Janssen Vaccines & Prevention B.V.*

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled Phase 1/2a Study for Safety and Immunogenicity Evaluations of various RSV.preF-based Vaccine Formulations in Adults Aged 60 Years and Older

Protocol VAC18195RSV1001; Phase 1/2a
Version: Original

VAC18195 (JNJ 64400141/ JNJ 64213175/ JNJ-86051823/ JNJ 78991172)

* 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.

Studies conducted at sites in the United States (US) will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Status: Approved
Date: 22 December 2021
EDMS number: EDMS-RIM-543812, 1.0

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 1/2a Study for Safety and Immunogenicity Evaluations of various RSV.preF-based Vaccine Formulations in Adults Aged 60 Years and Older

The respiratory syncytial virus (RSV) vaccine that will be investigated in the current study is a combination of adenovirus type 26 (Ad26)-based and/or preF protein-based vaccine components derived from RSV A and B subtypes, administered as intramuscular (IM) injections:

- Ad26.RSV.preF (JNJ-64400141; referred to in this document as Ad26.RSV-A.preF), a replication-incompetent Ad26 containing a deoxyribonucleic acid (DNA) transgene that encodes the prefusion conformation-stabilized F protein derived from the RSV A subtype.
- Ad26.RSV-B.preF2 (JNJ-86051823), a replication-incompetent Ad26 containing a DNA transgene that encodes the prefusion conformation-stabilized F protein derived from the RSV B subtype.
- RSV preF protein (JNJ-64213175; referred to in this document as RSV-A preF protein) is a prefusion conformation-stabilized F protein derived from the RSV A subtype.
- RSV-B preF protein (JNJ-78991172) is a prefusion conformation-stabilized F protein derived from the RSV B subtype.

OBJECTIVES AND ENDPOINTS

INITIAL SAFETY COHORT OBJECTIVE (COHORT 1): *To determine in small numbers of participants aged 60 years and older the safety of a vaccine formulation comprising a combination of Ad26.RSV A.preF and/or Ad26.RSV B.preF2 and/or RSV A preF and/or RSV B preF proteins before progression to vaccine components selection in a larger number of participants for further assessment of the safety and immunogenicity*

Objectives	***Endpoints***
PRIMARY	
• To assess the safety and reactogenicity of various combinations of RSV vaccine components	• Serious adverse events (SAEs) and adverse events of special interest (AESIs) from first dose administration until 6 months after vaccination • Solicited local and systemic adverse events (AEs) for 7 days after vaccine administration • Unsolicited AEs from the time of vaccine administration through the following 28 days

VACCINE COMPONENTS SELECTION OBJECTIVE (COHORTS 1 and 2): *To select an optimal RSV.preF based vaccine based on assessment of the safety and immunogenicity in participants aged 60 years and older receiving a vaccine formulation comprising a combination of Ad26.RSV A.preF and/or Ad26.RSV B.preF2 and/or RSV A preF and/or RSV B preF proteins.*

Objectives	***Endpoints***
PRIMARY	
• To assess the safety and reactogenicity of various combinations of RSV vaccine components	• SAEs and AESIs from first dose administration until 6 months after vaccination • Solicited local and systemic AEs for 7 days after vaccine administration

Objectives	*Endpoints*
	• Unsolicited AEs from the time of vaccine administration through the following 28 days
• To assess humoral immune responses elicited by various combinations of RSV vaccine components	• RSV neutralization antibody titers
SECONDARY	
• To assess humoral and cellular immune responses elicited by various combinations of RSV vaccine components using other immunological assays	• F protein binding antibodies (pre-F and/or post-F), and antigen-specific T-cell responses*
EXPLORATORY	
• To further explore vaccine-elicited immune responses after single vaccination with various combinations of RSV vaccine components	• Exploratory endpoints may include the following, but are not limited to: RSV neutralization antibody titers against additional A and/or B strains, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, antibody-dependent cell-mediated cytotoxicity [ADCC], antibody-dependent cell-mediated phagocytosis [ADCP], antibody isotyping, antibody sequencing for repertoire), including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum samples, transcriptome analysis and sequencing of the T-cell receptor (TCR) and/or B-cell receptor (BCR) or heavy/light chain (VH/VL) characterization, evaluation of the cellular immune response and the functional and memory immune response by intracellular cytokine staining (ICS)*, cellular phenotyping and memory B-cell ELISpot*
• To assess the durability of the immune response in selected groups	• Endpoints may include the following, but are not limited to: RSV neutralization antibody titers against RSV subtype A and B, RSV neutralization antibody titers against additional A and/or B strains, RSV F protein binding antibodies (pre-F and/or post-F), antigen-specific T-cell responses*, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, ADCC, ADCP, antibody isotyping, antibody sequencing for repertoire), including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum, transcriptome analysis and sequencing of the TCR and/or BCR or VH/VL characterization, evaluation of the cellular immune response and the functional and memory immune response by ICS*, cellular phenotyping and memory B-cell ELISpot*

* Only applicable for participants with blood draws for cellular responses.

EXPANDED SAFETY COHORT OBJECTIVE (COHORT 3): *To determine the safety and immunogenicity of the selected RSV.preF based vaccine in an expanded cohort of participants aged 60 years and older, comparing the formulation of the selected combination of RSV vaccine components (2x1 mL formulation, based on Cohort 1 and 2 results) and the formulation to be used for future clinical development (1x1 mL formulation); and to assess durability of the selected RSV.preF based vaccine and determine the effect of revaccination.*

Objectives	***Endpoints***
PRIMARY	
• To assess the safety and reactogenicity of the selected RSV.preF-based vaccine formulation (based on Cohort 1 and 2 results), compared to the formulation to be used for future clinical development	• SAEs and AESIs from first administration until 6 months after the last vaccination • Solicited local and systemic AEs for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
SECONDARY	
• To assess immune responses to the selected RSV.preF-based vaccine formulation (based on Cohort 1 and 2 results), compared to the formulation to be used for future clinical development	• RSV neutralization antibody titers
• To assess the durability of the immune response to the selected RSV.preF-based vaccine formulation in groups with and without revaccination	• RSV neutralization antibody titers
EXPLORATORY	
• Additional exploratory analyses may be performed to further investigate humoral and cellular vaccine-elicited immune responses to the selected RSV.preF-based vaccine formulation and durability	• Endpoints may include the following, but are not limited to: RSV neutralization antibody titers against additional A and/or B strains, F protein binding antibodies (pre-F and/or post-F), and antigen-specific T-cell responses*, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, ADCC, ADCP, antibody isotyping, antibody sequencing for repertoire), including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum, transcriptome analysis and sequencing of the TCR and/or BCR or VH/VL characterization, evaluation of the cellular immune response and the functional and memory immune response by ICS*, cellular phenotyping and memory B-cell ELISpot*
• To further assess immune responses to the selected RSV.preF-based vaccine formulation (based on Cohort 1 and 2 results), the formulation to be used for future clinical development, and the current Ad26/protein preF RSV vaccine	• Endpoints may include the following, but are not limited to: RSV neutralization antibody titers, RSV neutralization antibody titers against additional A and/or B strains, F protein binding antibodies (pre-F and/or post-F), and antigen-specific T-cell responses*, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, ADCC, ADCP, antibody isotyping, antibody

Objectives	*Endpoints*
	sequencing for repertoire), including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum, transcriptome analysis and sequencing of the TCR and/or BCR or VH/VL characterization, evaluation of the cellular immune response and the functional and memory immune response by ICS*, cellular phenotyping and memory B-cell ELISpot*

* Only applicable for participants with blood draws for cellular responses.

REVACCINATION AND DURABILITY COHORT OBJECTIVE (COHORT 4): *To assess durability of the selected RSV.preF based vaccine, to determine the effect of revaccination; and to determine the safety and immunogenicity of the selected formulation for future clinical development in a cohort of participants aged 60 years and older*

Objectives	*Endpoints*
PRIMARY	
• To assess immune responses, including durability to the selected RSV.preF-based vaccine formulation (formulation for future clinical development) in groups with and without revaccination	• RSV neutralization antibody titers
SECONDARY	
• To assess the safety and reactogenicity of the selected RSV.preF-based vaccine formulation (formulation for future clinical development)	• SAEs and AESIs from first administration until 6 months after the last vaccination • Solicited local and systemic AEs for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
EXPLORATORY	
• Additional exploratory analyses may be performed to further investigate humoral and cellular vaccine-elicited immune responses to the selected RSV.preF-based vaccine formulation and durability	• Endpoints may include the following, but are not limited to: RSV neutralization antibody titers against additional A and/or B strains, F protein binding antibodies (pre-F and/or post-F), anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, ADCC, ADCP, antibody isotyping, antibody sequencing for repertoire), and nasal antibodies to RSV, including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum and/or nasal samples, transcriptome analysis and sequencing of the TCR and/or BCR or VH/VL characterization

Hypothesis

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

Data will be analyzed descriptively.

OVERALL DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled Phase 1/2a study to evaluate safety and immunogenicity of various Ad26.RSV.preF and/or RSV preF protein combinations followed by expanded safety evaluation and durability/revaccination evaluation of the selected RSV.preF-based vaccine formulation in participants aged ≥60 years in stable health.

