Janssen Vaccines & Prevention B.V.*

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate a Range of Dose Levels of an Ad26.RSV.preF-based Vaccine in Adults Aged 60 Years and Older

Protocol VAC18193RSV2005; Phase 2a

VAC18193 (JNJ-64400141/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).

Status: Approved
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Prepared by: Janssen Vaccines & Prevention B.V.
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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1.1. Synopsis

A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate a Range of Dose Levels of an Ad26.RSV.preF-based Vaccine in Adults Aged 60 Years and Older

The respiratory syncytial virus (RSV) vaccine that will be investigated in the current 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 (preF) derived from the RSV A2 strain.
- RSV preF protein (JNJ-64213175), a recombinant preF protein derived from the RSV A2 strain.

The aim of this dose-ranging study is to determine the safety and immunogenicity of different dose levels of Ad26.RSV.preF in the Ad26/protein preF RSV vaccine to support the refinement of the acceptance criteria for drug product release and stability by generating additional information on clinical safety (for the upper release limit) and immunogenicity (for the lower release limit).

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Cohort 1	
Primary	
• To explore the dose-response relationship of humoral immune responses induced by different dose levels of the Ad26.RSV.preF-based vaccine	• Antibody titers to RSV preF protein using preF enzyme-linked immunosorbent assay (ELISA) at 14 days after vaccination
Secondary	
• To explore the dose-response relationship of humoral and cellular immune responses induced by different dose levels of the Ad26.RSV.preF-based vaccine	• Antibody titers to RSV preF protein using preF ELISA at 3 and 6 months after vaccination • RSV A2 neutralizing antibody levels at 14 days and 3 and 6 months after vaccination • Interferon (IFN)-γ enzyme-linked immunospot (ELISpot) assay at 14 days and 3 and 6 months after vaccination
• To assess the safety and reactogenicity of different dose levels of the Ad26.RSV.preF-based vaccine	• Serious adverse events (SAEs) from the time of vaccination until the end of the study • Solicited local and systemic adverse events (AEs) from the time of vaccination until 7 days after vaccination • Unsolicited AEs from the time of vaccination until 28 days after vaccination

Objectives	Endpoints
Cohort 1	
Exploratory	
• To explore additional vaccine-elicited immune responses	Assays that may be used include, but are not limited to: • Post-F protein binding antibodies (ELISA) • Antigen-specific T-cell immune responses • RSV cross-neutralization of B and/or other A strain(s) • Anti-F protein antibody specificity characterization • Analysis of immunoglobulin (Ig)A and/or IgG antibodies binding to RSV F protein in prefusion and/or postfusion form in nasal samples • Analysis of neutralizing antibodies to Ad26

Objectives	Endpoints
Cohorts 2 and 3	
Primary	
• To assess the safety and reactogenicity of different dose levels of the Ad26.RSV.preF-based vaccine	• Solicited local and systemic AEs from the time of vaccination until 7 days after vaccination • Unsolicited AEs from the time of vaccination until 28 days after vaccination
Secondary	
• To assess the humoral and cellular immune responses induced by different dose levels of the Ad26.RSV.preF-based vaccine	• Antibody titers to RSV preF protein using preF ELISA at 14 days and 3 and 6 months after vaccination • RSV A2 neutralizing antibody levels at 14 days and 3 and 6 months after vaccination • IFN-γ ELISpot assay at 14 days and 3 and 6 months after vaccination
• To assess the safety of different dose levels of the Ad26.RSV.preF-based vaccine	• SAEs from the time of vaccination until the end of the study
Exploratory	
• To explore additional vaccine-elicited immune responses	Assays that may be used include, but are not limited to: • Post-F protein binding antibodies (ELISA) • Antigen-specific T-cell immune responses • RSV cross-neutralization of B and/or other A strain(s)

	• Anti-F protein antibody specificity characterization • Analysis of IgA and/or IgG antibodies binding to RSV F protein in prefusion and/or postfusion form in nasal samples • Analysis of neutralizing antibodies to Ad26

Hypothesis

No formal statistical testing of safety or immunogenicity data is planned; data will be analyzed descriptively.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, interventional Phase 2a study in male and female adults aged ≥60 years who are in stable health, to explore the dose-response relationship, safety, and immunogenicity of a range of dose levels of the Ad26.RSV.preF-based vaccine. Participants will be randomly assigned to different dose levels of Ad26.RSV.preF in the Ad26/protein preF RSV vaccine or to placebo in 3 cohorts. The study vaccine will be administered as a single IM injection.

Cohort	Group	N	Day 1 (Vaccination)
1 (dose-down)	1	50	Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg
	2	50	Ad26.RSV.preF 3.3×10^{10} vp + RSV preF protein 150 µg
	3	50	Ad26.RSV.preF 1.1×10^{10} vp + RSV preF protein 150 µg
	4	50	Ad26.RSV.preF 3.7×10^{9} vp + RSV preF protein 150 µg
	5	25	Placebo
2 (dose-up)	6	50	Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg
	7	50	Ad26.RSV.preF 1.3×10^{11} vp + RSV preF protein 150 µg
	8	25	Placebo
3 (dose-up)	9	25	Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg
	10	50	Ad26.RSV.preF 1.6×10^{11} vp + RSV preF protein 150 µg
	11	25	Placebo

N = number of participants; vp = viral particles.

The study duration will be approximately 6 months per participant. The end of the study is defined as the last participant's last visit.

An internal Data Review Committee (DRC) will be commissioned for this study, and pre-specified study vaccination pausing rules will be applied to ensure safety of the participants.

In the dose-down cohort (Cohort 1), a target of approximately 225 participants will be randomized in parallel in a 2:2:2:2:1 ratio to 5 groups. In the dose-up Cohort 2, a target of approximately 125 participants will be randomized in parallel in a 2:2:1 ratio to 3 groups. In the dose-up Cohort 3, a target of approximately 100 participants will be randomized in parallel in a 1:2:1 ratio to 3 groups. Cohorts 1 and 2 may be enrolled in parallel, whereas Cohorts 2 and 3 will be enrolled in a staggered manner. A study site will not simultaneously enroll participants in more than one cohort.

Initially, a sentinel group of 5 participants will be enrolled in Cohort 2 in a 2:2:1 ratio to Groups 6 to 8, respectively, before enrolling additional participants (Step 1). A blinded 24-hour postvaccination safety review will be performed by the principal investigator(s) (PI[s]) and sponsor team members (ie, at least the study responsible physician/study responsible scientist). In the absence of any clinical safety concerns, an additional 15 participants will be enrolled in a 2:2:1 ratio (Step 2). After review of the 7-day (Day 8) postvaccination safety data of these 20 participants by the DRC, the remaining participants in the cohort

will be randomized in a 2:2:1 ratio (Step 3). When all participants in Cohort 2 have completed the Day 8 postvaccination visit or discontinued earlier, all available safety data up to at least 7 days after vaccination of all participants in the cohort will be reviewed by the DRC. Based on this review, the sponsor may decide to not initiate enrollment of Cohort 3.

The enrollment of Cohort 3 will be conducted similarly to Cohort 2. Steps 1 and 2 will be performed with a sentinel group of 4 participants and with 12 participants, respectively, both enrolled in a 1:2:1 ratio. After review of the 7-day (Day 8) postvaccination safety data of these 16 participants by the DRC, the remaining participants in the cohort will be randomized in a 1:2:1 ratio.

After vaccination with study vaccine on Day 1, participants will remain under observation at the study site for a minimum of 30 minutes for presence of any acute reactions and solicited events, or longer if deemed necessary by the investigator. Any unsolicited and solicited local (injection site) or systemic AEs will be documented by the study-site personnel following this observation period. Each participant will record solicited local and systemic AEs and body temperature in the participant diary, beginning on the evening of the vaccination day and daily for 7 days after vaccination.

Nasosorption samples using synthetic absorptive matrix (SAM) strips, blood samples to assess humoral and cellular immune responses, and clinical safety laboratory blood samples (Cohorts 2 and 3 only) will be collected. Participant safety throughout the study will further be evaluated via physical examinations and vital signs.

NUMBER OF PARTICIPANTS

A target of approximately 450 participants will be randomly assigned to different dose levels of Ad26.RSV.preF in the Ad26/protein preF RSV vaccine or to placebo in 3 cohorts. In Cohort 1, a target of approximately 225 participants will be randomized, whereas in Cohorts 2 and 3, a target of 125 and 100 participants will be randomized, respectively.

VACCINATION GROUPS AND DURATION

The study duration will be approximately 6 months per participant. Participants in Cohort 1 will be screened on Day 1 (prevaccination), whereas participants in Cohorts 2 and 3 will be screened within 28 days before study vaccine administration to analyze clinical safety laboratory parameters before vaccination. The study further comprises study vaccination (active or placebo) on Day 1 and a 6-month safety and immunogenicity follow-up period.

If a participant meets any of the contraindications to vaccination at the scheduled time for study vaccination on Day 1, enrollment at a later date is permitted at the discretion of the PI and after discussion with the sponsor.

Study Vaccine Administration

On Day 1, participants will receive a single IM injection of study vaccine (ie, the Ad26/protein preF RSV vaccine or placebo) in the deltoid muscle. The injection will occur at the study site. The Ad26/protein preF RSV vaccine is composed of Ad26.RSV.preF (JNJ-64400141) and RSV preF protein (JNJ-64213175). Ad26.RSV.preF will be administered at a dose level ranging from 3.7×10^{9} viral particles (vp) to 1.6×10^{11} vp, and RSV preF protein at a constant dose level of 150 µg. Due to the different dose levels of Ad26.RSV.preF, the injection volumes of the study vaccine may differ between the cohorts. Ad26.RSV.preF and RSV preF protein will be supplied as solutions in separate single-use vials. Placebo will consist of 0.9% saline.

IMMUNOGENICITY EVALUATIONS

Venous blood samples of approximately 10 and 50 mL will be collected for the determination of humoral and cellular immune responses, respectively. Nasosorption samples using SAM strips will be collected for

immunogenicity assessments including, but not limited to, determination of antigen-specific immunoglobulin (IgG and IgA).

Assay	Purpose
Primary and secondary endpoints	
Pre-F protein binding antibody (ELISA)	Analysis of antibodies binding to RSV F protein in prefusion form
RSV A2 neutralization	Analysis of neutralizing antibodies to the A2 strain
IFN-γ (ELISpot)	T-cell IFN-γ responses to RSV F protein peptides
Exploratory endpoints	
Post-F protein binding antibody (ELISA)	Analysis of antibodies binding to RSV F protein in postfusion form
Antigen-specific T-cell immune responses	Analysis of T-cell responses to RSV F protein peptide-stimulated PBMCs (including, but not limited to, $CD4^+$/$CD8^+$, IL-2, IFN-γ, TNF-α, activation markers and memory) using ICS or CyTOF
RSV strain cross-neutralization	Analysis of cross-neutralizing antibodies to B and/or other A strain(s)
Antibody specificity and functional characterization	Analysis of pre- and post-F antibody specificity by functional assays such as ELISA, competition ELISA, and epitope mapping. Functional characterization of antibodies including, but not limited to, ADCC, ADCP, avidity, immunoglobulin isotype, and functional VNAs to other respiratory viruses
Analysis of nasal antibodies to RSV including, but not limited to, IgA and IgG	Analysis of nasal antibodies binding to RSV F protein in prefusion and/or postfusion form in nasal samples
Adenovirus neutralization assay	Analysis of neutralizing antibodies to Ad26

ADCC = antibody-dependent cell-mediated cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; CD = cluster of differentiation; CyTOF = cytometry by time of flight; ICS = intracellular cytokine staining; IL = interleukin; PBMC = peripheral bone marrow cell; TNF = tumor necrosis factor; VNA = virus neutralization assay.

