discontinued study vaccination may not be assigned to another participant. Discontinuation of study vaccination is only possible between screening and vaccination.

## 7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Any AE that requires discontinuation from the study
- Repeated failure to comply with protocol requirements

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

An early exit visit (by telephone) will be conducted for those participants who are unable to continue participation in the study and withdraw from the study before Day 183, but who do not withdraw consent (see Schedule of Activities). Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent; by telephone). They have the right to refuse.

**Withdrawal of Consent**

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the ICF apply

(eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

### 7.2.1. Withdrawal From the Use of Research Samples

**Withdrawal From the Use of Samples in Future Research**

The participant may withdraw consent for use of samples for future research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 3). 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.

## 7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

# 8. STUDY ASSESSMENTS AND PROCEDURES

**Overview**

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

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: vital signs, other safety assessments, blood draws. If needed, assessments may be performed at another day within the applicable visit window. Actual dates and times of assessments will be recorded in the source document and/or the eCRF.

Participants will be provided a thermometer (to measure body temperature), ruler (to measure local injection site reactions), and participant diary to record body temperature and solicited local (injection site) and systemic signs and symptoms.

The participant diary includes instructions on how to capture the data and grading scales to assess severity of the signs and symptoms. The study staff is responsible for providing appropriate training to the participant to avoid missing or incorrect data. The participant diary will be reviewed by the study-site personnel at the visit indicated in the Schedule of Activities.

The total blood volume to be collected from each participant will be approximately 30 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

### Visit Windows

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

| Clinic Visit # | Visit Day | Visit Window | Primary Purpose |
|---|---|---|---|
| 3 | 8 | ± 2 days | 7 days after study vaccination, Safety visit, by telephone |
| 4 | 15 | -3 days / +7 days | 14 days after study vaccination, Immunogenicity and Safety visit |
| 5 | 29 | ± 7 days | 28 days after study vaccination, Safety visit, by telephone |
| 6 | 183 | ± 14 days | 6 months after study vaccination, Immunogenicity and Safety visit |

The timings of the post-vaccination visits will be determined relative to the actual day of study vaccination.

### Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

### Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for Ad26/protein preF RSV vaccine (IB Ad26/protein preF RSV vaccine 2021)
- Study Site Investigational Product and Procedures Manual
- Laboratory manual

- Investigational Product Preparation Instructions
- Participant diary and instructions for use
- Ruler (to measure diameter of any erythema and swelling)
- Thermometer
- Laboratory kits
- Contact Information page(s)
- Study protocol
- IWRS Manual
- Electronic data capture (eDC) Manual/eCRF completion guidelines
- Wallet card
- Sample ICF

## 8.1. Immunogenicity Assessments

Venous blood samples of approximately 10 mL will be collected for the determination of humoral immune responses at the timepoints indicated in the Schedule of Activities. Sample collection and processing will be performed by the study-site personnel according to current versions of approved standard operating procedures.

The RSV A strain pre-F ELISA antibody titers are the primary (at Day 15) and exploratory (at Month 6) endpoint for this study. In previous studies using the vaccine regimen, high pre-F ELISA titers were commonly associated with high VNA-A2 titers following vaccination. CCI [redacted] To complement the pre-F ELISA responses and further characterize the functional antibody responses, RSV neutralizing antibody responses (VNA-A2) will also be evaluated.

Humoral immunogenicity evaluations are summarized in Table 3.

**Table 3: Summary of Immunogenicity Assays (Humoral)**

| Assay | Purpose |
|---|---|
| ***Primary and exploratory endpoints*** | |
| F-protein antibodies (RSV-A pre-F ELISA) | Analysis of antibodies binding to RSV-A F-protein in pre-fusion form |
| ***Secondary and exploratory endpoints*** | |
| RSV A neutralization assay (VNA A2) | Analysis of neutralizing antibodies against the RSV A2 strain |

ELISA = enzyme-linked immunosorbent assay; VNA = virus neutralization assay

## 8.2. Safety Assessments

Safety assessments will include the monitoring of AEs and vital signs.

AEs will be reported and followed by the investigator as specified in Section 8.3 and Appendix 2.

Any clinically significant abnormalities will be followed by the investigator until clinical resolution (return to baseline) or until a clinically stable condition is reached, or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts.

The study will include the following evaluations of safety and reactogenicity according to the timepoints provided in the Schedule of Activities.

### 8.2.1. Physical Examinations

At any clinic visit, an abbreviated, symptom-directed physical examination may be performed if deemed necessary by the investigator based on any clinically relevant issues, clinically relevant symptoms, and medical history.

Physical examinations will be performed by the investigator or appropriately trained delegate. Any clinically relevant abnormalities or changes in severity noted during the review of body systems should be documented in the eCRF as an AE or SAE if it meets the criteria for an AE or SAE according to the protocol reporting requirements.

### 8.2.2. Vital Signs

Body temperature (oral route preferred), heart rate (beats per minute), respiratory rate (breaths per minute), and systolic and diastolic blood pressure (mmHg) will be measured pre- and post-vaccination. At non-vaccination visits, vital signs will be measured if deemed necessary by the investigator. Height and weight will be measured during screening.

Blood pressure and heart rate measurements will be assessed, if possible, with a completely automated device. Manual techniques will be used only if an automated device is not available.

Sitting systolic and diastolic blood pressure and heart and respiratory rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Confirmatory vital signs measurement can be performed if inconsistent with a prior measurement. Any abnormalities or changes in severity noted during the review of vital signs should be documented in the eCRF.

## 8.3. AEs, SAEs, AESIs and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, AESIs (including potential AESIs, refer to Section 8.3.6) and Product Quality Complaints (PQCs), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established standard

operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, AESIs, and PQCs can be found in Appendix 2.