The study design includes 4 cohorts: an initial dose escalation safety cohort (Cohort 1 in a total of 132 participants), an extension of Cohort 1 for vaccine components selection (Cohort 2 in a total of 528 participants), an expanded safety cohort (Cohort 3 in a total of 400 participants), and a revaccination/durability cohort (Cohort 4 in a total of 540 participants). Data from Cohorts 1 and 2 will be combined to select the components of the RSV.preF-based vaccine formulation to be used in Cohorts 3 and 4, and further clinical development.

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

Initial Safety Cohort (Cohort 1)

In the initial safety cohort, participants will be randomized progressively to 1 of 4 groups with additional safety checks in place in a sentinel subgroup before extending enrollment to the next group (Table 1). Sentinel participants in the same group will be enrolled at the same site. Vaccine components evaluated in Cohorts 1 and 2 will be administered as 2 IM injections of 1 mL in the same deltoid muscle.

- Group 1: Initially, 4 sentinel participants will be enrolled: 2 participants in Arm 1a, 1 participant in Arm 1b, and 1 participant in Arm 1c. (Note: The 2:1:1 distribution in the sentinel participants is applied to facilitate further randomization). Enrollment will be paused to allow for 24-hour safety assessments in these 4 sentinel participants by the principal investigator(s) (PI), the sponsor's study responsible physician/scientist (SRP/S), and the sponsor's medical leader (ML). In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 14 participants will be randomized in a 5:1:1 ratio and vaccinated. Seven days after vaccination available safety data will be reviewed by the PI(s), SRP/S, ML, and the sponsor's medical safety officer (MSO) before proceeding to Group 2.
- Group 2: Initially, 12 sentinel participants will be enrolled; 2 participants in Arms 2, 3, 4, 5, and 6; 1 participant in Arm 1b; and 1 participant in Arm 1c. (Note: The 2:2:2:2:2:1:1 distribution in the sentinel participants is applied to facilitate further randomization). Enrollment will be paused to allow for 24-hour safety assessments in the 12 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 54 participants will be randomized in a 5:5:5:5:5:1:1 ratio and vaccinated. Seven days after vaccination, available safety data will be reviewed by the PI(s), SRP/S, ML, and MSO before proceeding to Group 3.
- Group 3: Initially, 6 sentinel participants will be enrolled; 2 participants in Arms 7 and 8; 1 participant in Arm 1b; and 1 participant in Arm 1c. (Note: The 2:2:1:1 distribution in the sentinel participants is applied to facilitate further randomization). Enrollment will be paused to allow for 24-hour safety assessments in these 6 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 24 participants will be randomized in a 5:5:1:1 ratio and vaccinated. Seven days after vaccination, available safety data will be reviewed by the PI(s), SRP/S, ML, and MSO before proceeding to Group 4.
- Group 4: Initially, 4 sentinel participants will be enrolled; 2 participants in Arm 9; 1 participant in Arm 1b; and 1 participant in Arm 1c. (Note: The 2:1:1 distribution in the sentinel participants is applied to facilitate further randomization). These sentinel participants will be dosed at least 1 hour apart.

Enrollment will be paused to allow 24-hour safety assessments in the 4 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 14 participants will be randomized in a 5:1:1 ratio and vaccinated.

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

Progression to Cohort 2 will be based on acceptable safety in the initial safety cohort (Cohort 1), as determined by DRC review of Day 8 safety data in all Cohort 1 participants. If there are clinically relevant safety findings in any of the study arms in Cohort 1, further evaluation of these study arms will not be continued in Cohort 2.

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

Group	Arm	N	Vaccine Components in 2×1 mL Formulation Day 1				
			Ad26.RSV-A.preF	Ad26.RSV-B.preF2	RSV-A preF protein	RSV-B preF protein	Placebo
1	1a	12		1×10^{11} vp		150µg	
	1b	3	1×10^{11} vp		150µg		
	1c	3					Placebo
2	2	12			150µg	150µg	
	3	12	2.5×10^{10} vp	2.5×10^{10} vp	150µg	150µg	
	4	12	5×10^{10} vp	5×10^{10} vp	150µg	150µg	
	5	12	1×10^{11} vp		300µg		
	6	12	1×10^{11} vp		150µg	150µg	
	1b	3	1×10^{11} vp		150µg		
	1c	3					Placebo
3	7	12	1×10^{11} vp	5×10^{10} vp	150µg	150µg	
	8	12	1.5×10^{11} vp		300µg		
	1b	3	1×10^{11} vp		150µg		
	1c	3					Placebo
4	9	12	1×10^{11} vp	1×10^{11} vp	150µg	150µg	
	1b	3	1×10^{11} vp		150µg		
	1c	3					Placebo
COHORT 1 TOTAL		**132**					

N number of participants; vp virus particles

Vaccine Components Selection Cohort (Cohorts 1 and 2)

The safety and immunogenicity data obtained from Cohort 1 will be combined with those obtained in Cohort 2 to support vaccine components selection. In Cohort 2, approximately 528 participants will be randomized in parallel to 1 of 11 arms (in a 1:1:1:1:1:1:1:1:1:1:1 ratio to Arms 1a to 9; Table 2). No pauses for safety assessments during enrollment are planned.

For a subset of the participants, additional cellular immunogenicity assessments will be performed. This subset will be referred to as the Cellular Immuno Subset and will consist of approximately 50 active study vaccine participants per arm (all participants in Cohort 1 and approximately 38 participants per arm in Cohort 2). The Cellular Immuno Subset will be recruited in study sites that have PBMC collection capability.

Participants in Cohorts 1 and 2 will continue follow-up up to 3 years post vaccination.

Based on safety and immunogenicity results available at the time of primary analysis, the sponsor will decide on the optimal vaccine composition to be used in the expanded safety cohort (Cohort 3), the revaccination/durability cohort (Cohort 4), and further clinical development. Additional factors such as

manufacturability and ease of administration may be taken into account to select the optimal vaccine formulation for the expanded safety phase.

Table 2: Study Design: Supporting Vaccine Components Selection Cohort (Cohort 2)

Arm	N	Vaccine Components in 2×1 mL Formulation Day 1				
		Ad26.RSV-A.preF	Ad26.RSV-B.preF2	RSV-A preF protein	RSV-B preF protein	Placebo
1a	48		1×10^{11} vp		150µg	
1b	48	1×10^{11} vp		150µg		
1c	48					Placebo
2	48			150µg	150µg	
3	48	2.5×10^{10} vp	2.5×10^{10} vp	150µg	150µg	
4	48	5×10^{10} vp	5×10^{10} vp	150µg	150µg	
5	48	1×10^{11} vp		300µg		
6	48	1×10^{11} vp		150µg	150µg	
7	48	1×10^{11} vp	5×10^{10} vp	150µg	150µg	
8	48	1.5×10^{11} vp		300µg		
9	48	1×10^{11} vp	1×10^{11} vp	150µg	150µg	
COHORT 2 TOTAL	**528**					

N number of participants; vp virus particles
Notes: Data from Cohort 1 and Cohort 2 will be pooled for safety and immunogenicity analysis.

Expanded Safety Cohort (Cohort 3)

In the expanded safety cohort, approximately 400 participants will be randomized in parallel to 1 of 5 arms (in a 6:3:3:2:2 ratio to Arms 10, 11a, 11b, 12 and 13; Table 3). No pauses in enrollment for safety assessments are planned. Participants will receive either the selected 2×1 mL formulation based on the results from Cohorts 1 and 2, the selected 1mL formulation for future clinical development, placebo, or the current Ad26/protein preF RSV vaccine (1×10^{11} vp Ad26.RSV-A.preF/150 µg RSV-A preF protein).

Vaccine components evaluated in Cohorts 1 and 2 will be administered as 2 IM injections of 1 mL in the same deltoid muscle. However, once the optimal composition is selected, manufacturing formulation will be adjusted to ensure the administration of a single 1 mL vaccine dose in subsequent cohorts. Participants in Arms 11a and 11b will receive the selected vaccine in a 1 mL formulation and a second injection with placebo (1 mL) for blinding purposes. Cohort 3 thus will compare the 2×1 mL formulation of the selected combination of RSV vaccine components from Cohorts 1 and 2 (Arm 10) with the 1 mL formulation to be used for future clinical development (Arms 11a and 11b) with follow-up for 1 year post-vaccination in a double-blind placebo-controlled fashion. Participants in Arm 13 will receive the current Ad26/protein preF RSV vaccine (1×10^{11} vp Ad26.RSV-A.preF/150 µg RSV-A preF protein) in a 1 mL formulation and a second injection with placebo (1 mL) for blinding purposes. Participants in Arms 11a, 11b and 12 will continue the study to assess durability and the effect of revaccination with follow-up up to 5 years post first vaccination. The timing of revaccination (at least 12 months relative to the first dose) will be based on Ad26/protein preF RSV vaccine clinical data.