SAFETY EVALUATIONS

Key safety assessments will include the monitoring of AEs, physical examinations, vital signs, and clinical safety laboratory assessments.

AEs and special reporting situations, whether serious or nonserious, that are related to study procedures or that are related to noninvestigational 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. All other unsolicited AEs and special reporting situations, whether serious or nonserious, will be reported from the time of vaccination until 28 days after vaccination. All AEs and SAEs leading to discontinuation of the study vaccination (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 other SAEs (regardless of the causal relationship) are to be reported from the time of vaccination until the end of the study/early withdrawal.

Any solicited local (injection site) or systemic AEs occurring during the 30-minute postvaccination observation period (or longer if deemed necessary by the investigator) will be documented by the study-site personnel following this observation period. Solicited AEs collected through a participant diary will be recorded from the time of vaccination until 7 days after vaccination.

STATISTICAL METHODS

Sample Size Determination

Immunogenicity (Cohort 1)

The primary objective of Cohort 1 is to explore the dose-response relationship of humoral immune responses (as measured by preF ELISA) induced by different dose levels of the Ad26/protein preF RSV vaccine.

Assuming:

- 10% of exclusions (eg, drop-outs, missing samples, and major protocol deviations impacting immunogenicity data)
- a standard deviation on the log_2 scale of the preF ELISA of 1.3 on Day 15 and 1.1 on Day 183 for all dose levels
- 4 dose levels

The linear model $log_2\ (preF\ ELISA_{timepoint}) = GMT\ preF\ ELISA_{Ad26/protein\ preF\ RSV\ vaccine\ (1x10^{11}\ vp\ /150\ \mu g),timepoint} + slope \times \#titration\ steps$ provides a standard error for the slope of 0.052 on Day 15 and 0.040 on Day 183 with 50 participants per arm. This is deemed sufficient for this exploratory study.

Safety (Cohorts 1, 2, and 3)

Placebo recipients are included for blinding and safety purposes and will provide additional control specimens for immunogenicity assays.

The observation of 0 events (eg, SAEs) is associated with 95% confidence that the true event rate is below the rates specified in the below table for the considered number of participants.

Sample Size	N=25	N=50	N=75
UL 95% one-sided CI	11.3%	5.8%	3.9%

CI = confidence interval; N = number of participants; UL = upper limit.

The table below provides the probability of observing at least one AE in a group of the considered sample size given several true AE rates.

True AE Rate (%)	Probability of Observing at Least One AE in N Participants (%)		
	N=25	N=50	N=75
0.5	12	22	31
1	22	39	53
2.5	47	72	85
10	93	99	100
25	100	100	100
50	100	100	100

N = number of participants.

Analysis Sets

Vaccine assignment will follow the as-treated principle.

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

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

The analysis of all immunogenicity endpoints will be based on the PPI set. For key tables, sensitivity immunogenicity analyses might also be performed on the FAS.

Immunogenicity Analyses

No formal statistical testing of immunogenicity data is planned. Immunogenicity data will be analyzed descriptively by cohort and group. In addition, for a selection of tables, data may be pooled over cohorts.

To explore the dose-response relationship between preF ELISA and different dose levels of the Ad26/protein preF RSV vaccine, a linear regression model will be fitted for each timepoint separately, using data of the active groups of Cohort 1, with the log-transformed preF ELISA titers at the considered timepoint as dependent variable, the number of titration steps as independent variable, and the geometric mean titer (GMT) of preF ELISA of the Ad26/protein preF RSV vaccine (1×10^{11} vp/150 μg) at the considered timepoint as a fixed intercept.

The linear model $log_2\ (preF\ ELISA_{timepoint}) = GMT\ preF\ ELISA_{Ad26/protein\ preF\ RSV\ vaccine\ (1x10^{11}\ vp/150\ ug),timepoint} + slope \times \#titration\ steps$ will initially be fitted for the active groups of Cohort 1 but may be extended in a later stage with data of the active groups of Cohorts 2 and 3. A similar model may be fitted as well for other assays.

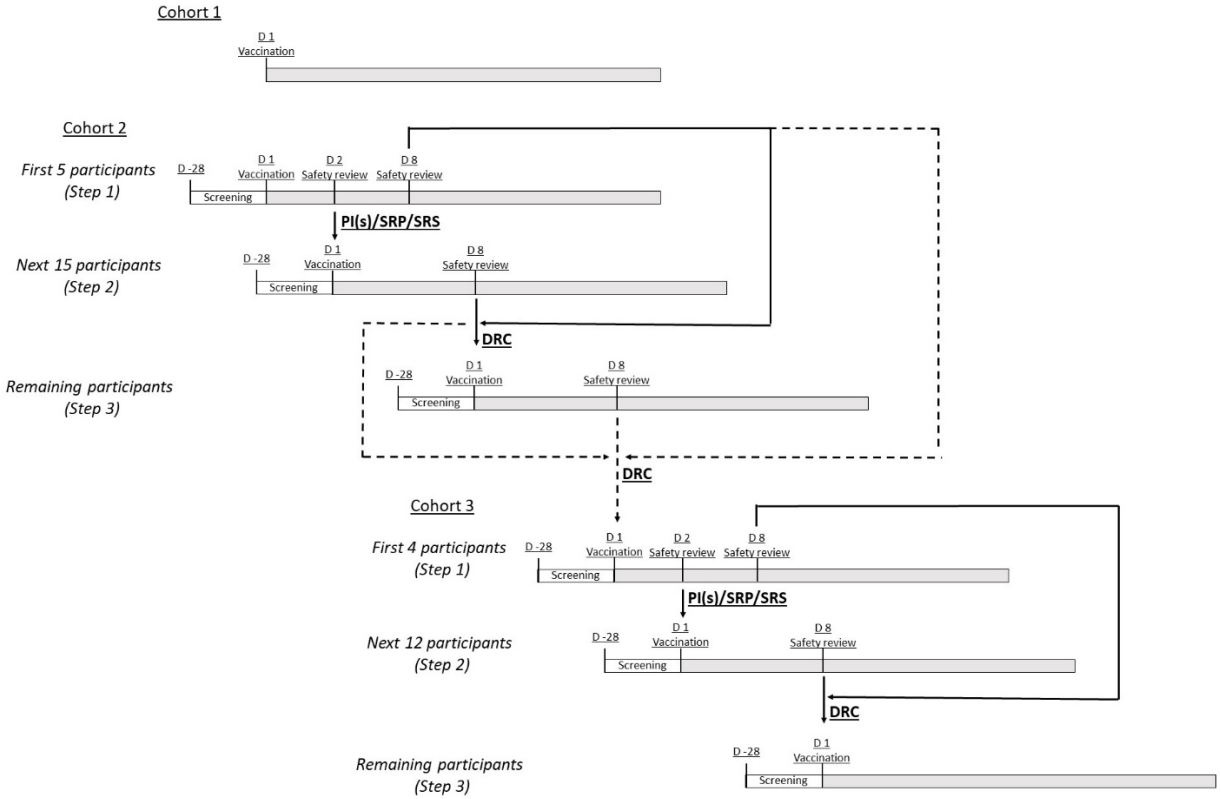
Depending on the model fit, other models (eg, log-linear models or EMAX models) may be explored as well.

Safety Analyses

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by cohort and group. In addition, for a selection of tables, data of Cohorts 2 and 3 may be pooled. All safety analyses will be based on the FAS.

1.2. Schema

Figure 1: Schematic Overview of the Study



D = Day.

Note that the scale of the timelines is arbitrary for clarity purposes.

In Cohort 2, a blinded 24-hour (Day 2) postvaccination safety review of the sentinel group of 5 participants will be performed by the PI(s) and sponsor team members (Step 1). In the absence of any clinical safety concerns, an additional 15 participants will be enrolled (Step 2). After review of the 7-day (Day 8) postvaccination safety data of these 20 participants by the DRC, the remaining participants in the cohort will be enrolled (Step 3). Based on the review of all available safety data up to at least 7 days after vaccination of all participants in Cohort 2 by the DRC (dashed line), the sponsor may decide to not initiate enrollment of Cohort 3.

The enrollment of Cohort 3 will be conducted similarly to Cohort 2. Steps 1 and 2 will be performed with a sentinel group of 4 participants and with 12 participants, respectively. After review of the 7-day (Day 8) postvaccination safety data of these 16 participants by the DRC, the remaining participants in the cohort will be enrolled.

1.3. Schedule of Activities

1.3.1. Cohort 1

Clinic Visit #	1	2[a]☎	3	4[a]☎	5	6	Early Exit[b]
Visit Timing	Vac	Vac + 7 d	Vac + 14 d	Vac + 28 d	Vac + 84 d (3 m)	Vac + 26 wk (6 m)	
Visit Day(s)	1	8	15	29	85	183	
Visit Window		±2 d	-3 d/+7 d	±7 d	±14 d	±14 d	
Visit Type	SCREENING AND STUDY VACCINATION	Safety	Safety and Immunogenicity	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Early Exit
Written informed consent[c]	❶						
Inclusion/exclusion criteria	❶						
Demographics	❶						
Medical history/prestudy therapy[d]	❶						
Physical examination[e]	❶		❼		❼	❼	❼
Vital signs[f]	❷		●		●	●	●
Randomization	❶						
Participant diary distribution	●						
Contraindications to vaccination[g]	❶						
Cellular immunity sample, mL	❶ 50		● 50		● 50	● 50	❹ 50
Humoral immunity sample, mL	❶ 10		● 10		● 10	● 10	❹ 10
Nasosorption sample	❶		●		●	●	●
Vaccination	●						
30-minute postvaccination observation[h]	●						
Solicited AE recording[i]	- - *Continuous* - -						❺
Unsolicited AE recording[j]	---------- *Continuous* ---------						❻
SAE recording[k]	---------- *Continuous* ----------						●
Concomitant therapy[l]	---------- *Continuous* ----------						●
Participant diary review of solicited AEs by study-site personnel[m]		●					
Blood draw volumes							
Approximate daily blood draw, mL	60	-	60	-	60	60	60
Approximate cumulative study blood draw, mL	60	60	120	120	180	240	-

d = day; m = month; Vac = vaccination; wk = week.

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

a. Can be electronic (eg, e-mail, text messages) or by phone.
b. 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).
c. Signing of the ICF should be done before any study-related activity.
d. Prestudy therapies administered up to 30 days before vaccination must be recorded.
e. A physical examination (including height and body weight) will be carried out at screening. At all other visits, an abbreviated, symptom-directed physical examination will be performed if deemed necessary by the investigator.
f. Systolic and diastolic blood pressure (supine) 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). Vital signs measurements should be taken before nasal sampling and blood draws, if applicable.
g. Investigator must check for acute illness or body temperature of ≥38.0°C (≥100.4ºF) at the time of vaccination. In such cases, the participant may be vaccinated up to, and no later than, 10 days after the scheduled vaccination, or be withdrawn from vaccination at the discretion of the investigator.
h. After vaccination, participants will be closely observed for a minimum of 30 minutes to monitor for the development of any acute reactions and solicited events, or longer if deemed necessary by the investigator. Any unsolicited and solicited local (injection site) or systemic AEs, and vital signs (heart and respiratory rate, systolic and diastolic blood pressure [supine], and body temperature) will be documented by the study-site personnel following this observation period.
i. Participants will be asked to note in the participant diary occurrences of injection site pain/tenderness, erythema, and swelling at the injection site daily. The extent (largest diameter) of any erythema and swelling should be measured using the supplied ruler and recorded daily. Body temperature (oral route preferred) should be measured at approximately the same time each day, preferably in the evening, using the supplied thermometer. If more than one measurement is made on any given day, the highest body temperature of that day will be used in the participant diary.
j. AEs and special reporting situations related to study procedures or to noninvestigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other AEs (unsolicited) and other special reporting situations will be reported from the time of vaccination until 28 days after vaccination. All AEs leading to discontinuation of study vaccination (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.
k. SAEs related to study procedures or to noninvestigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All SAEs leading to discontinuation of study vaccination (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 other SAEs (regardless of the causal relationship) are to be reported from the time of vaccination until the end of the study/early withdrawal.
l. Concomitant therapies such as analgesic/antipyretic medications and nonsteroidal anti-inflammatory drugs, corticosteroids, and antihistaminic must be recorded until 28 days after vaccination. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 10.3, Appendix 3.
m. Participants will be contacted at Day 8 to review the information noted in the participant diary. If the participant diary review is missed, the diary information will be reviewed during the following visit. The participant diary will be collected at the Day 15 visit.