### 8.3.1. Time Period and Frequency for Collecting AE, SAE, and AESI Information

**All AEs**

AEs and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal.

Clinically relevant medical events not meeting the above criteria and occurring between signing of ICF and moment of vaccination will be collected on the Medical History eCRF page as pre-existing conditions.

Solicited AEs, collected through a participant diary, will be recorded from the time of vaccination until 7 days post-vaccination.

All other unsolicited AEs and special reporting situations, whether serious or non-serious, will be reported from the time of vaccination until 28 days post-vaccination.

All SAEs and AEs leading to discontinuation from the study (regardless of the causal relationship) are to be reported from the moment of vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

See Section 7.2 for procedures associated with withdrawal of consent.

All AEs will be followed until resolution or until clinically stable.

**SAEs**

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, but no later than 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 eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone

reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

**AESIs**

TTS is considered to be an AESI. Thrombotic events and/or thrombocytopenia (defined as platelet count below the lower limit of normal [LLN] range for the testing lab) are considered to be potential AESIs. All AESIs, including potential AESIs, will be reported to the sponsor from the moment of study vaccination until 6 months after the study vaccination (see Section 8.3.6).

### 8.3.2. Method of Detecting AEs, SAEs and AESIs

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

**Solicited AEs**

Solicited AEs are used to assess the reactogenicity of the study vaccine and are predefined local (injection site) and systemic events for which the participant is specifically questioned and which are noted by participants in their participant diary.

After vaccination, participants will remain under observation at the study site for at least 15 minutes for presence of any acute reactions and solicited events.

In addition, participants will record solicited signs and symptoms in a participant diary for 7 days post-vaccination. All participants will be provided with a participant diary and instructions on how to complete the participant diary (see Overview in Section 8). If a paper diary is used for this study, the study staff will transcribe the information provided by the participant into the relevant sections of the eCRF. If an e-diary is used, diary information will be transferred to the sponsor. After review and verbal discussion of the initial diary entries with the participant, the investigator will complete their own assessment in the relevant sections of the eCRF. Once a solicited sign or symptom from a participant diary is considered to be of severity Grade 1 or above, it will be recorded as a solicited AE.

***Solicited Local (Injection Site) AEs***

Participants will be asked to note in the participant diary occurrences of injection site pain/tenderness, erythema and swelling at the study vaccine injection site daily for 7 days post-vaccination (day of vaccination and the subsequent 7 days). The extent (largest diameter) of any erythema and swelling should be measured (using the ruler supplied) and recorded daily. The case definitions for solicited injection site events can be found in the references (Gidudu 2012; Kohl 2007).

***Solicited Systemic AEs***

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the temperature (oral route preferred) in the participant

diary in the evening of the day of vaccination, and then daily for the next 7 days approximately at the same time each day. If more than 1 measurement is made on any given day, the highest temperature of that day will be used in the eCRF.

Fever is defined as endogenous elevation of body temperature ≥38.0°C (≥100.4°F), as recorded in at least 1 measurement (Marcy 2004).

Participants will also be instructed on how to note signs and symptoms in the participant diary on a daily basis for 7 days post-vaccination (day of vaccination and the subsequent 7 days), for the following events: fatigue, headache, nausea, and myalgia.

**Unsolicited AEs**

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

For details regarding AESIs, refer to Section 8.3.6.

### 8.3.3. Follow-up of AEs, SAEs and AESIs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, AESI, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

AEs and the special reporting situation of pregnancy, will be followed by the investigator as specified in Appendix 2.

### 8.3.4. Regulatory Reporting Requirements for SAEs

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 suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

### 8.3.5. Pregnancy

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

If a participant becomes pregnant during the study, a determination regarding study vaccination discontinuation must be made by the investigator in consultation with the sponsor. Follow-up

information regarding the outcome of the pregnancy will be required. If the partner of a male participant becomes pregnant during the study, follow-up information regarding the outcome of the pregnancy will be requested upon the consent provided by the partner.

### 8.3.6. Adverse Events of Special Interest

AESIs (including potential AESIs) are significant AEs that are judged to be of special interest because of clinical importance, known or suspected class effects, or based on nonclinical signals. AESIs and potential AESIs will be carefully monitored during the study by the sponsor.

AESIs and potential AESIs must be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious AEs) or causality following the procedure described above for SAEs.

AESIs must be reported using the AESI form in the eCRF using the eCRF completion guidelines.

Specific requirements for the AESI are described below.

#### 8.3.6.1. Thrombosis with Thrombocytopenia Syndrome

As described in Section 2.2, TTS has been observed very rarely following vaccination with Janssen COVID vaccine and is considered to be an AESI in this study. TTS is a syndrome characterized by a combination of both a thrombotic event and thrombocytopenia. (American Society of Hematology 2021; Brighton Collaboration 2021)

Because this syndrome is rare and not completely understood, all cases of thrombosis and/or thrombocytopenia will be considered a potential case of TTS and should be reported to the sponsor within 24 hours of awareness using the AESI form. Each potential AESI will be reviewed to identify a TTS case. A potential TTS case is defined as:

- Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Section 10.6, Appendix 6,

  and/or

- Thrombocytopenia, defined as platelet count below LLN for the testing lab

Symptoms, signs, or conditions suggestive of a thrombotic event or thrombocytopenia should be recorded and reported as a potential AESI even if the final or definitive diagnosis has not yet been determined, and alternative diagnoses have not yet been eliminated or shown to be less likely. Follow-up information and final diagnoses, if applicable, should be submitted to the sponsor as soon as they become available.