For a subset of the participants, additional cellular immunogenicity assessments will be performed. This subset will be referred to as the Cellular Immuno Subset and will consist of approximately 240 participants: 40 participants per arm in Arms 10, 12 and 13, and 60 participants per arm in Arms 11a and 11b. The Cellular Immuno Subset will be recruited in study sites that have PBMC collection capability.

Table 3: Study Design: Expanded Safety Cohort (Cohort 3)

Arm	N	Day 1	Day X*
10**	150	Selected 2×1 mL formulation (based on Cohort 1 and 2 results)	-
11a	75	Selected formulation for future clinical development (1 mL) + placebo (1 mL)	Selected formulation for future clinical development
11b	75	Selected formulation for future clinical development (1 mL) + placebo (1 mL)	Placebo
12	50	Placebo (2×1 mL)	Selected formulation for future clinical development
13**	50	1×10^{11} vp Ad26.RSV-A.preF/150 µg RSV-A preF protein (1 mL) + placebo (1 mL)	-
COHORT 3 TOTAL	**400**		

* Timing of revaccination to be defined based on Ad26/protein preF RSV vaccine clinical data (Studies VAC18193RSV1004, VAC18193RSV2001, and VAC18193RSV3001)
** Arms 10 and 13 will be completed after 1 year of follow-up

Revaccination and Durability Cohort (Cohort 4)

In the revaccination and durability cohort, approximately 540 participants will be randomized in parallel to 1 of 3 arms (in a 5:5:2 ratio to Arms 14, 15 and 16; Table 4). No pauses in enrollment for safety assessments are planned. Participants in Arms 14 and 15 will receive the selected formulation for future clinical development on Day 1 and participants in Arm 16 will receive placebo on Day 1. Participants in Arm 14 (revaccination arm) and Arm 16 will receive the selected formulation at the same revaccination timepoint as participants in Arm 11a and 12 of Cohort 3. Participants in Arm 15 will receive placebo at the same revaccination timepoint as participants in Arm 11b of Cohort 3.

Table 4: Study Design: Revaccination and Durability Cohort (Cohort 4)

Arm	N	Day 1	Day X[a]
14	225	Selected formulation for future clinical development	Selected formulation for future clinical development
15	225	Selected formulation for future clinical development	Placebo
16	90	Placebo	Selected formulation for future clinical development
COHORT 4 TOTAL	**540**		

[a] Timing of revaccination to be defined based on Ad26/protein preF RSV vaccine clinical data (Studies VAC18193RSV1004, VAC18193RSV2001, and VAC18193RSV3001)

NUMBER OF PARTICIPANTS

A target of 1,600 participants will be enrolled in the study.

INTERVENTION GROUPS AND DURATION

The study duration will be approximately 1,095 days (3 years) per participant in Cohorts 1 and 2; 365 days (1 year) per participant in Cohort 3, Arms 10 and 13; and 5 years per participant in Cohort 3, Arms 11a, 11b, and 12 and Cohort 4. The study comprises a maximum 28-day screening period, administration of study vaccine (active or placebo), a minimum 28-day follow-up period after vaccination, and a follow-up period up to 3 years after vaccination for Cohorts 1 and 2; 1 year after vaccination for Cohort 3, Arms 10 and 13; and up to 5 years after the first vaccination for Cohort 3, Arms 11a, 11b and 12, and Cohort 4.

Study Vaccine Administration

The investigational medicinal products (IMPs) to be administered to participants in this study are Ad26/protein preF RSV vaccine, Ad26.RSV-B.preF2 mixed with RSV-B preF protein, RSV-A preF protein mixed with RSV-B preF protein, Ad26/protein preF RSV vaccine mixed with RSV-B preF protein, Ad26/protein preF RSV vaccine mixed with Ad26.RSV-B.preF2 and RSV-B preF protein. All IMPs will be administered IM into the deltoid muscle:

- Ad26.RSV-A.preF (JNJ-64400141) will be used at a dose level of 2.5×10^{10} vp, 5×10^{10} vp, 1×10^{11} vp, or 1.5×10^{11} vp.
- RSV-A preF protein (JNJ-64213175) will be used at a dose level of 150 µg or 300 µg.
- Ad26.RSV-B.preF2 (JNJ-86051823) will be used at a dose level of 2.5×10^{10} vp, 5×10^{10} vp or 1×10^{11} vp.
- RSV-B preF protein (JNJ-78991172) will be used at a dose level of 150 µg.

Placebo will be 0.9% saline.

IMMUNOGENICITY EVALUATIONS

Blood samples will be collected for the determination of immune responses.

Possible immunogenicity evaluations may include (but are not limited to) the assays summarized in the table below:

Assay	Purpose
Primary Endpoints*	
RSV neutralization assay	Analysis of neutralizing antibodies against the RSV A2 strain
	Analysis of neutralizing antibodies against an RSV B strain
Secondary Endpoints	
F protein antibodies (ELISA; pre-F and/or post-F)	Analysis of antibodies binding to RSV F protein in prefusion and/or post-fusion form
IFN-γ ELISpot**	T-cell IFN-γ responses to RSV F protein peptides
Exploratory Endpoints	
RSV neutralization assay	Analysis of neutralizing antibodies against additional A and/or B strains
F protein antibody specificity characterization	Pre- and post-F specificity by binding or functional assays as ELISA, and/or competition ELISA. Adsorption of serum or plasma with pre-F and post-F protein before any antibody assay, epitope mapping, functional VNAs
G and/or N protein antibodies (ELISA)	Analysis of antibodies binding to RSV G and/or N protein
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics may include, but not limited to, ADCC, ADCP, avidity, Fc cell interaction, other respiratory viral neutralizing or binding assays, Ig isotype, and antibody assessments for antibody repertoire

ICS and/or cellular phenotyping and/or cellular function characterization**	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 markers), cellular phenotyping by extracellular markers for several immune cells including but not limited to B-cells and T-cells, and B-cell memory ELISpot for B-cell memory formation analysis
Transcriptome analysis	Regulation of genes (clusters), expression patterns, that for example could predict specific immune responses after vaccination
Chemokine/cytokine analysis	Levels of chemokines and cytokines in serum
Sequencing of T-cells and/or B-cells	Including but not limited to sequencing of TCR and BCR including VH/VL (heavy/light chain) characterization

* Analysis of neutralizing antibodies against the RSV A2 and RSV B strain is a primary endpoint in the vaccine components selection cohort (Cohorts 1 and 2) and in the revaccination and durability cohort (Cohort 4), and a secondary endpoint in the expanded safety cohort objective (Cohort 3).

** Only applicable for participants with blood draws for cellular responses.

ADCC: antibody dependent cell mediated cytotoxicity; ADCP: antibody dependent cell mediated phagocytosis; BCR: B cell receptor; ELISA: enzyme linked immunosorbent assay; ELISpot: enzyme linked immunospot; F: fusion; ICS: intracellular cytokine staining; IFN γ: interferon gamma; IL 2: interleukin 2, Ig: immunoglobulin; PBMC: peripheral blood mononuclear cell; RSV: respiratory syncytial virus; TCR: T cell receptor; VH: heavy chain variable domain; VL: light chain variable domain; VNA: virus neutralizing antibody

SAFETY EVALUATIONS

Key safety assessments will include the monitoring of AEs, vital signs, physical examinations (all cohorts), and safety laboratory assessments (Cohorts 1 and 2 only).

AEs and special reporting situations, whether serious or non-serious, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated informed consent form (ICF) is obtained until the end of the study/early withdrawal. Solicited AEs, collected through a participant diary, will be recorded for each vaccination from the time of vaccination until 7 days post-vaccination.

All other unsolicited AEs and special reporting situations, whether serious or non-serious, will be reported for each vaccination from the time of vaccination until 28 days post-vaccination. All SAEs and AEs leading to discontinuation from the study (regardless of the causal relationship) and all AESIs are to be reported from the moment of vaccination until 6 months post vaccination. All COVID-19 cases will be collected for all participants for the duration of the study. All AEs will be followed until resolution or until clinically stable.

STATISTICAL METHODS

Sample Size Determination

For Cohort 1, a sample size of 12 participants per arm is considered sufficient for an initial safety evaluation.

For Cohort 2, the objective is to compare immunomarker levels, including virus neutralizing antibody (VNA) levels, of the various combinations of vaccine components (Arms 1a, and Arms 2 to 9) to Arm 1b (1×10^{11} vp Ad26.RSV-A.preF/150 µg RSV-A preF protein), based on the estimated geometric mean titer (GMT) ratios and corresponding 95% confidence intervals (CIs). With a sample size of 55 evaluable participants per arm, and assuming a standard deviation for RSV-A2 VNA of 1.3[a] on the $\log_2$ scale, the

[a] Based on Day 29 VNA results from study VAC18193RSV1004: Cohort 2, Groups 14+17 and Cohort 3, Groups 19+20

precision of the estimated GMTs will be ~0.36 on the $\log_2$ scale. To account for approximately 10% dropout, a sample size of 60 participants per arm will be used. The table below shows the estimated 95% CIs for several GMT ratios, assuming a standard deviation for RSV-A2 VNA of 1.3 on the $\log_2$ scale for 55 participants for immunogenicity evaluation per arm.