1.3.2. Cohorts 2 and 3

Clinic Visit #	1	2	3	4	5[a] ☎	6	7	Early Exit[b]
Visit Timing		Vac	Vac + 7 d	Vac + 14 d	Vac + 28 d	Vac + 84 d (3 m)	Vac + 26 wk (6 m)	
Visit Day(s)	-28 to -1	1[c]	8	15	29	85	183	
Visit Window			±2 d	-3 d/+7 d	±7 d	±14 d	±14 d	
Visit Type	Screening	STUDY VACCINATION	Safety	Safety and Immunogenicity	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Early Exit
Written informed consent[d]	●							
Inclusion/exclusion criteria	●							
Demographics	●							
Medical history/prestudy therapy[e]	●	❶						
Physical examination[f]	●	❶❼	❼	❼		❼	❼	❼
Vital signs[g]	●	❷	●	●		●	●	●
Randomization		❶						
Participant diary distribution		●						
Inclusion/exclusion criteria check[h]		❶						
Contraindications to vaccination[i]		❶						
Clinical safety laboratory blood sample, mL	● 10	❶ 5	● 5					❸ 5
Cellular immunity sample, mL		❶ 50		● 50		● 50	● 50	❹ 50
Humoral immunity sample, mL		❶ 10		● 10		● 10	● 10	❹ 10
Nasosorption sample		❶		●		●	●	●
Vaccination		●						
30-minute postvaccination observation[j]		●						
Solicited AE recording[k]		- - *Continuous* - -						❺
Unsolicited AE recording[l]		- - - - - - - - - - *Continuous* - - - - - - - - -						❻
SAE recording[m]		- - - - - - - - - - *Continuous* - - - - - - - - - - - - - - - -						●
Concomitant therapy[n]		- - - - - - - - - - *Continuous* - - - - - - - - - - - - - - - -						●
Participant diary review of solicited AEs by study-site personnel			●					
Blood draw volumes								
Approximate daily blood draw, mL	10	65	5	60	-	60	60	65
Approximate cumulative study blood draw, mL	10	75	80	140	140	200	260	-

d = day; m = month; Vac = vaccination; wk = week.

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

a. Can be electronic (eg, e-mail, text messages) or by phone.
b. 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).
c. In addition, the first 4 participants in each cohort will be contacted by phone 24 hours after vaccination. In the absence of any clinical safety concerns, the remaining 8 participants of the cohort can be enrolled.
d. Signing of the ICF should be done before any study-related activity.
e. Prestudy therapies administered up to 30 days before vaccination must be recorded.
f. A physical examination (including height and body weight) will be carried out at screening. At all other visits, an abbreviated, symptom-directed physical examination will be performed if deemed necessary by the investigator.
g. Systolic and diastolic blood pressure (supine) 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). Vital signs measurements should be taken before nasal sampling and blood draws, if applicable.
h. To review inclusion criterion 3 and exclusion criteria 2, 8, 9, 10, 11, and 12.
i. Investigator must check for acute illness or body temperature of ≥38.0°C (≥100.4ºF) at the time of vaccination. In such cases, the participant may be vaccinated up to, and no later than, 10 days after the scheduled vaccination, or be withdrawn from vaccination at the discretion of the investigator.
j. After vaccination, participants will be closely observed for a minimum of 30 minutes to monitor for the development of any acute reactions and solicited events, or longer if deemed necessary by the investigator. Any unsolicited and solicited local (injection site) or systemic AEs, and vital signs (heart and respiratory rate, systolic and diastolic blood pressure [supine], and body temperature) will be documented by the study-site personnel following this observation period.
k. Participants will be asked to note in the participant diary occurrences of injection site pain/tenderness, erythema, and swelling at the injection site daily. The extent (largest diameter) of any erythema and swelling should be measured using the supplied ruler and recorded daily. Body temperature (oral route preferred) should be measured at approximately the same time each day, preferably in the evening, using the supplied thermometer. If more than one measurement is made on any given day, the highest body temperature of that day will be used in the participant diary.
l. AEs and special reporting situations related to study procedures or to noninvestigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All other AEs (unsolicited) and other special reporting situations will be reported from the time of vaccination until 28 days after vaccination. All AEs leading to discontinuation of study vaccination (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.
m. SAEs related to study procedures or to noninvestigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. All SAEs leading to discontinuation of study vaccination (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 other SAEs (regardless of the causal relationship) are to be reported from the time of vaccination until the end of the study/early withdrawal.
n. Concomitant therapies such as analgesic/antipyretic medications and nonsteroidal anti-inflammatory drugs, corticosteroids, and antihistaminic must be recorded until 28 days after vaccination. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 10.3, Appendix 3.

2. INTRODUCTION

The respiratory syncytial virus (RSV) vaccine that will be investigated in the current 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 (preF) derived from the RSV A2 strain.
- RSV preF protein (JNJ-64213175), a recombinant preF 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 versions of the Investigator's Brochures (IBs) for Ad26.RSV.preF and RSV preF protein.[8,9]

The term "study vaccine" used throughout the protocol refers to the Ad26/protein preF RSV vaccine or placebo.

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 dose-ranging study is to determine the safety and immunogenicity of different dose levels of Ad26.RSV.preF in the Ad26/protein preF RSV vaccine to support the refinement of the acceptance criteria for drug product release and stability by generating additional information on clinical safety (for the upper release limit) and immunogenicity (for the lower release limit).

2.2. Background

RSV is an important cause of serious respiratory infections in adults aged ≥60 years, immunocompromised individuals, and those with underlying chronic cardiopulmonary conditions.[5] Exact numbers on the burden of RSV disease in adults aged ≥60 years 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.[6] In the United States, 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.[5] These data support the importance of developing a safe and effective vaccine for certain adult populations, such as older adults. Currently, there are no vaccines or specific treatments available for RSV.

Several studies have suggested that decreased protection against RSV in older adults could be attributed to an age-related decline in interferon (IFN)-γ production by peripheral blood mononuclear cells, a reduced ratio of cluster of differentiation (CD)8^+ to $CD4^+$ T cells, and reduced numbers of circulating RSV-specific $CD8^+$ memory T cells.[4,12,13] High levels of serum

neutralizing antibody are associated with less severe infections in older adults.[19] The Ad26.RSV.preF vaccine component being evaluated in this protocol is based on the AdVac® platform which has been shown to promote a strong antibody response as well as cellular responses.[2,3,10,15]

2.2.1. Ad26.RSV.preF and RSV preF Protein Nonclinical Studies

Ad26.RSV.preF and RSV preF protein were immunogenic when IM administered as single components in various RSV-naïve or pre-exposed animal models. In RSV-naïve and pre-exposed mice, the combination of RSV preF protein with a suboptimal dose of Ad26.RSV.preF, either together in a 1-dose immunization or in a heterologous 2-dose schedule, gave higher virus neutralizing titers (VNTs) than immunization with Ad26.RSV.preF alone. In RSV pre-exposed nonhuman primates (NHPs), the combination of the human dose of both Ad26.RSV.preF and RSV preF protein induced high VNTs. Due to the high VNT response induced by the high dose of Ad26.RSV.preF alone, there was no significant difference observed with the VNT induced by the combination of RSV preF protein and Ad26.RSV.preF. In both RSV pre-exposed mice and NHPs, Ad26.RSV.preF induced Th1-skewed cellular responses, in combination with RSV preF protein and alone, as suggested by IFN-γ enzyme-linked immunospot (ELISpot) assays and intracellular cytokine staining (ICS). In contrast, RSV preF protein alone induced only low cellular responses. In RSV pre-exposed NHPs, immunization with the combination of Ad26.RSV.preF and RSV preF protein boosted pre-existing neutralizing antibody responses against a panel of different RSV A and B strains, including recent clinical isolates. VNTs against RSV A strains were monitored for 55 weeks in NHPs after a single injection and maintained above pre-exposure levels.

In the naïve cotton rat efficacy model, a 1-dose immunization with Ad26.RSV.preF and a 2-dose immunization regimen with alum-adjuvanted RSV preF protein induced VNTs and gave full lower and upper respiratory tract protection in 100% of animals after RSV A2 intranasal challenge. Due to the high efficacy of Ad26.RSV.preF alone in the naïve cotton rat model even at lowest doses that elicited an immune response, the value of the addition of RSV preF protein for protection of lower respiratory tract could not be evaluated. However, upper respiratory tract protection was significantly improved by addition of the preF protein to suboptimal doses of Ad26.RSV.preF.

2.2.2. Ad26.RSV.preF and RSV preF Protein Clinical Studies

At the time of protocol writing, 2 Phase 1 studies (VAC18193RSV1003 and VAC18193RSV1005) and 2 Phase 2a studies (VAC18193RSV2002 and VAC18193RSV2003) with Ad26.RSV.preF have been completed. Three Phase 1/2a studies (VAC18193RSV1004, VAC18194RSV2001, and VAC18194RSV2002) and one Phase 2b study (VAC18193RSV2001) are ongoing (Table 1).

Table 1: Overview of Clinical Studies With Ad26.RSV.preF

Study Identifier Study Status	Clinical Phase	Vaccine	N	Study Population
Senior Program				
VAC18193RSV1003 Completed	1	Ad26.RSV.preF	72	Adult participants aged 60 years and older in stable health
VAC18193RSV1005 Completed*	1	Ad26.RSV.preF	24	Adult participants aged 18 years and older in stable health (including 3 participants aged >65 years)
VAC18193RSV2002 Completed	2a	Ad26.RSV.preF	63	Healthy adult participants aged 18 to 50 years
VAC18193RSV2003 Completed	2a	Ad26.RSV.preF	180	Adult participants aged 60 years and older in stable health
VAC18193RSV1004 Ongoing	1/2a	Ad26.RSV.preF/ RSV preF protein	667	Adult participants aged 60 years and older in stable health
VAC18193RSV2001 Ongoing	2b	Ad26.RSV.preF/ RSV preF protein	5,800	Adult participants aged 65 years and older with and without comorbidities
Junior Program				
VAC18194RSV2001 Ongoing	1/2a	Ad26.RSV.preF	12 adults 36 toddlers	Healthy adult participants aged 18 to 50 years and healthy RSV-seropositive toddlers aged 12 to 24 months
VAC18194RSV2002 Ongoing	1/2a	Ad26.RSV.preF	48 toddlers	Healthy RSV-seronegative toddlers aged 12 to 24 months

* Clinical study report writing in progress.
Clinical studies are ordered to align with the order in the clinical development plan.
N = actual number of participants (for completed studies) or planned number of participants (for ongoing studies).