In the event of thrombocytopenia, study site personnel should report the absolute value for the platelet count and the reference range for the laboratory test used.

For either a thrombotic event or thrombocytopenia, complete blood count including platelet count and a coagulation profile available from participant's medical records should be entered in the

eCRF. In case these results are not available at the time of the event report in the eCRF, the study site is recommended to obtain a complete blood count including platelet count and a coagulation profile (to be performed at the local laboratory). Repeat testing at the local laboratory may be requested for confirmation upon sponsor discretion.

Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request (Table 4).

Table 4 provides non-exhaustive list(s) of laboratory tests that may be performed (upon sponsor request).

In addition, the sponsor may request additional laboratory tests on additional blood samples obtained as soon as possible after the potential AESI onset, either during an ad hoc unscheduled visit or the next scheduled visit, whichever comes first. Table 5 provides a non-exhaustive list of laboratory tests that may be requested by the sponsor in case of potential AESI reporting, for which additional samples may be needed.

**Table 4: Laboratory Tests That May Be Performed Upon Sponsor Request on Immunogenicity Samples Collected on Day 1, 15, and/or 183 After Potential AESI Reporting**

| Parameters | Timepoints |
|---|---|
| • Serum samples for assay such as but not limited to:<br>o Heparin Induced Thrombocytopenia (HIT)/PF4 Ab, IgG·(HIT assay)<br>If the above test is positive, also consider:<br>– Anti-cardiolipin antibody<br>– Beta-2 glycoprotein | • Days 1, 15 and 183 visits (aliquots of serum samples collected for immunogenicity test can be reconverted for participant's safety purposes). |

Note: results of the test should be reported in the narrative of the event and/or in the TTS AESI pages of the eCRF.

**Table 5: Laboratory Tests That May Be Requested by the Sponsor to be Performed at the Central Laboratory After Potential AESI Reporting**

| Parameters | Timepoints |
|---|---|
| • Serum/plasma/whole blood samples for coagulation-related assays such as but not limited to:<br>o Fibrinogen<br>o D-dimer·<br>o Lupus anticoagulant·<br>o Anti-cardiolipin antibody<br>o Beta-2 glycoprotein·<br>o Heparin Induced Thrombocytopenia (HIT)/PF4 Ab, IgG·(HIT assay)<br>o Platelet activation assay (if HIT/PF4 is positive)<br>o Homocysteine·<br>o COVID-19 serological test | • As soon as possible after the potential AESI onset upon sponsor request (during an ad hoc unscheduled visit or the next scheduled visit, whichever comes first). |

Note: results of the test should be reported in the narrative of the event and/or in the TTS AESI pages of the eCRF. Irrespective on samples for central laboratory tests collection, relevant data for TTS assessment reported in the medical records of the participant should be reported in eCRF narrative of the event and/or in the TTS AESI pages of the eCRF.

AESIs, including potential AESIs, will require enhanced data collection and evaluation. Every effort should be made to report as much information as possible about the event to the sponsor in a reasonable timeframe. Relevant laboratory results can be entered on the AESI form in the eCRF, using the eCRF completion guidelines.

If the investigator is not the treating physician, every effort should be made to collect the information requested in the form from the treating physician and enter the available information in the eCRF.

If an event meets the criteria for an SAE (Section 10.2.1), it should be reported using the same process as for other SAEs.

***Treatment and Follow-up Recommendation***

The medical management of thrombotic events with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (eg, American Society of Hematology 2021; British Society of Haematology 2021; CDC 2021). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended.

## 8.4. Medical Resource Utilization

Medical Resource Utilization parameters are not evaluated in this study.

# 9. STATISTICAL CONSIDERATIONS

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

## 9.1. Statistical Hypotheses

For a description of the hypotheses, see Section 3.

Non-inferiority of Group 2 versus Group 1 is demonstrated if the 2-sided 95% CI for the GMR ($GMT_{Group\ 2}/GMT_{Group\ 1}$) of the Day 15 pre-F ELISA titers lies entirely above 0.67. If non-inferiority of Group 2 versus Group 1 is not demonstrated, the study fails. If non-inferiority of Group 2 versus Group 1 is demonstrated, then non-inferiority of Group 3 versus Group 1 can be tested: similarly, non-inferiority of Group 3 versus Group 1 is demonstrated if the 2-sided 95% CI for the GMR ($GMT_{Group\ 3}/GMT_{Group\ 1}$) of the Day 15 pre-F ELISA titers lies entirely above 0.67.

## 9.2. Sample Size Determination

Sample size calculations are performed under the following assumptions:

- a 10% decrease in GMT of the groups with aged lots (Group 2 and Group 3) versus the group with the non-aged lot (Group 1) (ie, assuming a true GMR of Day 15 pre-F ELISA titers equal to 0.9)

- a standard deviation of 1.3 at the $\log_2$ scale for pre-F ELISA on Day 15[a]
- a non-inferiority margin of 0.67 (2/3)
- a 2-sided α of 5%
- hierarchical testing (ie, first Group 2 versus Group 1; if non-inferiority is demonstrated, then Group 3 versus Group 1)

A total of 236 evaluable participants per group are needed to have 95% power to demonstrate non-inferiority for each comparison separately. With this sample size, the overall power to demonstrate non-inferiority of Group 3 versus Group 1 as the second comparison in the hierarchy is at least 90%.

To account for exclusions from the Per-protocol Immunogenicity (PPI) Set (see Section 9.3 for the definitions of the analysis sets), dropouts, and missing samples, approximately 250 participants per group should be enrolled.

## 9.3. Populations for Analysis Sets

Vaccination assignment will follow the as-treated principle.