Note: Per arm, immunogenicity data from the initial safety cohort (Cohort 1) will be combined with those from Cohort 2 to support vaccine components selection, as applicable.

N per Arm	Observed GMT Ratio	Corresponding 95% CI
55	1	[0.71; 1.41]
	1.2	[0.85; 1.69]
	1.5	[1.07; 2.11]

CI = confidence interval; GMT = geometric mean titer; N = number of participants.

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

The revaccination and durability cohort (Cohort 4) should provide sufficient data on the selected vaccine formulation to support future clinical development. To have approximately 150 participants available per arm for evaluating durability of immune response at end of the 5-year study period, and assuming a dropout rate of 10% per year, approximately 300 participants per arm are needed.

Corresponding arms of Cohort 3 and 4 will be combined (Arm 11a [Cohort 3] + Arm 14 [Cohort 4], and Arm 11b [Cohort 3] + Arm 15 [Cohort 4], respectively) for the evaluation of durability of the immune response. Having 75 participants in Arm 11a and 11b in Cohort 3 requires enrollment of 225 participants in Arms 14 and 15 in Cohort 4. Enrollment of 90 participants in Arm 16 (placebo) results in enrollment of in total 540 participants in Cohort 4. Placebo arms from Cohort 3 and 4, Arm 12 and Arm 16, respectively, will be combined in the analyses, as applicable.

Populations for Analysis Sets

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

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

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

Immunogenicity Analyses

Continuous variables will be summarized descriptively. For continuous parameters, descriptive statistics of the actual values will be calculated at all timepoints, including geometric mean with 95% CI, median and quartiles, as applicable. Additionally, geometric mean fold rises from baseline and corresponding 95% CIs might be calculated. For combined primary endpoint data of Cohort 1 and Cohort 2, geometric mean ratios between each active arm and Arm 1b will be calculated at all available timepoints, with corresponding 95% CI, as applicable. For Cohort 3, Arms 11a and 11b will be combined and the active arms will be compared to each other at all available timepoints up to 1 year after vaccination on Day 1, by means of geometric mean ratios with corresponding 95% CI. For durability and revaccination evaluation Arm 11a (Cohort 3) and Arm 14 (Cohort 4) will be combined, Arm 11b (Cohort 3) and Arm 15 (Cohort 4) will be combined, and Arm 12 (Cohort 3) and Arm 16 (Cohort 4) will be combined. For immunogenicity analyses, baseline

is considered as the last assessment pre-vaccination. Graphical representations of immunologic parameters will be made as applicable.

Geometric means per arm, and geometric mean ratios between active arms, with corresponding 95% CIs will be estimated via an analysis of variance (ANOVA) including all active arms, using log-transformed post-vaccination immune parameter response as dependent variable and study arm as independent variable. The means and differences in mean and CIs will be back-transformed (by exponentiation) to CIs around a GMT or geometric mean titer ratio (GMR). This analysis will be performed for all available assays and all time points, separately per assay. Data of the same arms form different cohorts will be combined, as applicable.

As a sensitivity analysis, the ANOVA may also be performed adjusting for the respective baseline titers, by including baseline titer as additional covariate.

For categorical variables, frequency tables will be presented.

Safety Analyses

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by cohort and study arm, and by group (pooled over cohorts, as applicable). All safety analyses will be made on the FA Set.

1.2. Schema

Figure 1: Schematic Overview of the Study for Cohorts 1 and 2

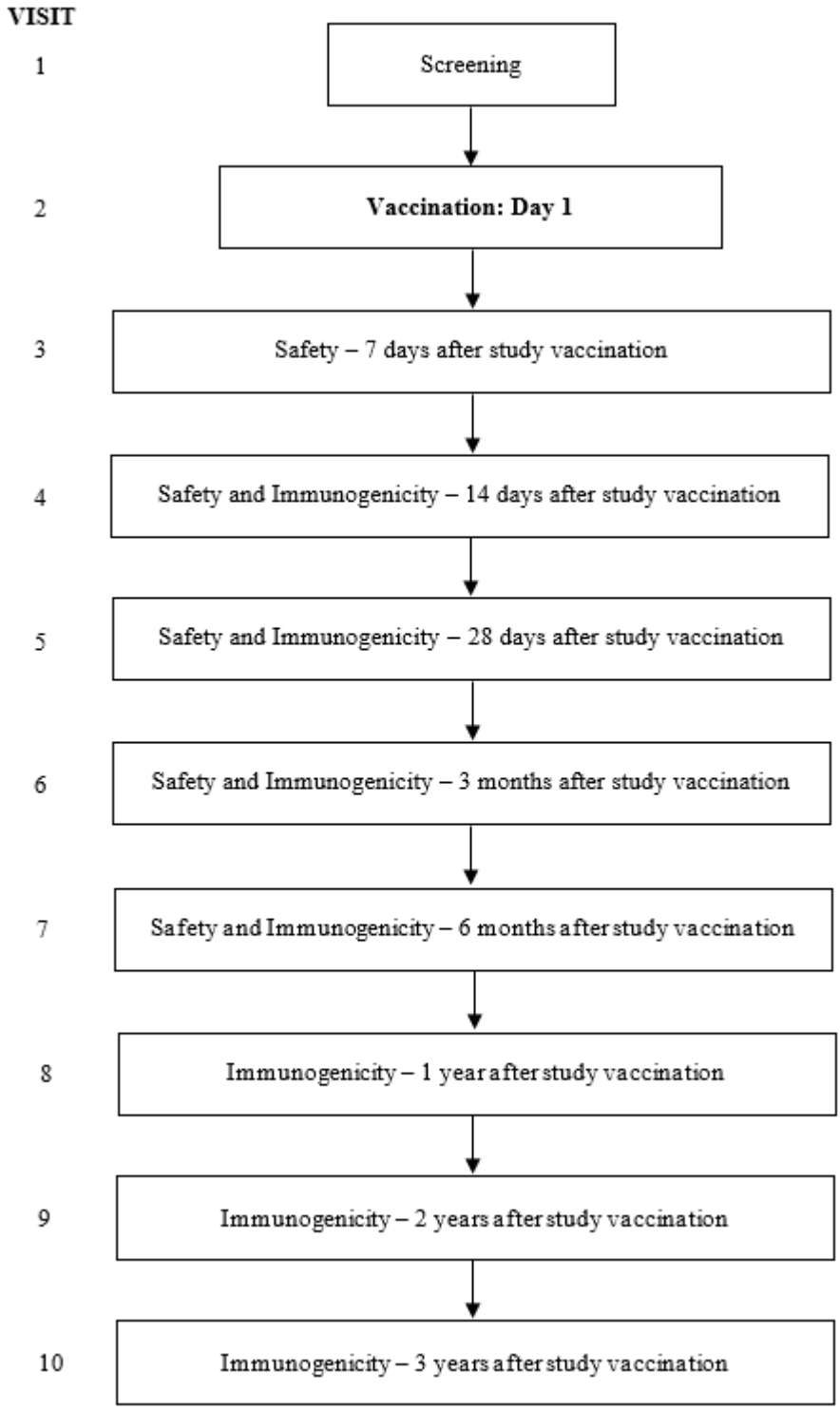
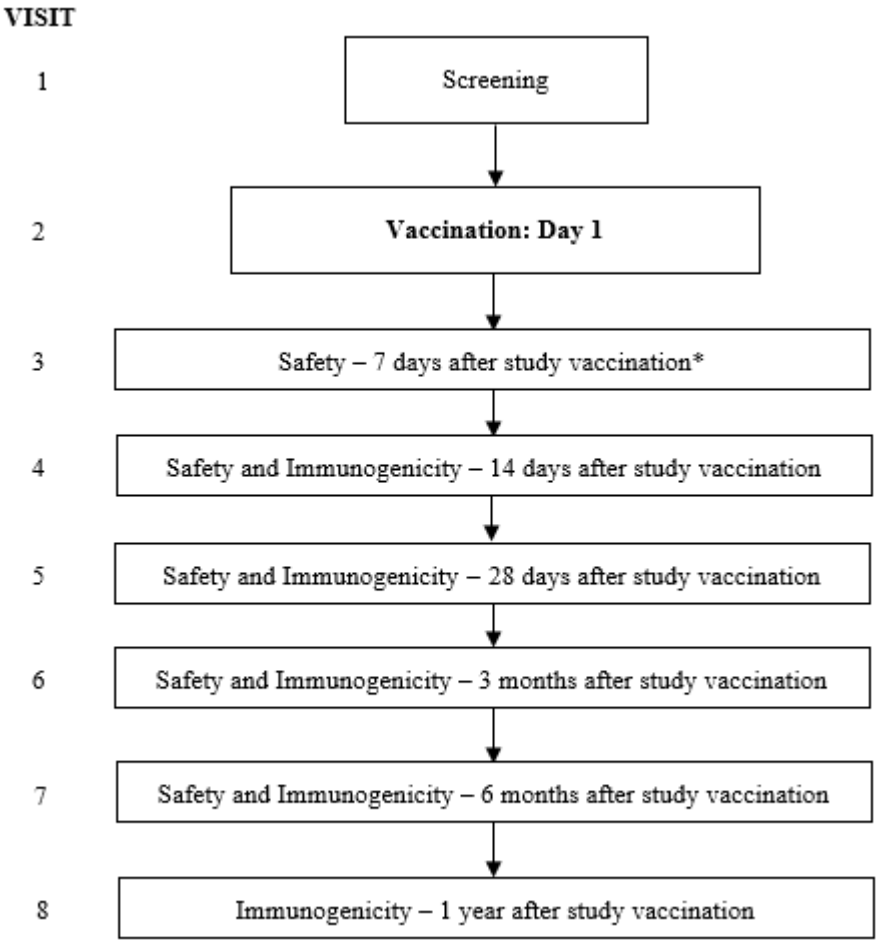
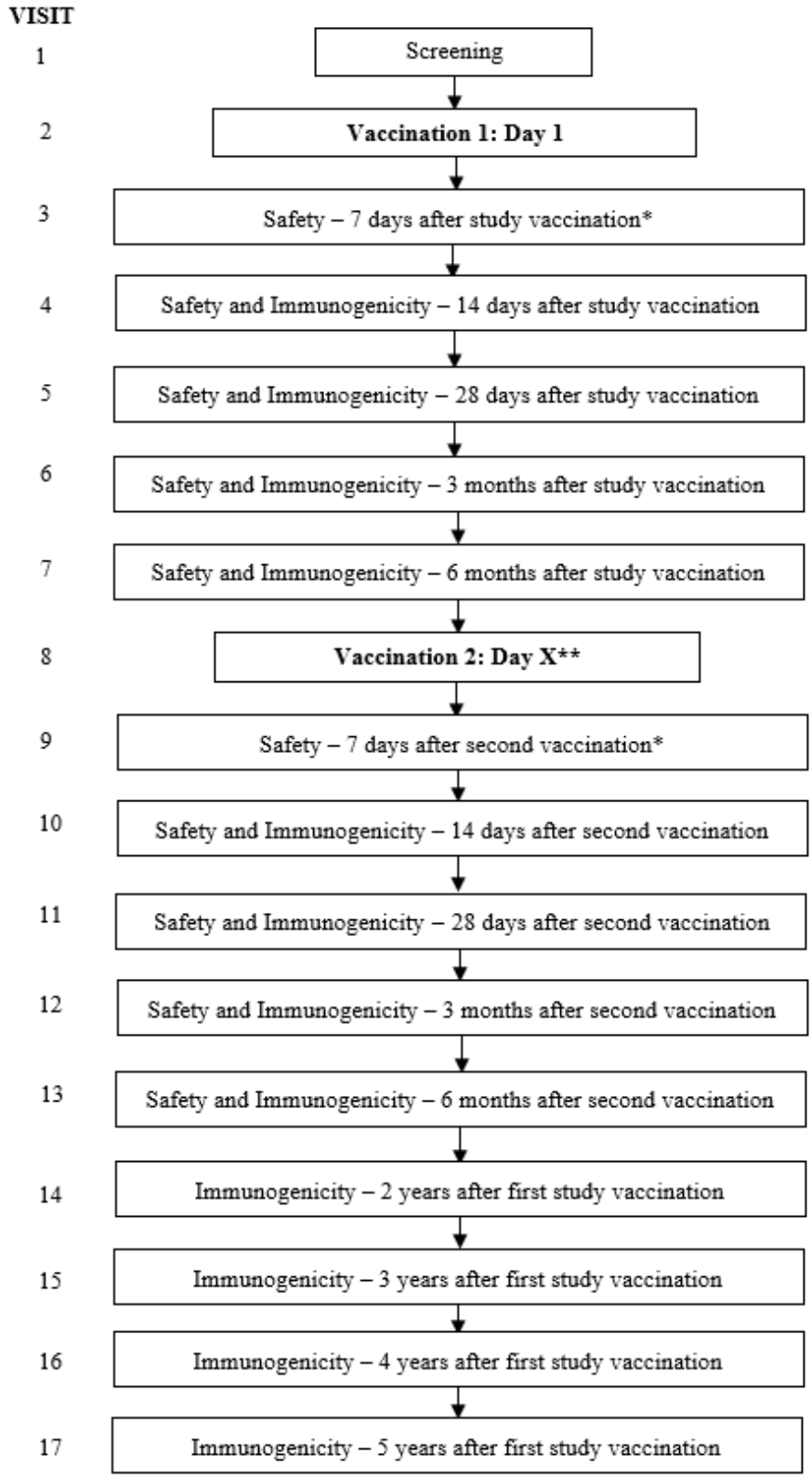