Study **VAC18193RSV1003** is a completed single-center, randomized, placebo-controlled, double-blind, first-in-human Phase 1 study for the Ad26.RSV.preF vaccine, and demonstrated that Ad26.RSV.preF was safe and well tolerated at 2 doses (5×10^{10} viral particles [vp] and 1×10^{11} vp) and can elicit durable (up to 2 years) humoral and cellular immune responses against RSV. The data suggested a trend towards higher humoral responses after vaccination with the higher dose level of Ad26.RSV.preF compared with the lower dose level.

After the safety, tolerability, and immunogenicity profile of Ad26.RSV.preF was first established in study VAC18193RSV1003, study **VAC18193RSV2002**, a completed single-center, randomized, placebo-controlled, double-blind exploratory Phase 2a human challenge study, was conducted in participants aged 18 to 50 years to evaluate the prophylactic efficacy of a single immunization of Ad26.RSV.preF against RSV infection in a virus challenge model. There was a statistically significant reduction in the viral load as measured by the area under the curve (VL-AUC) in the Ad26.RSV.preF group compared with placebo, and Ad26.RSV.preF vaccination was associated with lower peak viral loads (by quantitative reverse transcriptase polymerase chain reaction), lower VL-AUC (by quantitative culture), and a substantial reduction in the median area under the curve of the total clinical symptom score. Immunization with Ad26.RSV.preF substantially reduced the proportion of participants infected by RSV after challenge. Symptoms of RSV infection and RSV viral load by quantitative culture were markedly reduced in Ad26.RSV.preF vaccinated participants with breakthrough RSV infection compared with placebo. Vaccination with Ad26.RSV.preF induced favorable humoral immune responses compared with placebo as measured prior to RSV challenge.

With the availability of clinical trial material (CTM) for RSV preF protein and taking the results of the VAC18193RSV1003 and VAC18193RSV2002 studies into account, the following clinical studies with Ad26.RSV.preF and RSV preF protein were initiated and are ongoing:

Study **VAC18193RSV1004** is a multicenter, randomized, double-blind, placebo-controlled Phase 1/2a regimen selection study in 667 participants aged ≥60 years in stable health to evaluate the safety and immunogenicity of Ad26.RSV.preF alone, of combinations of Ad26.RSV.preF and RSV preF protein, and of separate administration of Ad26.RSV.preF and RSV preF protein. A significant increase in humoral immune responses including virus neutralization assays (VNAs) and preF antibody titers was observed in the groups combining Ad26.RSV.preF and RSV preF protein compared with Ad26.RSV.preF alone. No relevant differences between the combination groups and Ad26.RSV.preF alone were noted for cellular immune responses measured at the time of primary analysis. All regimens had acceptable safety and reactogenicity profiles, which were similar across groups. Available safety data support that this vaccine is safe and has an acceptable reactogenicity profile.

Study **VAC18193RSV2001** is a multicenter, randomized, double-blind, placebo-controlled Phase 2b proof-of-concept study in approximately 5,800 participants aged ≥65 years with and without comorbidities to confirm the potential for efficacy of the Ad26/protein preF RSV vaccine and to assess 3 case definitions of RSV-mediated lower respiratory tract disease.

2.3. Benefit-risk Assessment

Below, the known and potential benefits and risks of VAC18193 (JNJ-64400141/JNJ-64213175) are discussed. More detailed information about the known and expected benefits and risks of the Ad26/protein preF RSV vaccine may be found in the IBs for Ad26.RSV.preF[8] and RSV preF protein[9].

2.3.1. Known Benefits

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

2.3.2. Potential Benefits

The Ad26/protein preF RSV vaccine is under development for prophylaxis of RSV, however, vaccine efficacy has not yet been evaluated. Based on preliminary immunogenicity data, there could be a potential benefit from RSV vaccination in terms of immune response: vaccination could raise an immune response which might confer additional protection against a future RSV infection (Section 2.2.2). The individual benefit from vaccination for the participants at the current development stage is not known.

Participants may benefit from clinical testing and physical examination; others may benefit from the knowledge that they may aid in the development of an RSV vaccine.

2.3.3. Known Risks

All vaccines have the potential to cause adverse experiences. To date, limited clinical data with the Ad26/protein preF RSV vaccine showed an acceptable safety and reactogenicity profile (Section 2.2.2).

2.3.4. Potential Risks

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

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 at vaccine injection sites. Participants may exhibit general signs and symptoms associated with administration of a vaccine, or vaccination with placebo, 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 injury from falling. 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 allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine components (including any of the constituents of the study vaccine) will be excluded from the study. Study sites should have medical treatment available in case of severe allergic reactions following vaccine administration.

Risks Related to Adenoviral-vectored Vaccines

Safety data available from 23 clinical studies in 3,694 adults vaccinated with Ad26-vectored vaccine candidates, in which Ad26 with different inserts has been evaluated at dose levels ranging from 1×10^{9} to 1×10^{11} vp, indicate that no safety concerns would be anticipated from vaccination with Ad26.RSV.preF at dose levels up to and including 1×10^{11} vp.[1]

Postvaccination reactogenicity after administration of Ad26-based vaccines have consisted of mild to moderate adverse events (AEs), including local injection site reactions (most frequently injection site pain), and malaise, fatigue, headache, and myalgia. A trend towards an increase in the incidence of injection site pain and arthralgia, chills, fatigue, headache, malaise, myalgia, and nausea with an increase in Ad26 dose level was observed. There was no clear trend in the frequency of unsolicited AEs with increasing the Ad26 dose level. Transient decreases in neutrophil counts have been associated with adenovirus-based vaccines, and decrease in hemoglobin from baseline was the most frequent laboratory abnormality.[1]

Risks Related to RSV preF Protein

RSV preF protein is being evaluated in the ongoing studies VAC18193RSV1004 and VAC18193RSV2001. To date, limited clinical data have shown an acceptable safety and reactogenicity profile.

Risks from Collection of Nasosorption Samples

Nasosorption sampling is more comfortable and less invasive than using a conventional swab (which may cause nose bleeds).

Risks from Blood Draws

As with all clinical studies requiring blood sampling, there are risks associated with venipuncture and multiple blood sample collection. Blood drawing may cause pain, tenderness, bruising, bleeding, dizziness, vaso-vagal response, syncope, and, rarely, infection at the site where the blood is taken. The total blood volume to be collected is considered to be an acceptable amount of blood over this time period from the population in this study (Section 4.2.1). Participants with contraindications to IM injections and blood draws (eg, bleeding disorders) will be excluded.

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.

Concomitant Vaccination

Concomitant vaccination might have an influence on both the safety profile and immunogenicity of Ad26.RSV.preF and/or RSV preF protein. Likewise, Ad26.RSV.preF and/or RSV preF protein might have an influence on both the safety profile and immunogenicity of any concomitant vaccination. As a result, 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.

Reproductive Risks and Pregnancy

The effect of Ad26.RSV.preF and RSV preF protein on a fetus or nursing baby is unknown. Female 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. Women who have had hysterectomies are also eligible for the study. Because the effect on sperm is unknown, male participants must inform the study-site personnel if their partner becomes pregnant during the study. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Unknown Risks

There may be other risks that are not known. If any significant new risks are identified, the principal investigator (PI) and participants will be informed.

2.3.5. Overall Benefit-risk Assessment

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

- The dose level of 1×10^{11} vp for Ad26.RSV.preF and 150 µg for RSV preF protein (administered in all 3 cohorts) was selected from the primary analysis of Cohort 2 in study VAC18193RSV1004 and is currently under further evaluation in studies VAC18193RSV1004 and VAC18193RSV2001 (Section 4.1). Available safety data of study VAC18193RSV1004 support that this vaccine is safe and has an acceptable reactogenicity profile at a dose level up to 1×10^{11} vp (Section 2.2.2). As no data are available for higher dose levels, adequate safety measures will be taken to minimize the risk to participants (see below).
- Only participants who meet all inclusion criteria (Section 5.1) and none of the exclusion criteria (Section 5.2) 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 (including the recording of AEs, physical examinations, vital signs, and clinical safety laboratory assessments) 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 (Section 1.3).
  - After vaccination, participants will remain at the study site for a minimum of 30 minutes, or longer if deemed necessary by the investigator, and will be closely observed by study-site personnel. Necessary emergency equipment and medications must be available at the study site to treat severe allergic reactions. Participants will use a participant diary to document solicited local and systemic symptoms. Details are provided in Sections 8.2 and 8.3.
  - The investigator or the designee will document unsolicited AEs as indicated in Section 8.3.1.
  - After vaccination, participants will enter a 6-month safety and immunogenicity follow-up period. All AEs, serious adverse events (SAEs), and clinically significant laboratory abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until clinical resolution or until a clinically stable endpoint 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 7.4).

- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:
  - An internal Data Review Committee (DRC) will be commissioned for this study (Section 9.6). In addition to the planned review of postvaccination safety data of participants in Cohorts 2 and 3, the DRC will be consulted if at least one of the study vaccination pausing rules has been met and/or if the participant's safety may be threatened.
  - There are prespecified rules that would result in pausing of further vaccination of participants if predefined conditions occur, preventing exposure of new participants to study vaccine until the DRC reviews all available safety data and subsequent communication between the sponsor and the PI(s) takes place (Section 7.3). When a first DRC meeting has been triggered by the occurrence of a given study vaccination pausing rule, the DRC will convene thereafter for each additional participant meeting that pausing rule. Possible actions upon review include, but are not limited to, study suspension, study adaptation, or discontinuation of further vaccination.
  - In Cohort 2, a sentinel group of 5 participants will be enrolled before enrolling additional participants (Step 1) (Section 4.1). In the absence of any clinical safety concerns upon a blinded 24-hour postvaccination safety review, an additional 15 participants will be enrolled (Step 2). After review of the 7-day (Day 8) postvaccination safety data of these 20 participants by the DRC, the remaining participants will be enrolled (Step 3).
  - The enrollment of Cohort 3 will be conducted similarly to Cohort 2. Steps 1 and 2 will be performed with a sentinel group of 4 participants and with 12 participants, respectively, both enrolled in a 1:2:1 ratio. After review of the 7-day (Day 8) postvaccination safety data of these 16 participants by the DRC, the remaining participants in the cohort will be randomized in a 1:2:1 ratio.
  - Cohorts 2 and 3 will be enrolled in a staggered manner (Section 4.1). Based on the review of all available safety data up to at least 7 days after vaccination of all participants in Cohort 2 by the DRC, the sponsor may decide to not initiate enrollment of Cohort 3.
  - Contraindications to vaccination are included in Section 7.2.