The Full Analysis (FA) Set will include all participants who received study vaccine, regardless of the occurrence of protocol deviations. All safety and participant information analyses will be based on the FA Set.

The PPI Set will include all randomized participants who received study vaccine and for whom immunogenicity data are available. Samples taken after a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes will be excluded from the PPI analysis.

The list of major protocol deviations that would lead to elimination from the immunogenicity analysis will be specified in the SAP or major protocol violation criteria document, which will be finalized before database lock and unblinding.

The primary analysis set for analyses related to RSV immunogenicity is the PPI Set. As a sensitivity analysis, key tables may also be based on the FA Set.

## 9.4. Statistical Analyses

The SAP will be finalized prior to database lock of the primary analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the key endpoints.

[a] Based on the standard deviation of pre-F ELISA at 14 days after vaccine administration observed in Group 14 of study VAC18193RSV1004.

### 9.4.1. General Considerations

The primary analysis will be performed when all participants have completed the visit 28 days post-vaccination or discontinued earlier.

The significance level (α) is 5% (2-sided). As the 2 primary objectives are tested sequentially and as no interim analyses before the primary analysis are planned, no multiplicity adjustments are needed.

Refer to Section 9.3 for the choice of populations for the different analyses.

### 9.4.2. Participant Information

For all participants, demographic characteristics (eg, age, height, body weight, body mass index, race, and gender) and other baseline characteristics will be tabulated and summarized descriptively by group.

### 9.4.3. Immunogenicity Analyses

#### 9.4.3.1. Primary Endpoints

The primary immunogenicity objective will be assessed by calculating the 2-sided 95% CIs for the difference in log-transformed Day 15 pre-F ELISA titers for each of the comparisons (ie, Group 2 versus Group 1, and Group 3 versus Group 1).

The CIs will be calculated via an analysis of variance (ANOVA) including all groups (ie, Groups 1 to 3) with the log-transformed Day 15 pre-F ELISA titers as dependent variable and group as independent variable. The CIs around the difference will be back-transformed (by exponentiation) to CIs around a GMR ($GMT_{Group\ x}/GMT_{Group\ 1}$ where x is 2 or 3) and compared to the non-inferiority margin of 0.67 (2/3).

Non-inferiority of Group 2 versus Group 1 is demonstrated if the 2-sided 95% CI for the GMR ($GMT_{Group\ 2}/\ GMT_{Group\ 1}$) of the Day 15 pre-F ELISA titers lies entirely above 0.67. If non-inferiority of Group 2 versus Group 1 is not demonstrated, the study fails. If non-inferiority of Group 2 versus Group 1 is demonstrated, then non-inferiority of Group 3 versus Group 1 can be tested: similarly, non-inferiority of Group 3 versus Group 1 is demonstrated if the 2-sided 95% CI for the GMR ($GMT_{Group\ 3}/GMT_{Group\ 1}$) of the Day 15 pre-F ELISA titers lies entirely above 0.67.

As a sensitivity analysis to assess the impact of baseline titers, the primary endpoint will also be evaluated adjusting for the respective baseline titers. For immunogenicity, baseline is considered as the last assessment pre-vaccination. In a second sensitivity analysis, different variances between the study groups will be allowed. Therefore, the CIs will be calculated via Welch's ANOVA.

The pre-F ELISA titers will be summarized descriptively. For continuous parameters, descriptive statistics of the actual values (geometric mean and 95% CI) will be calculated at all timepoints. Additionally, geometric mean fold increases from baseline and corresponding 95% CIs will be

calculated. Graphical representations of immunogenicity parameters will be created as applicable. For categorical variables, frequency tables will be presented.

#### 9.4.3.2. Secondary and Exploratory Endpoints

No formal statistical testing of the secondary and exploratory immunogenicity endpoints is planned. These data will be analyzed descriptively by group. Descriptive statistics (eg, geometric mean and 95% CI) will be calculated for continuous immunogenicity parameters at all timepoints. Geometric mean fold rises from baseline and corresponding 95% CIs may also be calculated. Baseline is considered the last available assessment prior to vaccination. Graphical displays of immunogenicity parameters will be prepared, as applicable. GMRs ($GMT_{Group\ 2}/GMT_{Group\ 1}$ and $GMT_{Group\ 3}/GMT_{Group\ 1}$) will also be calculated for VNA A2 in a similar manner as for pre-F ELISA. Frequency tabulations will be calculated for discrete (qualitative) immunogenicity parameters, as applicable.

### 9.4.4. Safety Analyses

No formal statistical testing of safety data is planned. All safety data will be analyzed descriptively by group. All safety analyses will be based on the FA Set.

**AEs**

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the active phase (ie, AEs occurring from the time of vaccination up to 28 days post-vaccination), and all SAEs and AESIs will be included in the analysis. For each AE, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by group.

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

Summaries and/or listings may be provided separately for AEs with onset outside the above defined timeframe (ie, beyond 28 days post-vaccination).

Solicited local (injection site) and systemic AEs will be summarized descriptively. The overall frequencies per group as well as frequencies according to severity and duration will be calculated for solicited AEs. In addition, the number and percentages of participants with at least 1 solicited local (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.

**Vital Signs**

Baseline and emerging vital signs abnormalities will be listed.