Figure 2: Schematic Overview of the Study for Cohort 3, Arms 10 and 13



* Safety only visits will be by telephone.

Figure 3: Schematic Overview of the Study for the Revaccination/Durability Cohorts: Cohort 3 (Arms 11a, 11b and 12) and Cohort 4



* Safety only visits will be by telephone.
** Timing of revaccination to be defined based on Ad26/protein preF RSV vaccine clinical data (Studies VAC18193RSV1004, VAC18193RSV2001, and VAC18193RSV3001)

1.3. Schedule of Activities (SoA)

1.3.1. Schedule of Activities – Cohort 1 and 2

Clinic Visit #	1	2	3	4	5	6	7	8[a]	9[a]	10[a]	Early Exit [c]
Visit Timing		Vac	Vac + 7 d	Vac + 14 d	Vac + 28 d	Vac +84 d (3m)	Vac + 26 wk (6 m)	Vac + 12m	Vac + 24m	Vac + 36 m	
Visit Day(s)	-28 to 1	1	8[d]	15	29	85	183	365	730	1,095	
Visit Window			+3 d	+3 d	+7 d	+7 d	±14 d	±1 m	±1 m	±1 m	
Visit Type	SCREENING	STUDY VACCINATION	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Immunogenicity	Immunogenicity	Immunogenicity	Early Exit
Written informed consent [e]	●										
Inclusion/exclusion criteria	●										
Demographics	●										
Medical history[f]/prestudy therapies [g]	●										
Physical examination [h]	●	❶									
Vital signs, including body temperature [i]	●	❷									
Randomization		❶									
Pre vaccination symptoms [j]		❶									
Safety lab blood sample, mL [k]	● 10	❶ 5	● 5								❹ 5
Humoral immunogenicity sample, mL [k,m]		❶[l] 26		●[l] 26	● 26	● 26	● 26	● 26	● 26	● 26	❸ 26
Cellular immunogenicity sample, mL (in subset of participants) [k,m,n]		❶ 60		● 60		● 60	● 60	● 60	● 60	● 60	❸ 60
Vaccination		●									
30 minute postvaccination observation [o]		●									
Solicited AE recording		*Continuous*									❹
Unsolicited AE recording		*Continuous*									❺
SAE recording [p]		*Continuous*									●
AESI recording [p,q]		*Continuous*									
Concomitant therapies [r]		*Continuous*									●
History of SARS CoV 2 vaccination [s]		*Continuous*									
COVID 19 cases [t]		*Continuous*									
Participant diary distribution [u,v]		●									
Participant diary collection and review by site staff [v]			●								

Clinic Visit #	1	2	3	4	5	6	7	8[a]	9[a]	10[a]	Early Exit [c]
Visit Timing		Vac	Vac + 7 d	Vac + 14 d	Vac + 28 d	Vac +84 d (3m)	Vac + 26 wk (6 m)	Vac + 12m	Vac + 24m	Vac + 36 m	
Visit Day(s)	-28 to 1	1	8[d]	15	29	85	183	365	730	1,095	
Visit Window			+3 d	+3 d	+7 d	+7 d	±14 d	±1 m	±1 m	±1 m	
Visit Type	SCREENING	STUDY VACCINATION	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Immunogenicity	Immunogenicity	Immunogenicity	Early Exit
Blood draw volumes Participants with blood draws for humoral responses only											
Approximate daily blood draw, mL	10	31	5	26	26	26	26	26	26	26	31
Approximate cumulative study blood draw, mL	10	41	46	72	98	124	150	176	202	**228**	
Blood draw volumes Participants with blood draws for both humoral and cellular responses (N=50 per arm)											
Approximate daily blood draw, mL	10	91	5	86	26	86	86	86	86	86	91
Approximate cumulative study blood draw, mL	10	101	106	192	218	304	390	476	562	**648**	

AE adverse event; AESI adverse event of special interest; d day; m month; SAE serious adverse event; Vac vaccination

❶ pre vaccination; ❷ pre and post vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 14 days after the previous immunogenicity blood draw; ❹ if the early exit visit is within 7 days after vaccination; ❺ if the early exit visit is within 28 days after vaccination.

Footnotes are presented on page 27.