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with the Ad26/protein preF RSV vaccine are justified by the anticipated benefits that may be obtained.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Cohort 1	
Primary	
• To explore the dose-response relationship of humoral immune responses induced by different dose levels of the Ad26.RSV.preF-based vaccine	• Antibody titers to RSV preF protein using preF enzyme-linked immunosorbent assay (ELISA) at 14 days after vaccination
Secondary	
• To explore the dose-response relationship of humoral and cellular immune responses induced by different dose levels of the Ad26.RSV.preF-based vaccine	• Antibody titers to RSV preF protein using preF ELISA at 3 and 6 months after vaccination • RSV A2 neutralizing antibody levels at 14 days and 3 and 6 months after vaccination • IFN-γ ELISpot assay at 14 days and 3 and 6 months after vaccination
• To assess the safety and reactogenicity of different dose levels of the Ad26.RSV.preF-based vaccine	• SAEs from the time of vaccination until the end of the study • Solicited local and systemic AEs from the time of vaccination until 7 days after vaccination • Unsolicited AEs from the time of vaccination until 28 days after vaccination
Exploratory	
• To explore additional vaccine-elicited immune responses	Assays that may be used include, but are not limited to: • Post-F protein binding antibodies (ELISA) • Antigen-specific T-cell immune responses • RSV cross-neutralization of B and/or other A strain(s) • Anti-F protein antibody specificity characterization • Analysis of immunoglobulin (Ig)A and/or IgG antibodies binding to RSV F protein in prefusion and/or postfusion form in nasal samples • Analysis of neutralizing antibodies to Ad26

Objectives	Endpoints
Cohorts 2 and 3	
Primary	
• To assess the safety and reactogenicity of different dose levels of the Ad26.RSV.preF-based vaccine	• Solicited local and systemic AEs from the time of vaccination until 7 days after vaccination • Unsolicited AEs from the time of vaccination until 28 days after vaccination
Secondary	
• To assess the humoral and cellular immune responses induced by different dose levels of the Ad26.RSV.preF-based vaccine	• Antibody titers to RSV preF protein using preF ELISA at 14 days and 3 and 6 months after vaccination • RSV A2 neutralizing antibody levels at 14 days and 3 and 6 months after vaccination • IFN-γ ELISpot assay at 14 days and 3 and 6 months after vaccination
• To assess the safety of different dose levels of the Ad26.RSV.preF-based vaccine	• SAEs from the time of vaccination until the end of the study
Exploratory	
• To explore additional vaccine-elicited immune responses	Assays that may be used include, but are not limited to: • Post-F protein binding antibodies (ELISA) • Antigen-specific T-cell immune responses • RSV cross-neutralization of B and/or other A strain(s) • Anti-F protein antibody specificity characterization • Analysis of IgA and/or IgG antibodies binding to RSV F protein in prefusion and/or postfusion form in nasal samples • Analysis of neutralizing antibodies to Ad26

Refer to Section 8 for evaluations related to endpoints.

HYPOTHESIS

No formal statistical testing of safety or immunogenicity data is planned; data will be analyzed descriptively.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter, interventional Phase 2a study in male and female adults aged ≥60 years who are in stable health, to explore the dose-response relationship, safety, and immunogenicity of a range of dose levels of the Ad26.RSV.preF-based vaccine. A target of approximately 450 participants will be randomly assigned to different dose levels of Ad26.RSV.preF in the Ad26/protein preF RSV vaccine or to placebo in 3 cohorts (Table 2). The study vaccine will be administered as a single IM injection.

Table 2: Overview of the Cohorts, Groups, and Targeted Number of Participants

Cohort	Group	N	Day 1 (Vaccination)
1 (dose-down)	1	50	Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg
	2	50	Ad26.RSV.preF 3.3×10^{10} vp + RSV preF protein 150 µg
	3	50	Ad26.RSV.preF 1.1×10^{10} vp + RSV preF protein 150 µg
	4	50	Ad26.RSV.preF 3.7×10^{9} vp + RSV preF protein 150 µg
	5	25	Placebo
2 (dose-up)	6	50	Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg
	7	50	Ad26.RSV.preF 1.3×10^{11} vp + RSV preF protein 150 µg
	8	25	Placebo
3 (dose-up)	9	25	Ad26.RSV.preF 1×10^{11} vp + RSV preF protein 150 µg
	10	50	Ad26.RSV.preF 1.6×10^{11} vp + RSV preF protein 150 µg
	11	25	Placebo

N = number of participants.

The study duration will be approximately 6 months per participant. Participants in Cohort 1 will be screened on Day 1 (prevaccination), whereas participants in Cohorts 2 and 3 will be screened within 28 days before study vaccine administration to analyze clinical safety laboratory parameters before vaccination. (Section 1.3). The study further comprises study vaccination (active or placebo) 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 (Section 4.4).

In the dose-down cohort (Cohort 1), a target of approximately 225 participants will be randomized in parallel in a 2:2:2:2:1 ratio to 5 groups (Table 2). Participants in Groups 1 to 4 will receive different dose levels of Ad26.RSV.preF (ranging from 1×10^{11} vp to 3.7×10^{9} vp) and a constant dose level of RSV preF protein (150 µg) (Section 4.3). Participants in Group 5 will receive placebo.

In the dose-up Cohort 2, a target of approximately 125 participants will be randomized in parallel in a 2:2:1 ratio to 3 groups (Table 2). Participants in Groups 6 and 8 will receive 1×10^{11} vp Ad26.RSV.preF/150 µg RSV preF protein and placebo, respectively, while participants in Group 7 will receive 1.3×10^{11} vp Ad26.RSV.preF/150 µg RSV preF protein.

In the dose-up Cohort 3, a target of approximately 100 participants will be randomized in parallel in a 1:2:1 ratio to 3 groups. Participants in Groups 9 and 11 will receive 1×10^{11} vp

Ad26.RSV.preF/150 µg RSV preF protein and placebo, respectively, while participants in Group 10 will receive 1.6×10^{11} vp Ad26.RSV.preF/150 µg RSV preF protein (Section 4.3).

Cohorts 1 and 2 may be enrolled in parallel, whereas Cohorts 2 and 3 will be enrolled in a staggered manner (Figure 1). A study site will not simultaneously enroll participants in more than one cohort. Cohort enrollment to each study site will be controlled via the interactive web response system (IWRS).

Initially, a sentinel group of 5 participants will be enrolled in Cohort 2 in a 2:2:1 ratio to Groups 6 to 8, respectively, before enrolling additional participants (Step 1). A blinded 24-hour postvaccination safety review will be performed by the PI(s) and sponsor team members (ie, at least the study responsible physician [SRP]/study responsible scientist [SRS]). In the absence of any clinical safety concerns, an additional 15 participants will be enrolled in a 2:2:1 ratio (Step 2). After review of the 7-day (Day 8) postvaccination safety data of these 20 participants by the DRC, the remaining participants in the cohort will be randomized in a 2:2:1 ratio (Step 3). When all participants in Cohort 2 have completed the Day 8 postvaccination visit or discontinued earlier, all available safety data up to at least 7 days after vaccination of all participants in the cohort will be reviewed by the DRC. Based on this review, the sponsor may decide to not initiate enrollment of Cohort 3.

The enrollment of Cohort 3 will be conducted similarly to Cohort 2. Steps 1 and 2 will be performed with a sentinel group of 4 participants and with 12 participants, respectively, both enrolled in a 1:2:1 ratio. After review of the 7-day (Day 8) postvaccination safety data of these 16 participants by the DRC, the remaining participants in the cohort will be randomized in a 1:2:1 ratio.

The planned primary and final analyses of all cohorts are detailed in Section 9.5. The primary analyses of Cohorts 2 and 3 will be combined.

After vaccination with study vaccine on Day 1, participants will remain under observation at the study site for a minimum of 30 minutes for presence of any acute reactions and solicited events, or longer if deemed necessary by the investigator. Any unsolicited and solicited local (injection site) or systemic AEs will be documented by the study-site personnel following this observation period. Participants will be given a thermometer, ruler, and a daily assessment (participant) diary with instructions for the proper recording of events. Each participant will record solicited local and systemic AEs and body temperature in the participant diary, beginning on the evening of the vaccination day and daily for 7 days after vaccination. Body temperature should be taken at approximately the same time each day. Study-site personnel will collect and review participant diary information and confirm the entries at the next visit.

The reporting periods of AEs, SAEs, and special reporting situations are detailed in Section 8.3. Reporting periods for concomitant therapy are outlined in Section 6.5.

Nasosorption samples using synthetic absorptive matrix (SAM) strips will be collected on Day 1 (prevaccination) and at 14 days and 3 and 6 months after vaccination (Section 8.1). Blood

samples to assess humoral and cellular immune responses will be collected on Day 1 (prevaccination) and at 14 days and 3 and 6 months after vaccination (Section 8.1). Clinical safety laboratory blood samples (Cohorts 2 and 3 only) will be collected at the screening visit, on Day 1 (prevaccination), and at 7 days after vaccination (or at the early exit visit if this visit is within 8 days after vaccination and the participant discontinues the study without withdrawing consent) (Section 8.2.3). Participant safety throughout the study will further be evaluated via physical examinations and vital signs (Sections 8.2.1 and 8.2.2, respectively).

If a participant meets any of the contraindications to vaccination at the scheduled time for study vaccination on Day 1, enrollment at a later date is permitted at the discretion of the PI and after discussion with the sponsor (Section 7.2). Prior to vaccination on Day 1, a recheck of a selection of inclusion and exclusion criteria will be performed for participants in Cohorts 2 and 3 only. Participants who fail this recheck may be enrolled at a later date at the discretion of the PI and after discussion with the sponsor. Criteria for participant discontinuation/withdrawal from the study, together with the respective actions that must be undertaken, are described in Section 7.

An internal DRC will be commissioned for this study. Refer to Section 9.6 for details.

A diagram of the study design is provided in Section 1.2.

4.2. Scientific Rationale for Study Design

Blinding, Control, Vaccination Groups

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

Vaccine Component Selection

The rationale behind the selection of Ad26.RSV.preF and RSV preF protein is described in Section 2.2.

Dose Level Selection

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

Staggered Cohort Enrollment and Stepwise Approach

This is the first time that healthy participants will be vaccinated with Ad26.RSV.preF at a dose level of 1.3×10^{11} vp or 1.6×10^{11} vp. Therefore, Cohorts 2 and 3 will be enrolled in a staggered manner to allow a review of all available safety data up to at least 7 days after vaccination of all participants in Cohort 2 by the DRC before enrolling participants in Cohort 3. Based on this

review, the sponsor may decide to not initiate enrollment of Cohort 3. In addition, participants in Cohorts 2 and 3 will be enrolled in a stepwise approach.

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 in stable health who will receive no direct benefit from participation in the study, except for financial compensation for the time and inconveniences that may arise from participation in the study. Refer to Section 2.3 for details on potential and known benefits and risks, and for the safety measures taken to minimize risk to participants.

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 United States Department of Health and Human Services Office for Human Research Protections and Food and Drug Administration (FDA) guidelines.[17,18]

4.3. Justification for Dose Level

The dose level of 1×10^{11} vp for Ad26.RSV.preF and 150 µg for RSV preF protein (administered in all 3 cohorts) was selected from the primary analysis of Cohort 2 in study VAC18193RSV1004 and is currently under further evaluation in studies VAC18193RSV1004 and VAC18193RSV2001 (Section 2.2.2).

The lower dose levels for Ad26.RSV.preF in Cohort 1 of the current study were selected based on the assumption that half-log intervals in dose response are biologically meaningful for vaccines.

There are currently no safety data available of Ad26.RSV.preF at a dose level above 1×10^{11} vp. Two higher dose levels of Ad26.RSV.preF (ie, 1.3×10^{11} vp [Cohort 2] and 1.6×10^{11} vp [Cohort 3]) will therefore be assessed in this study. An increase of 0.3×10^{11} vp per dose level could lead to a potential increase of target fill concentration of approximately 15%.

In all cohorts, the dose level of RSV preF protein will be kept constant (150 µg). This dose level has been tested in other (ongoing) clinical studies (Section 2.2.2).

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor after completion of the final participant visit at that study site, in the timeframe specified in the clinical trial agreement.

Based on the review of all available safety data up to at least 7 days after vaccination of all participants in Cohort 2 by the DRC, the sponsor may decide to not initiate enrollment of Cohort 3.

Study Completion Definition

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

5. STUDY POPULATION

Screening for eligible participants will be performed prevaccination on Day 1 (Cohort 1) or within 28 days before study vaccine administration (Cohorts 2 and 3). 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.

Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the time of vaccination such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.