## 9.5. Planned Analyses

The following analyses are planned:

- **Primary analysis:** including safety and immunogenicity data up to 28 days post-vaccination. This analysis will be performed based on sponsor unblinded data (study-site personnel and participants will remain blinded until the end of the study).
- **Final analysis:** including SAE data up to study end and immunogenicity data up to Day 183. This analysis will be performed on unblinded data.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Abbreviations

| | |
|---|---|
| Ad26 | adenovirus serotype 26 |
| AE | adverse event |
| AESI | adverse event of special interest |
| ANOVA | analysis of variance |
| CI | confidence interval |
| COVID-19 | coronavirus disease-2019 |
| CTM | Clinical Trial Manager |
| CVST | cerebral venous sinus thrombosis |
| DNA | deoxyribonucleic acid |
| DMC | Data Monitoring Committee |
| eCRF | electronic case report form |
| eDC | electronic data capture |
| ELISA | enzyme-linked immunosorbent assay |
| FA | Full Analysis |
| FDA | (United States) Food and Drug Administration |
| FOIA | Freedom of Information Act |
| GCP | Good Clinical Practice |
| GMR | geometric mean titer ratio |
| GMT | geometric mean titer |
| HITT | heparin-induced thrombocytopenia and thrombosis |
| HIV | human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journal Editors |
| IEC | Independent Ethics Committee |
| IM | intramuscular |
| IRB | Institutional Review Board |
| IWRS | interactive web response system |
| LLN | lower limit of normal |
| LTM | Local Trial Manager |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PCC | protocol clarification communication |
| PPI | Per-protocol Immunogenicity |
| PQC | Product Quality Complaint |
| pre-F | prefusion conformation-stabilized F protein |
| RSV | respiratory syncytial virus |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus-2 |
| SUSAR | suspected unexpected serious adverse reaction |
| TTS | thrombosis with thrombocytopenia syndrome |
| vp | viral particles |

## 10.2. Appendix 2: AEs, SAEs, AESIs, PQCs, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.2.1. AE Definitions and Classifications

**AE**

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the study vaccine. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [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: For time period of sponsor's AE collection, see All AEs under Section 8.3.1, Time Period and Frequency for Collecting AE and SAE Information.

**SAE**

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

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

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

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

**Unlisted (Unexpected) AE/Reference Safety Information**

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For the Ad26/protein preF RSV vaccine, the expectedness of an AE will be determined by whether or not it is listed in the IB (IB Ad26/protein preF RSV vaccine 2021).

### 10.2.2. Attribution Definitions

**Assessment of Causality**

The causal relationship to study vaccine is determined by the investigator. The following selection should be used to assess all AEs.

**Related**

There is a reasonable causal relationship between study vaccine administration and the AE.

**Not Related**

There is not a reasonable causal relationship between study vaccine administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

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

### 10.2.3. Severity Criteria

All AEs will be coded for severity using a modified version of the FDA grading table, based on the version of September 2007 (FDA 2007), included in Appendix 4, Toxicity Grading Scale.

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

| | | |
|---|---|---|
| **Grade 1** | Mild | Symptoms causing no or minimal interference with usual social and functional activities |
| **Grade 2** | Moderate | Symptoms causing greater than minimal interference with usual social and functional activities |
| **Grade 3** | Severe | Symptoms causing inability to perform usual social and functional activities and requiring medical intervention |
| **Grade 4** | Potentially life-threatening | Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability OR emergency room visit or hospitalization |

The severity of solicited signs and symptoms will be graded in the participant diary by the participant based on the severity assessment provided in the participant diary and then verified by the investigator using the toxicity grading scale in Appendix 4. (Note: severity of the measured events will be derived from the diameter [for erythema and swelling] and the temperature measurements [for fever])

### 10.2.4. Special Reporting Situations

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

- Overdose of a sponsor study vaccine
- Suspected abuse/misuse of a sponsor study vaccine
- Accidental or occupational exposure to a sponsor study vaccine
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study vaccine from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

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.

### 10.2.5. Procedures

**All AEs**

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.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

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

**SAEs**

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant’s discontinuation from 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 (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the 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 participant 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.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

**Adverse Events of Special Interest**

AESIs, including potential AESIs, will be carefully monitored during the study by the sponsor and must be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious AEs) or causality assessment, following the procedure described above for SAEs and will require enhanced data collection.

### 10.2.6. PQC Handling

**Definition**

A 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, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

All complaints related to ANY part of the Ad26/protein preF RSV vaccine must be reported within 1 business day. In the event of public holiday, measures must be taken to ensure reporting no later than calendar day 3.

**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.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

### 10.2.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

## 10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

### 10.3.1. Regulatory and Ethical Considerations

**Investigator Responsibilities**

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

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

**Protocol Clarification Communications**

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

**Protocol Amendments**

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

During 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.

**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.

**Required Prestudy 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 principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

- Completed investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)

- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

**IEC or IRB**

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

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB 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 participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

**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 if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

**Other Ethical Considerations**

For study-specific ethical design considerations, refer to Section 4.2.1.

### 10.3.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

### 10.3.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing

IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

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

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

Participants who are rescreened are required to sign a new ICF.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

### 10.3.4. Data Protection

**Privacy of Personal Data**

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

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

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to their original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and

regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to their 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.

### 10.3.5. Long-Term Retention of Samples for Additional Future Research

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

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

### 10.3.6. Committees Structure

Safety issues that might arise from this study may be escalated to an independent DMC, as needed.

All potential AESI cases will be reviewed to determine if they meet the definition of TTS (see Section 8.3.6.1). A Charter will be developed to describe the roles and responsibilities of the Committee appointed to perform this review.

### 10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding the Ad26/protein preF RSV vaccine 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 the Ad26/protein preF RSV vaccine, 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 for the study. Results of analyses performed after the clinical study report has been issued will be reported in a separate report and will not require a revision of the clinical study report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**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. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

### 10.3.8. Data Quality Assurance

**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 may review the 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.