1.3.2. Schedule of Activities – Cohort 3 (Arms 10 and 13)

Clinic Visit #	1	2	3	4	5	6	7	8[a]	Early Exit [c]
Visit Timing		Vac	Vac + 7 d	Vac + 14 d	Vac + 28 d	Vac +84 d (3m)	Vac + 26 wk (6 m)	Vac + 12m	
Visit Day(s)	-28 to 1	1	8[b]	15	29	85	183	365	
Visit Window			+3 d	+3 d	+7 d	+7 d	±14 d	±1 m	
Visit Type	SCREENING	STUDY VACCINATION	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Immunogenicity	Early Exit
Written informed consent [e]	●								
Inclusion/exclusion criteria	●								
Demographics	●								
Medical history[f]/prestudy therapies [g]	●								
Physical examination [h]	●	❶							
Vital signs, including body temperature [i]	●	❷							
Randomization		❶							
Pre vaccination symptoms [j]		❶							
Humoral immunogenicity sample, mL [k,m]		❶[l] 26		●[l] 26	● 26	● 26	● 26	● 26	❸ 26
Cellular immunogenicity sample, mL (in subset of participants) [k, m]		❶ 60		● 60		● 60	● 60	● 60	❸ 60
Vaccination		●							
30 minute postvaccination observation [o]		●							
Solicited AE recording		*Continuous*							❹
Unsolicited AE recording		*Continuous*							❺
SAE recording [p]		*Continuous*							●
AESI recording [p,q]		*Continuous*							
Concomitant therapies [r]		*Continuous*							●
History of SARS CoV 2 vaccination [s]		*Continuous*							
COVID 19 cases [t]		*Continuous*							
Participant diary distribution [u,v]		●							
Participant diary collection and review by site staff [v]				●					
Blood draw volumes: ***Participants with blood draws for humoral responses only***									

Clinic Visit #	1	2	3	4	5	6	7	8[a]	Early Exit [c]
Visit Timing		Vac	Vac + 7 d	Vac + 14 d	Vac + 28 d	Vac +84 d (3m)	Vac + 26 wk (6 m)	Vac + 12m	
Visit Day(s)	-28 to 1	1	8[b]	15	29	85	183	365	
Visit Window			+3 d	+3 d	+7 d	+7 d	±14 d	±1 m	
Visit Type	SCREENING	STUDY VACCINATION	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Immunogenicity	Early Exit
Approximate daily blood draw, mL		26		26	26	26	26	26	26
Approximate cumulative study blood draw, mL		26	26	52	78	104	130	**156**	
Blood draw volumes: ***Participants with blood draws for both humoral and cellular responses (N=80)***									
Approximate daily blood draw, mL		86		86	26	86	86	86	86
Approximate cumulative study blood draw, mL		86	86	172	198	284	370	**456**	

AE adverse event; AESI adverse event of special interest; d day; m month; SAE serious adverse event; Vac vaccination

❶ pre vaccination; ❷ pre and post vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 14 days after the previous immunogenicity blood draw; ❹ if the early exit visit is within 7 days after vaccination; ❺ if the early exit visit is within 28 days after vaccination.

Footnotes are presented on page 27.

1.3.3. Schedule of Activities – Revaccination/Durability: Cohort 3 (Arms 11a, 11b and 12) and Cohort 4

Clinic Visit #	1	2	3	4	5	6	7	8[a]	9	10	11	12	13	14[a]	15[a]	16[a]	17[a]	Early Exit[c]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 1 +84 d (3m)	Vac 1 + 26 wk (6 m)	Vac 2	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 +84 d (3m)	Vac 2 + 26 wk (6 m)	Vac 1 + 24m	Vac 1 + 36m	Vac 1 + 48m	Vac 1 + 60m	
Visit Day(s)	-28 to 1	1	8[b]	15	29	85	183	X*	X+7[a]*	X+14*	X+28*	X+84*	X+182*	730	1,095	1,460	1,825	
Visit Window			+3 d	+3 d	+7 d	+7 d	±14 d	±1 m	+3 d	+3 d	+7 d	+7 d	±14 d	±1 m	±1 m	±1 m	±1 m	
Visit Type	SCREENING	STUDY VACCINATION 1	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 2 Immunogenicity	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Immunogenicity	Immunogenicity	Immunogenicity	Immunogenicity	Early Exit
Written informed consent[e]	●							●										
Inclusion/exclusion criteria	●																	
Demographics	●							●										
Medical history[f]/prestudy therapies[g]	●							●										
Physical examination[h]	●	❶						❶										
Vital signs, including body temperature[i]	●	❷						❷										
Randomization		❶						❶										
Verification of selected eligibility criteria								❶										
Pre vaccination symptoms[j]		❶						❶										
Humoral immunogenicity sample, mL[k,m]		❶[l] 26		●[l] 26	● 26	● 26	● 26	❶ 26		● 26	● 26	● 26	● 26	● 26	● 26	● 26	● 26	❸ 26
Cellular immunogenicity sample, mL (in subset of participants)[k,m]		❶ 60		● 60		● 60	● 60	❶ 60		● 60		● 60	● 60	● 60	● 60	● 60	● 60	❸ 60
Vaccination		●						●										
30 minute postvaccination observation[o]		●						●										
Solicited AE recording		*Continuous*						*Continuous*										❹
Unsolicited AE recording		*Continuous*						*Continuous*										❺
SAE recording[p]		*Continuous*						*Continuous*										●
AESI recording[p,q]		*Continuous*						*Continuous*										

Clinic Visit #	1	2	3	4	5	6	7	8[a]	9	10	11	12	13	14[a]	15[a]	16[a]	17[a]	Early Exit[c]
Visit Timing		Vac 1	Vac 1 + 7 d	Vac 1 + 14 d	Vac 1 + 28 d	Vac 1 +84 d (3m)	Vac 1 + 26 wk (6 m)	Vac 2	Vac 2 + 7 d	Vac 2 + 14 d	Vac 2 + 28 d	Vac 2 +84 d (3m)	Vac 2 + 26 wk (6 m)	Vac 1 + 24m	Vac 1 + 36m	Vac 1 + 48m	Vac 1 + 60m	
Visit Day(s)	-28 to 1	1	8[b]	15	29	85	183	X*	X+7[a]*	X+14*	X+28*	X+84*	X+182*	730	1,095	1,460	1,825	
Visit Window			+3 d	+3 d	+7 d	+7 d	±14 d	±1 m	+3 d	+3 d	+7 d	+7 d	±14 d	±1 m	±1 m	±1 m	±1 m	
Visit Type	SCREENING	STUDY VACCINATION 1	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	STUDY VACCINATION 2 Immunogenicity	Safety	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Safety and Immunogenicity	Immunogenicity	Immunogenicity	Immunogenicity	Immunogenicity	Early Exit
Concomitant therapies[r]		*Continuous*						*Continuous*										●
History of SARS CoV 2 vaccination[s]		*Continuous*																
COVID 19 cases[t]		*Continuous*																
Participant diary distribution[u,v]		●						●										
Participant diary collection and review by site staff[v]				●						●								
Blood draw volumes: Participants with blood draws for humoral responses only																		
Approximate daily blood draw, mL		26		26	26	26	26	26		26	26	26	26	26	26	26	26	26
Approximate cumulative study blood draw, mL		26	26	52	78	104	130	156	156	182	208	234	260	286	312	338	**364**	
Blood draw volumes: Participants with blood draws for both humoral and cellular responses (N=160)																		
Approximate daily blood draw, mL		86		86	26	86	86	86		86	26	86	86	86	86	86	86	86
Approximate cumulative study blood draw, mL		86	86	172	198	284	370	456	456	542	568	654	740	826	912	998	**1,084**	

AE adverse event; AESI adverse event of special interest; d day; m month; SAE serious adverse event; Vac vaccination

❶ pre vaccination; ❷ pre and post vaccination; ❸ blood samples for immunogenicity will only be taken if the early exit visit is at least 14 days after the previous immunogenicity blood draw; ❹ if the early exit visit is within 7 days after vaccination; ❺ if the early exit visit is within 28 days after vaccination.

* Timing of revaccination to be defined based on Ad26/protein preF RSV vaccine clinical data (Studies VAC18193RSV1004, VAC18193RSV2001, and VAC18193RSV3001). In case revaccination will be later than 12 months relative to the first dose, additional blood sampling 1 year post first vaccination may be included.