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. Sign an informed consent form (ICF) indicating that he or she understands the purpose, procedures, and potential risks and benefits of the study, is willing to participate in the study and attend all scheduled visits, and is willing and able to comply with all study procedures and adhere to the lifestyle restrictions specified in this protocol.

2. Male or female, aged ≥60 years on the day of signing the ICF.

3. In the investigator's clinical judgment, participants must be either in good or stable health. Participants may have underlying illnesses such as hypertension, type 2 diabetes

mellitus, hyperlipoproteinemia, or hypothyroidism, as long as their signs and symptoms are stable and medically controlled in the judgment of the investigator. Participants will be included on the basis of medical history and of physical examination and vital signs performed at screening (all cohorts), and of physical examination and/or vital signs performed prevaccination on Day 1 (Cohorts 2 and 3).

Note: Retesting of abnormal vital sign values that may lead to exclusion, or due to equipment malfunction, is allowed once without prior approval from the sponsor.

4. A woman must be postmenopausal (defined as no menses for 12 months without an alternative medical cause) and not intending to conceive by any methods.

   Note: Women who have had hysterectomies are also eligible for the study.

5. Agree to not donate blood from the time of vaccination until 3 months after vaccination.

6. Have a body mass index (BMI) <40 kg/m².

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

For participants in Cohorts 2 and 3 only:

10. Be healthy on the basis of clinical laboratory tests performed at screening. If the results of the laboratory screening tests are outside the central laboratory normal reference ranges and additionally within the limits of toxicity Grade 2 according to the United States FDA toxicity tables (ie, for tests in the FDA table) (Section 10.2, Appendix 2), the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant and appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.

    Note: Screening laboratory tests are to be done within 28 days before vaccination. If the results of the laboratory screening tests are outside the central laboratory normal reference ranges and deemed clinically significant by the investigator, repeat of screening laboratory tests will be permitted once using an unscheduled visit during the screening period to assess eligibility.

5.2. Exclusion Criteria

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

1. Has a contraindication to IM injections and blood draws (eg, bleeding disorders).

2. Has a clinically significant acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or body temperature of ≥38.0ºC

(≥100.4ºF) within 24 hours prior to the planned administration of study vaccine.

Note: Enrollment at a later date is permitted. For participants in Cohorts 2 and 3, clinical safety laboratory assessments should be repeated if vaccination is postponed and the time between clinical safety laboratory assessments and vaccination exceeds 28 days.

3. 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.

    b. Participants with history of malignancy within 5 years, which is considered cured with minimal risk of recurrence per investigator's judgement, can be enrolled.

4. Known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine components (including any of the constituents of the study vaccine).[8,9]

5. Has 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 or 2 diabetes mellitus) that is stable and inactive without the use of systemic immunomodulators and glucocorticoids may be enrolled at the discretion of the investigator.

    b. Chronic (>10 days) or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine.

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

    c. Administration of antineoplastic and immunomodulating agents (eg, cancer chemotherapeutic agents or systemic corticosteroids) or radiotherapy within 6 months before administration of study vaccine.

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

7. History of chronic urticaria (recurrent hives), eczema, or atopic dermatitis.

8. Received hematopoietic stem cell transplant in medical history, treatment with immunoglobulins 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 6 months before the planned administration of the study vaccine or has any plans to receive such treatment during the study.

9. Received or plans to receive:
    a. Licensed live attenuated vaccines – within 28 days before or after planned administration of study vaccine.
    b. Other licensed (not live) vaccines – within 14 days before or after planned administration of study vaccine.

10. 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 study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study.

    Note: Participation in an observational clinical study (ie, without intervention) is allowed upon approval of the sponsor.

11. Has a serious chronic disorder, including 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.

12. Had major surgery (as per the investigator's judgment) within 4 weeks before vaccination, will not have fully recovered from surgery prior to vaccination, or has major surgery within 6 months after administration of study vaccine.

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

13. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.

14. Has hepatitis B or C infection, including history of treated hepatitis C infection (per medical history).

15. Has human immunodeficiency virus type 1 or 2 infection (per medical history).

16. 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.

17. Cannot communicate reliably with the investigator.

18. Is unlikely to adhere to the requirements of the study or unlikely to complete the full course of observation in the opinion of the investigator.

19. Received an active RSV vaccine in a previous RSV vaccine study or an Ad26-vectored vaccine at any time prior to randomization.

20. Taken any disallowed therapies as noted in Section 6.5 before vaccination.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.5 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 (Sections 5.1 and 5.2, respectively).

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.

Individuals who do not meet all eligibility criteria (screen failure) but at some point in the future are expected to meet the eligibility criteria may be rescreened on one occasion only. Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.

6. STUDY VACCINE

6.1. Study Vaccine Administration

On Day 1, participants will receive a single IM injection of study vaccine (ie, the Ad26/protein preF RSV vaccine or placebo) in the deltoid muscle. The injection will occur at the study site according to the overview shown in Table 2. The Ad26/protein preF RSV vaccine is composed of Ad26.RSV.preF (JNJ-64400141) and RSV preF protein (JNJ-64213175) (Section 2).

Ad26.RSV.preF will be administered at a dose level ranging from 3.7×10^{9} vp to 1.6×10^{11} vp, and RSV preF protein at a constant dose level of 150 µg (Table 2). Refer to Section 4.3 for justification of the dose levels. Due to the different dose levels of Ad26.RSV.preF, the injection volumes of the study vaccine may differ between the cohorts. Ad26.RSV.preF and RSV preF

protein will be supplied as solutions in separate single-use vials. Placebo will consist of 0.9% saline. The use of concomitant therapy stated in Section 6.5 should be respected. Study vaccination pausing rules are listed in Section 7.3.

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

Ad26.RSV.preF and RSV preF protein will be manufactured and provided under the responsibility of the sponsor. Ad26.RSV.preF will be supplied as a frozen liquid to be thawed prior to use. Labels will contain information to meet the applicable regulatory requirements. Note that RSV preF protein CTM will be labelled as "RSV-F Vaccine". Refer to the IBs for Ad26.RSV.preF[8] and RSV preF protein[9] for details of the components and a list of excipients.

For a definition of study vaccine overdose, refer to Section 8.4.

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, who will have no other study function following vaccination, will prepare the appropriate vials and syringes, labeled with the participant's identification number, and provide the syringes for the study vaccine in a blinded manner to the blinded study vaccine administrator who will perform the injection. An unblinded study-site pharmacist, or other qualified individual, may also perform the vaccination but will have no other study function following vaccination.

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 study 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, or by a hospital/clinic pharmacist. 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 study site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Study Vaccine Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Within each cohort, participants will be randomly assigned to the groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. In Cohort 1, the randomization ratio is 2:2:2:2:1 to Groups 1 to 5, respectively, in Cohort 2, the randomization ratio is 2:2:1 to Groups 6 to 8, respectively, and in Cohort 3, the randomization ratio is 1:2:1 to Groups 9 to 11, respectively. The randomization will be balanced by using randomly permuted blocks**.** The IWRS will assign a unique code, which will dictate the group assignment for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

If randomized participants discontinue from the study before the study vaccine is administered, additional participants may be recruited to replace these participants at the discretion of the sponsor. Any replacement participant will be assigned to the same group as the original (discontinued) participant. The replacement participant's randomization number will equal the randomization number of the discontinued participant +1000 (eg, participant 0001 would be replaced by participant 1001). These additional participants should also be randomized through IWRS. No replacements or additional randomizations will be done for withdrawals after vaccination.

Blinding

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

At the sponsor level, unblinding (at the participant level) will occur at the time of the primary analysis for each cohort (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 study vaccine 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 study vaccine 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 if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor 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 investigator is advised not to reveal the study vaccine assignment to the study-site personnel or sponsor personnel/sponsor representative.

The pharmacist or qualified individual with primary responsibility for study vaccine preparation and dispensing will be unblinded to study vaccine allocation (Section 6.2).

Participants who have had their study vaccine assignment unblinded should continue to return for scheduled evaluations.

6.4. Study Vaccine Compliance

Study vaccine will be IM administered by a blinded study vaccine administrator (ie, a trained and qualified study nurse, medical doctor, or otherwise qualified healthcare professional) at the study site. The unblinded study-site pharmacist, or other qualified individual, may also perform the vaccination, but will have no other study function following vaccination. Details of each administration will be recorded in the eCRF (including date and time of injection). For blinding procedures, see Section 6.3.

6.5. Concomitant Therapy

Prestudy therapies administered up to 30 days before vaccination must be recorded in the eCRF at screening (all cohorts) and additionally on Day 1 for Cohorts 2 and 3.

Concomitant therapies such as analgesic/antipyretic medications and nonsteroidal anti-inflammatory drugs, corticosteroids, and antihistaminic must be recorded in the eCRF until 28 days after vaccination. All other concomitant therapies should also be recorded in the eCRF if administered in conjunction with new or worsening AEs reported per protocol requirements outlined in Section 10.3, Appendix 3.

Analgesic/antipyretic medications and nonsteroidal anti-inflammatory drugs may be used after vaccination only in cases of medical need (eg, fever or pain). Use of these medications as routine prophylaxis before vaccination is discouraged.

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

Use of systemic corticosteroids must be documented during the study. Use of ocular, topical, or inhaled steroids during the study is allowed, whereas chronic (>10 days) or recurrent use of systemic corticosteroids during the study is prohibited. Antineoplastic and immunomodulating agents or radiotherapy are prohibited during the study. If chronic use of systemic corticosteroids or antineoplastic or immunomodulating agents becomes medically indicated during the study for any participant, the sponsor should be notified.

Vaccination with licensed live attenuated vaccines within 28 days of 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 postexposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

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

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

6.6. Intervention 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.

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. Additional participants will be entered to ensure the protocol-specified number of participants complete the study.

7.2. Contraindications to Study Vaccination

The following events assessed by the investigator constitute a temporary contraindication to study vaccination:

- Acute illness at the planned time of vaccination. This does not include minor illnesses, such as diarrhea or mild upper respiratory tract infection.
- Fever (body temperature of ≥38.0°C [≥100.4ºF]) at the planned time of vaccination.

If any of these events occur at the planned time of vaccination, the participant may be vaccinated up to, and no later than, 10 days after the planned vaccination, or be withdrawn from vaccination at the discretion of the investigator.

Note: For participants in Cohorts 2 and 3, clinical safety laboratory assessments should be repeated if vaccination is postponed and the time between clinical safety laboratory assessments and vaccination exceeds 28 days.

7.3. Study Vaccination Pausing Rules

The PI(s) and sponsor team members (ie, SRP/SRS) will monitor the study vaccination pausing rules listed below. If vaccination is considered to raise significant safety concerns (ie, if at least one of the study vaccination pausing rules has been met), further vaccination of participants will be paused until the DRC review of all available data is carried out and subsequent communication between the sponsor and the PI(s) takes place. The DRC will review blinded data first but is entitled to and has the right to require submission of unblinded data if deemed necessary. When a first DRC meeting has been triggered by the occurrence of a given study vaccination pausing rule, the DRC will convene thereafter for each additional participant meeting that pausing rule. Possible actions upon review include, but are not limited to, study suspension, study adaptation, or discontinuation of further vaccination.

The following list of study vaccination pausing rules applies for concerned AEs that occur up to 28 days after vaccination and concerned SAEs:

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

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

For study vaccination pausing rule 5: to assess abnormal laboratory values, the test must be repeated at least once, within 48 hours of the study site becoming aware of the abnormal value.

After each DRC review of similar AEs, the DRC will indicate the conditions under which it requires further notification and review of the subsequent similar AEs.

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

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

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

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

In addition to the study vaccination pausing rules, the sponsor's medical monitor or the PI(s) (upon consultation with the sponsor's medical monitor) may initiate a DRC review for any single event or combination of events which, in their professional opinion, could jeopardize the safety of the participants or the reliability of the data.