### 10.3.9. Case Report Form Completion

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

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

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

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

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

### 10.3.10. Source Documents

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

completion and reason for early discontinuation of study vaccination or withdrawal from the study, if applicable.

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

The participant diary used to collect information regarding solicited signs and symptoms after vaccination will be considered source data.

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).

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

### 10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

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 may compare data entered into the eCRF with the source documents (eg, hospital/ clinic/physician's office medical records); a sample may be reviewed. 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.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

### 10.3.12. On-Site Audits

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

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

### 10.3.13. Record Retention

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

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

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

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

### 10.3.14. Study and Site Start and Closure

**First Act of Recruitment**

The first participant screened is considered the first act of recruitment and it becomes the study start date.

**Study/Site Termination**

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

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

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

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

## 10.4. Appendix 4: Toxicity Grading Scale

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

### A: Tables for Clinical Abnormalities

| **Local Reaction to Injectable Product** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)** |
|---|---|---|---|---|
| Pain/Tenderness[#] | Aware of symptoms but easily tolerated; Does not interfere with activity; Discomfort only to touch | Notable symptoms; Requires modification in activity or use of medications; Discomfort with movement | Incapacitating symptoms; Inability to do work, school, or usual activities; Use of narcotic pain reliever | Hospitalization; Pain/tenderness causing inability to perform basic self-care function |
| Erythema[#] | 25 – 50 mm | 51 – 100 mm | > 100 mm | Hospitalization; Necrosis or exfoliative dermatitis |
| Swelling[#] | 25 – 50 mm | 51 – 100 mm | > 100 mm | Hospitalization; Necrosis |

[#] Revised by the sponsor.

| **Vital Signs*** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)** |
|---|---|---|---|---|
| Fever (°C)**<br>(°F)** | 38.0 – 38.4<br>100.4 – 101.1 | 38.5 – 38.9<br>101.2 – 102.0 | 39.0 – 40.0<br>102.1 – 104.0 | > 40<br>> 104.0 |
| Tachycardia - beats per minute | 101 – 115 | 116 – 130 | > 130 | Hospitalization for arrhythmia[#] |
| Bradycardia - beats per minute*** | 50 – 54 | 45 – 49 | < 45 | Hospitalization for arrhythmia[#] |
| Hypertension (systolic) - mm Hg | 141 – 150 | 151 – 160[#] | > 160[#] | Hospitalization for malignant hypertension[#] |
| Hypertension (diastolic) - mm Hg | 91 – 95 | 96 – 100 | > 100 | Hospitalization for malignant hypertension[#] |
| Hypotension (systolic) - mm Hg | 85 – 89 | 80 – 84 | < 80 | Hospitalization for hypotensive shock[#] |
| Respiratory rate - breaths per minute | 17 – 20 | 21 – 25 | > 25 | Intubation |

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

** For oral temperature: no recent hot or cold beverages or smoking.

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

[#] Revised by the sponsor.

| Systemic (General) | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| Vomiting[#] | No interference with activity or 1-2 episodes/24 hours | Some interference with activity or > 2 episodes/24 hours | Prevents daily activity, requires outpatient IV hydration | Hospitalization; Hypotensive shock |
| Nausea[#] | Minimal symptoms; causes minimal or no interference with work, school, or self-care activities | Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities | Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities | Hospitalization; Inability to perform basic self-care functions |
| Diarrhea[#] | 2 – 3 loose stools or < 400 gms/24 hours | 4 – 5 stools or 400 – 800 gms/24 hours | 6 or more watery stools or > 800 gms/24 hours or oral rehydration necessary | Hospitalization; Hypotensive shock OR IV fluid replacement indicated |
| Headache[#] | Minimal symptoms; causes minimal or no interference with work, school, or self-care activities | Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities | Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever | Hospitalization; Inability to perform basic self-care functions |
| Fatigue[#] | Minimal symptoms; causes minimal or no interference with work, school, or self-care activities | Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities | Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever | Hospitalization; Inability to perform basic self-care functions |
| Myalgia[#] | Minimal symptoms; causes minimal or no interference with work, school, or self-care activities | Notable symptoms; Requires modification in activity or use of medications; Does NOT result in loss of work, school, or cancellation of social activities | Incapacitating symptoms; Requires bed rest and/or results in loss of work, school, or cancellation of social activities; Use of narcotic pain reliever | Hospitalization; Inability to perform basic self-care functions |

[#] Revised by the sponsor.

| Systemic Illness | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| Illness or clinical adverse event (as defined according to applicable regulations) | No interference with activity | Some interference with activity not requiring medical intervention | Prevents daily activity and requires medical intervention | Hospitalization[#] |

[#] Revised by the sponsor.