Table footnotes for all cohorts:

a. For visits more than 3 months apart, sites will be encouraged to make quarterly phone calls prior to the indicated visit timing to ensure participant engagement.
b. Safety only visits will be by telephone (Cohorts 3 and 4).
c. An early exit visit will be conducted as soon as possible for those participants who are unable to continue participation in the study, for whom consent is not withdrawn. Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent).
d. In addition, sentinel participants will be contacted by telephone 24 hours post-dose to collect safety information.
e. Signing of the ICF should be done before any study-related activity.
f. Medical history of all participants will be recorded in the eCRF, including whether each condition places the participant at increased risk for severe RSV disease. The conditions placing a participant at increased risk of severe RSV disease include congestive heart failure, coronary artery disease (such as angina pectoris, ischemic cardiomyopathy, history of myocardial infarct, or history of coronary artery bypass graft or coronary artery stent), and chronic lung disease (such as asthma and chronic obstructive pulmonary disease). Baseline information on risk factors for thrombosis and/or thrombocytopenia should also be recorded, as well as history of past COVID-19 infection.
g. Prestudy therapies administered up to 30 days pre-vaccination must be recorded on Day 1.
h. A physical examination, including height and body weight, will be carried out at on Day 1. At all other visits, an abbreviated, symptom-directed examination will be performed if deemed necessary by the investigator based on any clinically relevant issues, clinically relevant symptoms, and medical history.
i. Sitting systolic and diastolic blood pressure, heart rate, and respiratory rate after at least 5 minutes rest on Day 1. At non-vaccination visits, vital signs will be measured if deemed necessary by the investigator.
j. Investigator must check for clinically significant acute illness at the time of vaccination or body temperature of ≥38.0°C (≥100.4ºF) within 24 hours prior to the planned time of vaccination. In such cases, the participant may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator.
k. Blood sample volumes are approximate. Refer to the laboratory manual for additional details.
l. Aliquots of serums samples collected for immunogenicity test can be reconverted for participant's safety purposes upon sponsor request. Please refer to Appendix 2 for a non-exhaustive list of tests that will be requested on these sample in case of potential AESI reporting.
m. Blood for humoral immune responses will be drawn from all participants. Blood for cellular immune responses will be drawn from a subset of participants (from Cohorts 1, 2, and 3; not applicable to Cohort 4).
n. Based on results available at the time of primary analysis, the sponsor will decide which arms will continue with blood sampling for cellular immune responses beyond 6 months post vaccination in Cohorts 1 and 2.
o. After vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. Any unsolicited AEs, solicited local (injection site) or systemic AEs, and vital signs (sitting systolic and diastolic blood pressure, heart rate, and respiratory rate after at least 5 minutes rest, and body temperature) will be documented by the study site personnel following this observation period.
p. All (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be collected from ICF signature onwards until the end of the study for all participants. All other SAEs and AESIs will be collected from administration of study vaccine (Day 1) until 6 months after the last study vaccination. AEs leading to discontinuation from vaccination and/or study will be collected for the duration of the study.
q. AESIs, including potential AESIs, are to be reported from the moment of vaccination until 6 months after the last study vaccination.
r. Concomitant therapies will be collected from the time of study vaccination through 28 days post-vaccination when associated with an AE, and from ICF signature until 6 months after the last study vaccination when associated with an SAE or AESI.
s. Any history of SARS-CoV-2 vaccination (name/manufacturer of the vaccine and date of administration, whenever possible) prior to and during the study will be collected in the eCRF.
t. All COVID-19 cases will be collected for all participants for the duration of the study. COVID-19 cases reported by the participant will be reported in the eCRF by the investigator.

u. Rulers and thermometers will be distributed at these visits.
v. Participants will be contacted by telephone 2 to 4 days post-vaccination to remind them to fill in the participant diaries and to check that they are entering information correctly.

2. INTRODUCTION

The respiratory syncytial virus (RSV) vaccine that will be investigated in the current study is a combination of adenovirus type 26 (Ad26)-based and/or preF protein-based vaccine components derived from RSV A and B subtypes, administered as intramuscular (IM) injections:

- Ad26.RSV.preF (JNJ-64400141; referred to in this document as Ad26.RSV-A.preF), a replication-incompetent Ad26 containing a deoxyribonucleic acid (DNA) transgene that encodes the prefusion conformation-stabilized F protein derived from the RSV A subtype.
- Ad26.RSV-B.preF2 (JNJ-86051823), a replication-incompetent Ad26 containing a DNA transgene that encodes the prefusion conformation-stabilized F protein derived from the RSV B subtype.
- RSV preF protein (JNJ-64213175; referred to in this document as RSV-A preF protein) is a prefusion conformation-stabilized F protein derived from the RSV A subtype.
- RSV-B preF protein (JNJ-78991172) is a prefusion conformation-stabilized F protein derived from the RSV B subtype.

A combination of Ad26.RSV-A.preF and RSV-A preF protein, referred to as Ad26/protein preF RSV vaccine, was shown to be efficacious against RSV-A and RSV-B in preventing RSV-mediated lower respiratory tract disease (LRTD) in humans in the ongoing Phase 2b study VAC18193RSV2001. The efficacy of the Ad26/protein preF RSV vaccine will be further evaluated in an ongoing Phase 3 study (VAC18193RSV3001). The current study will be the first-in-human (FIH) study for Ad26.RSV-B.preF2, RSV-B preF protein, the Ad26.RSV-B.preF2/RSV-B preF protein combination, and the various combinations of RSV-A and RSV-B components. After initial safety assessments, the study will continue with vaccine components and dose selection followed by expanded safety evaluation and evaluation of durability of immune responses of the selected vaccine formulation and the effect of revaccination.

Both Ad26.RSV-B.preF2 and RSV-B preF protein have been evaluated in nonclinical pharmacology studies that have shown improved humoral immune responses and protective efficacy against circulating RSV B strains compared with the Ad26.RSV-A.preF and RSV-A preF protein components, respectively, in rodent models.

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

For the most comprehensive nonclinical and clinical information regarding Ad26.RSV-B.preF2 and RSV-B preF protein, refer to the latest version of the IB and addenda (if applicable) (IB VAC18195 2021).

A brief summary of the clinical information available at the time of protocol writing is provided below.

The term “study vaccine” throughout the protocol, refers to Ad26.RSV-A.preF, RSV-A preF protein, Ad26.RSV-B.preF2, RSV-B preF protein, or placebo as defined in Section 6.1.

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

2.1. Study Rationale

Study VAC18193RSV2001 showed that the Ad26/protein preF RSV vaccine could prevent RSV-mediated LRTD with 80% efficacy. CCI [redacted] Two strategies to improve protection against RSV B subtypes will be explored in the current study: 1) increase the dose of the Ad26/protein preF RSV vaccine; 2) introduce additional components based on the preF protein of the RSV B subtype (Ad26.RSV-B.preF2 and/or RSV-B preF protein). This RSV-B F protein is based on the consensus sequence of RSV B subtype sequences present in the public database. Following these 2 strategies, various combinations of vaccine components will be evaluated in this study.

This study is designed to evaluate the safety and immunogenicity of different formulations of RSV.preF-based vaccines in adults aged 60 years and older, to select the optimal dose based on safety and immunogenicity data, and to assess durability of immune responses of the selected vaccine formulation as well as the effect of revaccination. The RSV.preF-based vaccines to be evaluated in the current study include various combinations of 2 or more of the following components: Ad26.RSV-A.preF, Ad26.RSV-B.preF2, RSV-A preF protein and RSV-B preF protein. The details on the combinations of RSV vaccine components to be evaluated in each group are described in Section 4.

2.2. Background

RSV is a negative-sense, single stranded RNA virus that belongs to the family of *Paramyxoviridae*. RSV is traditionally classified into 2 subtypes, RSV A and RSV B, which diverged approximately 350 years ago and are mainly based on antigenic variations in the RSV G protein (Pandya 2019). Adults infected with RSV usually experience mild, cold-like symptoms of upper respiratory tract infection and recover within 2 weeks. However, infection can progress to severe LRTD causing substantial morbidity and mortality in vulnerable populations, such as adults with underlying comorbidities and the elderly, ie, aged 60 years and older. In long-term care facilities, RSV is estimated to infect 5% to 10% of the residents per year with significant rates of pneumonia (10% to 20%) and death (2% to 5%) (Falsey 2000). In one epidemiology study of RSV burden, it was estimated that 11,000 elderly persons die annually of RSV in the United States (Thompson 2003). Despite this high disease burden, there are currently no licensed preventive vaccines against RSV infection.

To address this unmet medical need, the sponsor is developing the Ad26/protein preF RSV vaccine for use in adults, which is currently in clinical evaluation. This vaccine contains the combination

of an Ad26 viral vector expressing the RSV A2 preF protein (Ad26.RSV-A.preF) and the preF protein of RSV A2 (RSV-A preF protein). The F protein is highly similar between RSV A and B subtypes and its prefusion form has been shown to be immunogenic (Sullender 2000, Williams 2020). Antibodies against preF protein have also been suggested as correlates of protection for RSV (Mazur 2019). Results showed that the vaccine containing Ad26.RSV-A.preF and RSV-A preF protein components has a favorable reactogenicity profile as well as induced durable humoral and cellular immune responses (IB Ad26/protein preF RSV vaccine 2021). In a currently ongoing Phase 2b clinical study (VAC18193RSV2001), this vaccine has been shown to prevent RSV-mediated LRTD due to both RSV A and B infection. However, further exploratory analyses suggested that the observed VE against RSV B subtypes was lower compared to VE against RSV A subtypes. In case these findings would be confirmed in larger studies, there might be opportunity to identify possibilities to improve the VE of the current vaccine against RSV B subtypes.

Nonclinical Studies

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

For the most comprehensive nonclinical information regarding Ad26.RSV-B.preF2 and RSV-B preF protein, refer to the latest version of the IB and addenda (if applicable) (IB VAC18195 2021).

Clinical Studies

The immunological benefit of combining Ad26.RSV-A.preF with RSV-A preF protein was first shown in study VAC18193RSV1004. A significant increase in virus neutralizing titers was observed at 28 days post-dose 1 in the groups combining Ad26.RSV-A.preF and RSV-A preF protein compared to Ad26.RSV-A.preF 1×10^{11} viral particles (vp) alone. Based on this study, the current Ad26/protein preF RSV vaccine, based on the RSV-A subtype, at a dose level of 1×10^{11} vp/150 µg was selected for future clinical development.