7.4. Participant Discontinuation/Withdrawal From the Study

Each participant has the right to withdraw from the study at any time for any reason without affecting the right to treatment by the investigator. The investigator should make an attempt to contact participants who did not return for scheduled visits or follow-up. Although the participant is not obliged to give reason(s) for withdrawing prematurely, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the participant's rights.

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Repeated failure to comply with protocol requirements or to cooperate with the study-site personnel
- Decision by the sponsor or the investigator to stop or cancel the study
- Decision by local regulatory authorities or IEC/IRB to stop or cancel the study

Any unnecessary study discontinuation should be avoided. When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. All efforts should be made to complete and report the observations as thoroughly as possible. Study vaccine assigned to the withdrawn participant may not be assigned to another participant. Participants who withdraw will be replaced, as long as the participant has not been vaccinated (Section 6.3).

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 (Section 1.3). Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent). They have the right to refuse.

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

7.4.1. 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 research (refer to Long-term Retention of Samples for Additional Future Research in Section 10.4, Appendix 4). 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.

7.5. Lost to Follow-up

A participant will be considered lost to follow-up if he or she 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 study-site personnel 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), and to determine the reason for discontinuation/withdrawal. These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she 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 participants to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of immunogenicity and safety measurements applicable to this study. Unscheduled visits may be performed based on the investigator's clinical judgment and may include further evaluations, as needed.

In addition, a participant diary to record body temperature and solicited injection site and systemic signs and symptoms will be provided to the participants on the day of study vaccination (Day 1). The participant diary includes instructions on how to capture the data and grading scales to assess severity of the signs and symptoms. The study-site personnel will be 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 Day 8 visit. If the participant diary review is missed, the participant diary will be reviewed during the following visit. Thermometers will be given to all participants on the day of study vaccination (Day 1) and should be returned to the study site at the end of the study/early withdrawal. Participants will also be provided with a ruler on the day of study vaccination (Day 1) to measure local injection site reactions.

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

The total blood volume to be collected from each participant will be approximately 240 mL (Cohort 1) or 260 mL (Cohorts 2 and 3).

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

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 (Section 1.3) 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.RSV.preF[8]
- IB for RSV preF protein[9]
- Study Site Investigational Product and Procedures Manual
- Laboratory manual
- Investigational Product Preparation Instructions

- Participant diary and instructions for use
- Rulers (to measure diameter of any erythema and induration/swelling)
- Thermometers
- Laboratory kits
- Contact Information page(s)
- Study protocol
- IWRS Manual
- Electronic data capture (eDC) Manual/eCRF completion guidelines
- Any other manual, as applicable
- Wallet card
- Sample ICF

8.1. Immunogenicity Assessments

Venous blood samples of approximately 10 and 50 mL will be collected for the determination of humoral and cellular immune responses, respectively (Table 3), at the timepoints indicated in the Schedule of Activities (Section 1.3). Nasosorption samples using SAM strips will be collected at the timepoints indicated in the Schedule of Activities (Section 1.3), and will be used for immunogenicity assessments including, but not limited to, determination of antigen-specific immunoglobulin (IgG and IgA) (Table 3).

Sample collection and processing will be performed by the study-site personnel according to current versions of approved standard operating procedures.

Table 3: Summary of Possible Immunogenicity Assays (Humoral and Cellular)

Assay	Purpose
Primary and secondary endpoints	
Pre-F protein binding antibody (ELISA)	Analysis of antibodies binding to RSV F protein in prefusion form
RSV A2 neutralization	Analysis of neutralizing antibodies to the A2 strain
IFN-γ (ELISpot)	T-cell IFN-γ responses to RSV F protein peptides
Exploratory endpoints	
Post-F protein binding antibody (ELISA)	Analysis of antibodies binding to RSV F protein in postfusion form
Antigen-specific T-cell immune responses	Analysis of T-cell responses to RSV F protein peptide-stimulated PBMCs (including, but not limited to, $CD4^+$/$CD8^+$, IL-2, IFN-γ, TNF-α, activation markers and memory) using ICS or CyTOF
RSV strain cross-neutralization	Analysis of cross-neutralizing antibodies to B and/or other A strain(s)
Antibody specificity and functional characterization	Analysis of pre- and post-F antibody specificity by functional assays such as ELISA, competition ELISA, and epitope mapping. Functional characterization of antibodies including, but not limited to, ADCC, ADCP, avidity, immunoglobulin isotype, and functional VNAs to other respiratory viruses

Analysis of nasal antibodies to RSV including, but not limited to, IgA and IgG	Analysis of nasal antibodies binding to RSV F protein in prefusion and/or postfusion form in nasal samples
Adenovirus neutralization assay	Analysis of neutralizing antibodies to Ad26

ADCC = antibody-dependent cell-mediated cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; CyTOF = cytometry by time of flight; IL = interleukin; PBMC = peripheral bone marrow cell; TNF = tumor necrosis factor.

Immunogenicity samples will be prioritized as outlined in the laboratory manual.

8.2. Safety Assessments

Safety will be evaluated throughout the study from signing of the ICF until the last study-related activity, or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts.

Key safety assessments will include the monitoring of AEs, physical examinations, vital signs, and clinical safety laboratory assessments.

AEs will be reported and followed by the investigator as specified in Section 8.3 and Section 10.3, Appendix 3.

Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) 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.

Details regarding the DRC are provided in Section 9.6.

The study will include the following evaluations of safety and reactogenicity according to the timepoints provided in the Schedule of Activities (Section 1.3).

8.2.1. Physical Examinations

A physical examination (including height and body weight) will be carried out at screening (Cohorts 2 and 3) or on Day 1 (prevaccination) (Cohort 1). At all other visits, an abbreviated, symptom-directed physical examination will be performed if deemed necessary by the investigator based on clinically relevant issues, clinically relevant symptoms, and medical history. A symptom-directed physical examination may be repeated if deemed necessary by the investigator.

Physical examinations will be performed by the investigator or by a designated medically-trained clinician. Any clinically relevant abnormalities or changes in severity observed during the review of body systems should be documented in the eCRF.

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 assessed.

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.

Systolic and diastolic blood pressure (supine) 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). Vital signs measurements should be taken before nasal sampling and blood draws, if applicable.

Confirmatory vital signs measurements can be performed if inconsistent with a prior measurement. Any clinically relevant abnormalities or changes in severity should be documented in the eCRF.

8.2.3. Clinical Safety Laboratory Assessments

In Cohorts 2 and 3, blood samples for biochemistry and hematology will be collected as noted in Table 4 at the timepoints indicated in the Schedule of Activities (Section 1.3). All clinical safety laboratory analyses will be performed at the central laboratory.

Table 4: Protocol-required Clinical Laboratory Assessments

Biochemistry Panel	Hematology Panel
sodium	hemoglobin
potassium	white blood cell count with differential
creatinine	platelet count
blood urea nitrogen	prothrombin time[a]
aspartate aminotransferase	activated partial thromboplastin time[a]
alanine aminotransferase	

a. Will be measured at screening only.

Review and Grading of Laboratory Data

The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Laboratory values will be initially evaluated by the investigator according to central laboratory criteria. Abnormal values outside the central laboratory normal range will be graded according to the FDA Guidance document "Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (Section 10.2, Appendix 2). Laboratory values within central laboratory normal limits will not be FDA graded and will be considered as normal.

Reporting Laboratory Abnormalities as AEs

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

Repeat of Clinically Significant Laboratory Tests

For any clinically significant abnormal laboratory value that has increased in grade over baseline, the test must be repeated at the next scheduled visit or sooner based on the investigator's judgment, however Grade 3 or higher abnormalities should be retested within 48 hours.

Screening Procedures (Cohorts 2 and 3 Only)

For entry into the study, each participant must be healthy on the basis of clinical laboratory tests performed at screening. Refer to inclusion criterion 10 in Section 5.1 for more details.

8.3. AEs and SAEs

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

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints (PQCs), refer to Section 10.3, Appendix 3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

AEs and special reporting situations, whether serious or nonserious, that are related to study procedures or that are related to noninvestigational 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 date of vaccination will be collected on the Medical History eCRF page as pre-existing conditions.

Any solicited local (injection site) or systemic AEs occurring during the 30-minute postvaccination observation period (or longer if deemed necessary by the investigator) will be documented by the study-site personnel following this observation period. Solicited AEs collected through a participant diary will be recorded from the time of vaccination until 7 days after vaccination.

All other unsolicited AEs and special reporting situations, whether serious or nonserious, will be reported from the time of vaccination until 28 days after vaccination. All AEs and SAEs leading to discontinuation of the study vaccination (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 other SAEs (regardless of the causal relationship) are to be reported from the time of vaccination until the end of the study/early withdrawal.

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event. Information regarding SAEs will be transmitted to the sponsor using the SAE Form 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 within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax).

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

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs or SAEs. 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 (at the injection site) and systemic events for which the participant is specifically questioned and which are noted by participants in their participant diary.

After vaccination with study vaccine on Day 1, participants will remain under observation at the study site for a minimum of 30 minutes for presence of any acute reactions and solicited events, or longer if deemed necessary by the investigator. In addition, participants will record solicited signs and symptoms in the participant diary for 7 days after vaccination. All participants will be provided with the participant diary and instructions on how to complete the diary (Section 8). The study-site personnel will transcribe the information provided by the participant into the relevant sections of the eCRF. After review and verbal discussion of the initial participant diary entries with the participant, the investigator will complete his or her own assessment in the relevant sections of the eCRF. Once a solicited sign or symptom from the participant diary is considered to be of severity Grade 1 or above during the investigator's assessment, it will be recorded as a solicited AE.

Solicited Injection Site AEs

Participants will be asked to note in the participant diary occurrences of injection site pain/tenderness at the study vaccine injection site daily for 7 days after vaccination (day of vaccination and the subsequent 7 days). The extent (largest diameter) of any erythema and swelling at the injection site should be measured (using the ruler supplied) and recorded daily. The case definitions for solicited injection site events can be found in Gidudu et al.[7] and Kohl et al.[11]

Solicited Systemic AEs

Participants will be instructed on how to record daily body temperature using a thermometer provided for home use. Participants should record the body 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 one measurement is made on any given day, the highest body temperature of that day will be used in the eCRF.

Fever is defined as endogenous elevation of body temperature ≥38.0°C [≥100.4ºF], as recorded in at least one measurement.[14]

Participants will also be instructed on how to note signs and symptoms in the participant diary on a daily basis for 7 days after 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.

8.3.3. Follow-up of AEs and SAEs

AEs, including pregnancies in partners of male participants, will be followed by the investigator as specified in Section 10.3, Appendix 3.

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 female 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 the SAE Form.

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

8.4. 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 intervention 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 AE/SAE and laboratory abnormalities until resolution.
- Document the quantity of the excess dose in the eCRF.
- Report as a special reporting situation.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics 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

No formal statistical testing of safety or immunogenicity data is planned; data will be analyzed descriptively.

9.2. Sample Size Determination

9.2.1. Immunogenicity (Cohort 1)

The primary objective of Cohort 1 is to explore the dose-response relationship of humoral immune responses (as measured by preF ELISA) induced by different dose levels of the Ad26/protein preF RSV vaccine.