## B: Tables for Laboratory Abnormalities

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

| Serum * | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4)** |
|---|---|---|---|---|
| Sodium – Hyponatremia mEq/L | 132 – 134 | 130 – 131 | 125 – 129 | < 125 |
| Sodium – Hypernatremia mEq/L | 144 – 145 | 146 – 147 | 148 – 150 | > 150 |
| Potassium – Hyperkalemia mEq/L | 5.1 – 5.2 | 5.3 – 5.4 | 5.5 – 5.6 | > 5.6 |
| Potassium – Hypokalemia mEq/L | 3.5 – 3.6 | 3.3 – 3.4 | 3.1 – 3.2 | < 3.1 |
| Glucose – Hypoglycemia mg/dL | 65 – 69 | 55 – 64 | 45 – 54 | < 45 |
| Glucose – Hyperglycemia<br>Fasting mg/dL<br>Random – mg/dL | <br>100 – 110<br>110 – 125 | <br>111 – 125<br>126 – 200 | <br>>125<br>> 200 | Insulin requirements or hyperosmolar coma |
| Blood Urea Nitrogen BUN mg/dL | 23 – 26 | 27 – 31 | > 31 | Requires dialysis |
| Creatinine – mg/dL | 1.5 – 1.7 | 1.8 – 2.0 | 2.1 – 2.5 | > 2.5 or requires dialysis |
| Calcium – hypocalcemia mg/dL | 8.0 – 8.4 | 7.5 – 7.9 | 7.0 – 7.4 | < 7.0 |
| Calcium – hypercalcemia mg/dL | 10.5 – 11.0 | 11.1 – 11.5 | 11.6 – 12.0 | > 12.0 |
| Magnesium – hypomagnesemia mg/dL | 1.3 – 1.5 | 1.1 – 1.2 | 0.9 – 1.0 | < 0.9 |
| Phosphorous – hypophosphatemia mg/dL | 2.3 – 2.5 | 2.0 – 2.2 | 1.6 – 1.9 | < 1.6 |
| CPK – mg/dL | 1.25 – 1.5 x ULN*** | 1.6 – 3.0 x ULN | 3.1 –10 x ULN | > 10 x ULN |
| Albumin – Hypoalbuminemia g/dL | 2.8 – 3.1 | 2.5 – 2.7 | < 2.5 | -- |
| Total Protein – Hypoproteinemia g/dL | 5.5 – 6.0 | 5.0 – 5.4 | < 5.0 | -- |
| Alkaline phosphate – increase by factor | 1.1 – 2.0 x ULN | 2.1 – 3.0 x ULN | 3.1 – 10 x ULN | > 10 x ULN |
| Liver Function Tests – ALT, AST increase by factor | 1.1 – 2.5 x ULN | 2.6 – 5.0 x ULN | 5.1 – 10 x ULN | > 10 x ULN |
| Bilirubin – when accompanied by any increase in Liver Function Test increase by factor | 1.1 – 1.25 x ULN | 1.26 – 1.5 x ULN | 1.51 – 1.75 x ULN | > 1.75 x ULN |
| Bilirubin – when Liver Function Test is normal; increase by factor | 1.1 – 1.5 x ULN | 1.6 – 2.0 x ULN | 2.0 – 3.0 x ULN | > 3.0 x ULN |

| **Serum *** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)**** |
|---|---|---|---|---|
| Cholesterol | 201 – 210 | 211 – 225 | > 226 | -- |
| Pancreatic enzymes – amylase, lipase | 1.1 – 1.5 x ULN | 1.6 – 2.0 x ULN | 2.1 – 5.0 x ULN | > 5.0 x ULN |

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

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

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

| **Hematology*** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)** |
|---|---|---|---|---|
| Hemoglobin (Female) - gm/dL | 11.0 – 12.0 | 9.5 – 10.9 | 8.0 – 9.4 | < 8.0 |
| Hemoglobin (Female) change from baseline value - gm/dL | Any decrease – 1.5 | 1.6 – 2.0 | 2.1 – 5.0 | > 5.0 |
| Hemoglobin (Male) - gm/dL | 12.5 – 13.5 | 10.5 – 12.4 | 8.5 – 10.4 | < 8.5 |
| Hemoglobin (Male) change from baseline value - gm/dL | Any decrease – 1.5 | 1.6 – 2.0 | 2.1 – 5.0 | > 5.0 |
| WBC Increase - cell/$mm^3$ | 10,800 – 15,000 | 15,001 – 20,000 | 20,001 – 25, 000 | > 25,000 |
| WBC Decrease - cell/$mm^3$ | 2,500 – 3,500 | 1,500 – 2,499 | 1,000 – 1,499 | < 1,000 |
| Lymphocytes Decrease - cell/$mm^3$ | 750 – 1,000 | 500 – 749 | 250 – 499 | < 250 |
| Neutrophils Decrease - cell/$mm^3$ | 1,500 – 2,000 | 1,000 – 1,499 | 500 – 999 | < 500 |
| Eosinophils - cell/$mm^3$ | 650 – 1500 | 1501 – 5000 | > 5000 | Hypereosinophilic |
| Platelets Decreased - cell/$mm^3$ | 125,000 – 140,000 | 100,000 – 124,000 | 25,000 – 99,000 | < 25,000 |
| PT – increase by factor (prothrombin time) | 1.0 – 1.10 x ULN** | 1.11 – 1.20 x ULN | 1.21 – 1.25 x ULN | > 1.25 ULN |
| PTT – increase by factor (partial thromboplastin time) | 1.0 – 1.2 x ULN | 1.21 – 1.4 x ULN | 1.41 – 1.5 x ULN | > 1.5 x ULN |
| Fibrinogen increase - mg/dL | 400 – 500 | 501 – 600 | > 600 | -- |
| Fibrinogen decrease - mg/dL | 150 – 200 | 125 – 149 | 100 – 124 | < 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC) |

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

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

| **Urine*** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** | **Potentially Life Threatening (Grade 4)** |
|---|---|---|---|---|
| Protein | Trace | 1+ | 2+ | Hospitalization or dialysis |
| Glucose | Trace | 1+ | 2+ | Hospitalization for hyperglycemia |
| Blood (microscopic) – red blood cells per high power field (RBC/HPF) | 1 – 10 | 11 – 50 | > 50 and/or gross blood | Hospitalization or packed red blood cells (PRBC) transfusion |

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

## 10.5. Appendix 5: Study Conduct During a Natural Disaster

**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, isolation or quarantine of participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study-site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the COVID-19 pandemic, scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key immunogenicity endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

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

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing study assessments, 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:

### Screening and Randomization

- Enrollment of new participants may continue based on the investigator's assessment of risks versus benefits, depending on the situation at a particular site, and the ability to monitor participant safety.