Assuming:

- 10% of exclusions (eg, drop-outs, missing samples, and major protocol deviations impacting immunogenicity data)
- a standard deviation on the $\log_2$ scale of the preF ELISA of 1.3 on Day 15 and 1.1 on Day 183 for all dose levels
- 4 dose levels

The linear model $log_2\ (preF\ ELISA_{timepoint}) = GMT\ preF\ ELISA_{Ad26/protein\ preF\ RSV\ vaccine\ (1x10^{11}\ vp/150\ \mu g),timepoint} + slope \times \#titration\ steps$ provides a standard error for the slope of 0.052 on Day 15 and 0.040 on Day 183 with 50 participants per arm. This is deemed sufficient for this exploratory study.

9.2.2. Safety (Cohorts 1, 2, and 3)

Placebo recipients are included for blinding and safety purposes and will provide additional control specimens for immunogenicity assays.

The observation of 0 events (eg, SAEs) is associated with 95% confidence that the true event rate is below the rates specified in the below table for the considered number of participants.

Table 5: Upper Limit of the 95% One-sided Confidence Interval if no Cases are Observed for Different Sample Sizes

Sample Size	N=25	N=50	N=75
UL 95% one-sided CI	11.3%	5.8%	3.9%

CI = confidence interval; N = number of participants; UL = upper limit.

The table below provides the probability of observing at least one AE in a group of the considered sample size given several true AE rates.

Table 6: Probability of Observing at Least One AE in a Group of the Considered Sample Size Given Several True AE Rates

True AE Rate (%)	Probability of Observing at Least One AE in N Participants (%)		
	N=25	N=50	N=75
0.5	12	22	31
1	22	39	53
2.5	47	72	85
10	93	99	100
25	100	100	100
50	100	100	100

N = number of participants.

9.3. Populations for Analyses

Vaccine assignment will follow the as-treated principle.

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

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

The analysis of all immunogenicity endpoints will be based on the PPI set. For key tables, sensitivity immunogenicity analyses might also be performed on the FAS.

9.4. Statistical Analyses

The SAP will be finalized prior to database lock of the primary analysis and 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 most important endpoints including primary and key secondary endpoints.

9.4.1. Participant Information

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

9.4.2. Immunogenicity Analyses

No formal statistical testing of immunogenicity data is planned. Immunogenicity data will be analyzed descriptively by cohort and group. In addition, for a selection of tables, data may be pooled over cohorts.

Descriptive statistics (eg, geometric mean and 95% confidence interval [CI] for ELISA and VNA data; median and quartiles for ELISpot) will be calculated for continuous immunologic parameters at all timepoints. For the humoral assays, geometric mean fold rises from baseline and corresponding 95% CIs might additionally be calculated. Baseline is considered as the last available assessment before vaccination. Graphical representations of immunologic parameters will be made as applicable.

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

To explore the dose-response relationship between preF ELISA and different dose levels of the Ad26/protein preF RSV vaccine, a linear regression model will be fitted for each timepoint separately, using data of the active groups of Cohort 1, with the log-transformed preF ELISA titers at the considered timepoint as dependent variable, the number of titration steps as independent variable, and the geometric mean titer (GMT) of preF ELISA of the Ad26/protein preF RSV vaccine (1×10^{11} vp/150 μg) at the considered timepoint as a fixed intercept.

The linear model $log_2\ (preF\ ELISA_{timepoint}) = GMT\ preF\ ELISA_{Ad26/protein\ preF\ RSV\ vaccine\ (1x10^{11}\ vp/150\ ug),timepoint} + slope \times \#titration\ steps$ will initially be fitted for the active groups of Cohort 1 but may be extended in a later stage with data of the active groups of Cohorts 2 and 3. A similar model may be fitted as well for other assays.

Depending on the model fit, other models (eg, log-linear models or EMAX models) may be explored as well.

The incidence of neutralizing antibodies to Ad26 might be summarized for participants who are positive for antibodies to Ad26.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

The primary analysis set for the immunogenicity analysis is the PPI set. As a sensitivity analysis, key tables may also be based on the FAS.

9.4.3. Safety Analyses

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by cohort and group. In addition, for a selection of tables, data of Cohorts 2 and 3 may be pooled. All safety analyses will be based on the FAS.

AEs (Solicited and Unsolicited)

Solicited local (injection site) and systemic AEs will be summarized descriptively. Solicited AEs shown in the tables and listings will be based on the overall assessment of the investigator. 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 one solicited local (at the injection site) or systemic AE will be presented.

The verbatim terms used in the eCRF by the investigator to report AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the active vaccination phase (ie, AEs occurring from the time of vaccination until 28 days after vaccination) and all SAEs will be included in the analysis. For each AE, the number and percentage of participants who experience at least one occurrence of the given event will be summarized by group. Frequency tables of unsolicited AEs, separately for all and study vaccine-related, will be presented by system organ class and preferred term.

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 or an SAE.

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

Clinical Laboratory Tests (Cohorts 2 and 3 only)

Laboratory abnormalities will be determined according to the FDA toxicity grading tables (Section 10.2, Appendix 2) or, for tests for which no grades are available, in accordance with the normal ranges of the clinical laboratory. Any laboratory value shown as a "graded" value in the FDA table that is within central laboratory normal ranges will not be graded for severity.

Vital Signs

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

Physical Examination

A listing for physical examination abnormalities will be generated.

9.5. Planned Analyses

The following analyses will be performed:

- Cohort 1 primary analysis will include 14-day immunogenicity and 28-day safety data of all groups in Cohort 1. The sponsor will be unblinded for Cohort 1 at the time of the primary analysis of Cohort 1, and the blind will be maintained at the participant and study site level up to study end.
- Cohorts 2 and 3 primary analysis will include 28-day safety data of all groups in Cohorts 2 and 3. If 14-day immunogenicity data are available at the time of the primary analysis, these will be included as well, otherwise these will be analyzed at a later timepoint. The sponsor will be unblinded for Cohorts 2 and 3 at the time of the primary analysis, and the blind will be maintained at the participant and study site level up to study end.
- Final analysis at the end of the study will include safety and immunogenicity data from all cohorts. Data collected up to the time of the last visit for the last participant will be included in the analysis. This analysis will be performed on unblinded data.

Note: The final analysis might be done per cohort, depending on the timing.

9.6. Data Monitoring Committee or Other Review Board

An internal DRC will be established for this study (Section 4.1). The DRC will convene, according to their charter, to discuss any safety issues and any situation meeting a specific study vaccination pausing rule (Section 7.3). The DRC will consist of sponsor personnel not directly involved in the conduct of the study and who have expertise in clinical study conduct and vaccines, at least one medical expert in the relevant therapeutic area, at least one statistician; and a safety expert. Committee membership responsibilities, authorities, and procedures will be documented in its charter. The PI(s) and SRP/SRS will inform the DRC of any AE of concern.

In addition, the DRC will review:

- All Cohort 2 safety data collected up to the time the 20th participant in Cohort 2 completed his/her Day 8 visit (or discontinued earlier).
- All Cohort 2 safety data collected up to the time the last participant in Cohort 2 completed his/her Day 8 visit (or discontinued earlier).
- All Cohort 3 safety data collected up to the time the 16th participant in Cohort 3 completed his/her Day 8 visit (or discontinued earlier).

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

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

Safety data from the planned analyses (Section 9.5) will be shared with the DRC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

Ad26	adenovirus serotype 26
AE	adverse event
BMI	body mass index
CD	cluster of differentiation
CI	confidence interval
CTM	clinical trial material
DNA	deoxyribonucleic acid
DRC	Data Review Committee
eCRF	electronic case report form(s)
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	geometric mean titer
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	intracellular cytokine staining
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IM	intramuscular(ly)
IRB	Institutional Review Board
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
NHP	nonhuman primate
PI	principal investigator
PPI	Per-protocol Immunogenicity
PQC	Product Quality Complaint
preF	prefusion conformation-stabilized F protein
RSV	respiratory syncytial virus
SAE	serious adverse event
SAM	synthetic absorptive matrix
SAP	statistical analysis plan
SRP	study responsible physician
SRS	study responsible scientist
SUSAR	suspected unexpected serious adverse reaction
Th	T helper
VL-AUC	viral load as measured by the area under the curve
VNA	virus neutralization assay
VNT	virus neutralizing titer
vp	viral particles

Definitions of Terms

Electronic source (eSource) system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in an eCRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: 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).

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) ** (°F)**	38.0 - 38.4 100.4 - 101.1	38.5 - 38.9 101.2 - 102.0	39.0 - 40.0 102.1 - 104.0	> 40 > 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
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	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 Fasting mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >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
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.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

AE

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or noninvestigational) 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 noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) product (Definition per 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.

SAE

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

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

ATTRIBUTION DEFINITIONS

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

Related: there is a reasonable possibility that the study vaccine contributed to the AE.

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

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

SEVERITY CRITERIA

All AEs and laboratory data will be coded for severity using a modified version of the FDA grading table, based on version of September 2007[16], included in Section 10.2, Appendix 2.

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 requires 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 ER visit or hospitalization

SPECIAL REPORTING SITUATIONS

Safety events of interest on 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)

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.

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)
- Study 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 discontinuation of the participant’s participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the 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)

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

- Hospitalizations not intended to treat an acute illness or 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.

CONTACTING SPONSOR REGARDING SAFETY

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

PQC HANDLING

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, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

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

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (Section 8.3.1). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

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

10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

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.

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

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 vaccines to the study site:

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

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

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

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)

- IBs (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(s) and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the 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 study 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.

Other Ethical Considerations

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

FINANCIAL DISCLOSURE

Investigators and subinvestigators 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 course of the study and for one year after completion of the study.

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

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 his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

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

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 his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

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

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 poststudy storage period. Included are samples from participants who were screened but not randomized which may also be used to develop tests/assays related to Ad26.RSV.preF, RSV preF protein, and RSV 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 (Section 7.4.1).

COMMITTEES STRUCTURE

Data Review Committee

A DRC will be established for this study (Section 9.6).

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.

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

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.

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.

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

The following participant- and investigator-completed assessments will be recorded and will be considered source data: solicited AEs after vaccination and body temperature. The participant diary used to collect information regarding solicited signs and symptoms after vaccination will be considered source data.

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.

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 will compare the 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 study site.

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

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.

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

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.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first study site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

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

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

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

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

10.5. Appendix 5: Protocol Amendment History

This is an original protocol.

11. REFERENCES

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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 course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

SIGNATURES

Signed by	Date	Justification
PPD	16Mar2020, 16:29:52 PM, UTC	Document Approval

Janssen Vaccines & Prevention B.V.*

Clinical Protocol

COVID-19 Appendix

Protocol Title

A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate a Range of Dose Levels of an Ad26.RSV.preF-based Vaccine in Adults Aged 60 Years and Older

Protocol VAC18193RSV2005; Phase 2a

VAC18193 (JNJ-64400141/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).

Status:	Approved
Date:	11 June 2020
Prepared by:	Janssen Vaccines & Prevention B.V.
EDMS number:	EDMS-RIM-81100, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

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

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key 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 via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

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

GUIDANCE SPECIFIC TO THIS PROTOCOL:

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.
- Baseline visits for participants recently screened for this study should be postponed if the current situation does not allow for an orderly conduct of the study.

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, clinical assessments, blood samples, nasal samples and physical examination), 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 an (unblinded) pharmacist or other qualified individual at the study site. If this is not possible, a solution may be considered in consultation with the sponsor and taking into consideration participant safety.

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.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
VAC18193 (JNJ-64400141/JNJ-64213175) Clinical Protocol VAC18193RSV2005

INVESTIGATOR AGREEMENT

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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 intervention, the conduct of the study, and the obligations of confidentiality.

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Name (typed or printed): _____

Institution and Address: _____

_____

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Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Vaccines & Prevention B.V.

Signature: PPD PPD Date: _____
(Day Month Year)

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

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 4
Status: Approved, Date: 11 June 2020