### Site Visits

- When site visits are not possible due to local/national guidelines, sites should collect the assessments via telephone visits or home-based visits, if the participant allows. The actual visit date and the type of visit (ie, telephone or home-based visit) should be captured in the eCRF according to the eCRF completion guidelines. Procedures that cannot be performed during a home-based visit (eg, blood samples), should be excluded.

### Vaccine Administration

- When planning for vaccination visits, local/national or institutional guidelines will be followed. The study vaccine must be administered by a blinded qualified individual at the study site. If this is not possible, a solution may be considered in consultation with the sponsor and taking into consideration participant safety.

### Informed Consent Form

- Consenting and re-consenting of participants for the measures taken (including also remote consenting by phone or video consultation) will be performed as applicable and according to local guidance for informed consent applicable during the COVID-19 pandemic. The process is to be documented in the source documents.

### Source Data Verification/Monitoring

- In case on-site monitoring visits are not be possible, the site monitor may contact the investigator to arrange monitoring visits and activities remotely (in accordance with site and local requirements). Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

### Site Audits

- During the COVID-19 pandemic and at the impacted sites, study site GCP audits with direct impact/engagement from the investigator and study site personnel would not be conducted in order 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.

## 10.6. Appendix 6: Thrombotic Events to be Reported as Potential AESIs

At the time of protocol writing, the list of thrombotic events to be reported to the sponsor as potential AESIs is provided below. Further guidance may become available on thrombotic events of interest.

- MedDRA PTs for large vessel thrombosis and embolism

  Aortic embolus, aortic thrombosis, aseptic cavernous sinus thrombosis, brain stem embolism, brain stem thrombosis, carotid arterial embolus, carotid artery thrombosis, cavernous sinus thrombosis, cerebral artery thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, mesenteric artery embolism, mesenteric artery thrombosis, mesenteric vein thrombosis, splenic artery thrombosis, splenic embolism, splenic thrombosis, thrombosis mesenteric vessel, visceral venous thrombosis, hepatic artery embolism, hepatic artery thrombosis, hepatic vein embolism, hepatic vein thrombosis, portal vein embolism, portal vein thrombosis, portosplenomesenteric venous thrombosis, splenic vein thrombosis, spontaneous heparin-induced thrombocytopenia syndrome, femoral artery embolism, iliac artery embolism, jugular vein embolism, jugular vein thrombosis, subclavian artery embolism, subclavian vein thrombosis, obstetrical pulmonary embolism, pulmonary artery thrombosis, pulmonary thrombosis, pulmonary venous thrombosis, renal artery thrombosis, renal embolism, renal vein embolism, renal vein thrombosis, brachiocephalic vein thrombosis, vena cava embolism, vena cava thrombosis, truncus coeliacus thrombosis

- MedDRA PTs for more common thrombotic events

  Axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, MedDRA PTs for acute myocardial infarction*, MedDRA PTs for stroke*

Source: Shimabukuro T. CDC COVID-19 Vaccine Task Force. Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine. Advisory Committee on Immunization Practices (ACIP). April 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04-23.html.

*Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19 (as of 29 January 2021) https://www.cdc.gov/vaccinesafety/pdf/VAERS-v2-SOP.pdf

## 10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

### Amendment 1 (23 September 2021)

**Overall Rationale for the Amendment:** Based on Health Authority feedback, neutralizing antibody responses (assessed in the virus neutralization assay-A2 [VNA-A2]) will be added as secondary endpoint to the study to support the conclusions drawn from the comparisons using pre-F ELISA data as the primary endpoint.

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis<br>3 OBJECTIVES AND ENDPOINTS<br>8.1 Immunogenicity Assessments<br>9.4.3.2 Secondary and Exploratory Endpoint | Adding RSV neutralizing antibody responses (assessed in the virus neutralization assay-A2 [VNA-A2]) as secondary endpoint.<br>*Note: no change in volume of blood sampling required.* | Following Health Authority feedback. |
| 2.2 Background<br>11 REFERENCES | Experience with Ad26-vectored vaccines was added. | For alignment with the other supportive Phase 3 study protocols. |
| 4.2.1 Study-Specific Ethical Design Considerations | The results of this study may be made available to all participants through a plain language summary at the conclusion of the study according to local standards/restrictions. | For alignment with the other supportive Phase 3 study protocols. |
| 2.3.1 Risks Related to Study Participation<br>8.3.5 Pregnancy | In case of pregnancy, postnatal sequelae in the infant will not be followed-up.<br>*Note: Follow up info regarding the outcome of the pregnancy of the study participant themselves or of the partner of the participant will be requested (upon consent).* | According to the current Janssen SOP 'Receipt, Follow-up, and Reporting of Janssen Medicinal Product Individual Case Safety Reports', follow-up of postnatal sequelae in the infant is not a requirement.<br>The sponsor protocol template is planned to be modified to reflect this change. |
| 8.3.1 Time Period and Frequency for Collecting AE, SAE, and AESI Information<br>8.3.6.1 Thrombosis with Thrombocytopenia Syndrome | The word 'symptomatic' was deleted from the definition of thrombocytopenia. | Definition of thrombocytopenia is broadened to include all cases of thrombocytopenia the investigators observe (including asymptomatic thrombocytopenia observed in participant's routine blood test or blood test performed concomitantly to any AE/SAE/hospitalization, or any other) in the period of 6 months after vaccination; these should be reported as potential TTS cases (please refer to Section 8.3.6). |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. | Minor errors were noted |

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## 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 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 | 26-Nov-2021 13:09:12 (GMT) | Document Approval |