The Ad26/protein preF RSV vaccine is currently being evaluated in study VAC18193RSV2001, a multicenter, randomized, double-blind, placebo-controlled Phase 2b proof-of-concept efficacy study in ~5,800 participants aged ≥65 years, with and without comorbidities. The study was designed to demonstrate efficacy of the Ad26.RSV.preF/ RSV preF protein vaccine (1×10^{11} vp/150 µg) for at least 1 of the 3 case definitions of RSV-mediated LRTD. The primary analysis after the end of the first RSV season showed high, statistically significant VE against RSV-mediated LRTD for all case definitions, ranging from 80% for the most severe endpoint (case definition #1) to 69.8% for the mildest endpoint (case definition #3). The vaccine was safe and well tolerated. Study VAC18193RSV2001 is currently ongoing to evaluate the duration of protection beyond the first season and immune responses after revaccination in a subset of participants. Additionally, the Ad26/protein preF RSV vaccine is also being evaluated in study VAC18193RSV3001, a multicenter, randomized, double-blind, placebo-controlled Phase 3 efficacy study in participants aged 60 years and older, with or without comorbidities.

The Ad26/protein preF RSV vaccine was also evaluated in study VAC18193RSV2005, an ongoing, multicenter, randomized, double-blind, placebo-controlled Phase 2a study to explore the dose-response relationship, safety, and immunogenicity of a range of dose levels of the Ad26.RSV.preF component in the Ad26/protein preF RSV vaccine in participants aged 60 years and older who are in stable health, with and without comorbidities. The primary analysis has been completed. All Ad26.RSV.preF dose levels evaluated in the study, ranging from 3.7×10^{9} vp to 1.6×10^{11} vp, in combination with the 150 µg dose of RSV preF protein evaluated in this study showed comparable vaccine induced humoral and cellular immune responses and an acceptable safety and reactogenicity profile.

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

This will be the first-in-human study to collect clinical information regarding Ad26.RSV-B.preF2, RSV-B preF protein, the Ad26.RSV-B.preF2/RSV-B preF protein combination, or the various combinations of RSV A and RSV B components.

Clinical Safety Experience with Ad26-based Vaccines

Safety data of Ad26-vectored vaccines from the Adenoviral Vaccine Safety Database V6.0 (cut-off date: 31 December 2020) (AdVac Safety Database 2021), including vaccines against Ebola virus (Ad26.ZEBOV), HIV (Ad26.ENVA.01, Ad26.Mos.HIV, and Ad26.Mos4.HIV), malaria (Ad26.CS.01), RSV (Ad26.RSV.FA2 and Ad26.RSV.preF), filovirus (Ad26.Filo), Zika virus (Ad26.ZIKV.001), and HPV (Ad26.HPV16 and Ad26.HPV18) have been evaluated in adults. Studies with Ad26.COV2.S (COVID-19 vaccine program) were still blinded at the cut-off date and therefore only blinded SAE data and blinded pregnancy data from the Janssen Global Safety Database were included in the AdVac Safety Database.

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

Thrombosis With Thrombocytopenia Syndrome

In the context of worldwide vaccination following Emergency Use Authorization (EUA), conditional licensure, or approval by health authorities, thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), in some cases accompanied by internal bleeding, has been observed following vaccination with the Janssen COVID-19 (Ad26.COV2.S) vaccine. As of 31 August 2021, out of 33,584,049 doses of

Ad26.COV2.S administered post-marketing, the following spontaneous reported/solicited reports of probable TTS cases were identified. [a]

- A total of 104 post-marketing events that met the Brighton TTS Case Definition Criteria Level 1 to 3 (Brighton Collaboration 2021). This corresponds to a reporting ratio of 3.1 per million doses overall.
- A total of 67 post-marketing events that met the CDC TTS Case Definition Criteria Tier 1 to 2 (Shimabukuro 2021). This corresponds to a reporting ratio 2 per million doses overall.

Reports include severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis and arterial thrombosis, in combination with thrombocytopenia. Venous thrombosis cases have also been reported at more common sites, eg, in the lower extremities. The onset of associated symptoms has usually been 1 to 4 weeks, but sometimes even later following vaccination. TTS cases have been reported mostly in women under 60 years of age although some cases of TTS have also been reported in men and in individuals older than 60 years of age. Thrombosis in combination with thrombocytopenia has been fatal in some cases. The exact pathophysiology of TTS is unclear. This event has not been observed to date with any other Janssen Ad26-based vaccines. Participants should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain or leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision, skin bruising and/or petechiae beyond the site of vaccination, changes in mental status or the occurrence of seizures.

2.3. Benefit-Risk Assessment

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

More detailed information about the known and expected benefits and risks of Ad26.RSV-B.preF2 and RSV-B preF protein may be found in the IB and addenda (if applicable) (IB VAC18195 2021).

2.3.1. Risks for Study Participation

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

Risks Related to Ad26/protein preF RSV Vaccine

The Ad26/protein preF RSV vaccine is currently being studied in 4 ongoing studies in more than 6,500 participants aged 60 years and older, including participants with comorbidities, to assess safety and immunogenicity and to investigate whether the vaccine prevents RSV disease. In these studies, the most commonly reported solicited local adverse events (AEs) were injection site

[a] Probable TTS is defined as a thrombotic/thromboembolic event reported in combination with a low platelet count [thrombocytopenia]

pain/tenderness and swelling (mild to moderate). The most frequently reported solicited systemic AEs were fatigue, muscle pain, headache, chills, joint pain, and nausea, which were mild to moderate in severity. These solicited AEs were short-lived and resolved within a few days. Overall, available results from these studies show the vaccine to be well-tolerated with no safety concerns.

Risks Related to RSV-B Components

This study will be the FIH study for Ad26.RSV-B.preF2, RSV-B preF protein, and the various combinations of RSV A and RSV B components. No clinical data are available to date.

For the most comprehensive nonclinical information regarding Ad26.RSV-B.preF2 and RSV-B preF protein, refer to the latest version of the Investigator's Brochure (IB VAC18195 2021).

General Risks Related to Vaccination

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

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

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

After vaccination, participants will remain at the study site for at least 30 minutes and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions.

Pregnancy and Birth Control

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

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

Participants with Immunosuppression/Reduced Immune Response

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

Risks from Blood Draws

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

Risks from Genetic Testing

Genetic test results could indicate risks for certain diseases, which could potentially lead to discrimination or other problems for the participant. However, the results are for exploratory research purposes only and will not be provided to the participant.

Concomitant Vaccination

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

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

Unknown Risks

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

2.3.2. Benefits for Study Participation

Participants may benefit from clinical testing and physical examination.

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

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

This study will be the FIH study for Ad26.RSV-B.preF2, RSV-B preF protein, and the various combinations of RSV A and RSV B components. No clinical data are available to date.

2.3.3. Benefit-Risk Assessment for Study Participation

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

- The dose levels of Ad26.RSV-A.preF and RSV-A preF protein used in the current study were determined from the primary analysis of Cohort 2 in study VAC18193RSV1004 and are currently under further evaluation in studies VAC18193RSV1004, VAC18193RSV2001 and VAC18193RSV3001. Additional dose levels of Ad26.RSV.preF were evaluated in studies VAC18193RSV1004 and VAC18193RSV2005. The available safety data from all studies show the vaccine to be well-tolerated with no safety concerns. For details on the justification for dose levels selected for this study, see Section 4.3. In the primary analysis of study VAC18193RSV2001, vaccine efficacy was demonstrated for the 1×10^{11} vp/150 µg dose level in adults aged 65 years and above, for the prevention of LRTD caused by RSV.
- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:

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

  After each vaccination, participants will remain at the study site for at least 30 minutes and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use a participant diary to document solicited signs and symptoms. Details are provided in Section 8.2.

  The investigator or the designee will document unsolicited AEs, SAEs, and AESIs as indicated in Sections 8.2 and 8.3 and Appendix 4.

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

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

  All AEs, SAEs, and AESIs will be followed by the investigator until clinical resolution or until a clinically stable condition is reached, or until the participant has been deemed lost to follow-up after demonstration of due diligence of follow-up efforts. An early exit visit will be conducted for those participants who are unable to continue participation in

the study and withdraw from the study before the end of the study, but who do not withdraw consent. Participants who wish to withdraw consent from participation in the study will be offered an early exit visit (prior to formal withdrawal of consent) (Section 7.2).

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

  Clinical laboratory assessments will be performed at screening. Details are provided in Section 10.2, Appendix 2, Clinical Laboratory Tests.

  In Cohort 1, sentinel participants will be evaluated for safety before extending enrollment to the next group. In Group 4, the sentinel participants will be dosed at least 1 hour apart. A telephone call will be made to each of the sentinel participants on Day 2 (approximately 24 hours post-vaccination) to collect safety data. The blinded 24-hour post-vaccination safety data in these sentinel participants will be reviewed by the principal investigator (PI) and sponsor's study responsible physician/scientist (SRP/S). Randomization and vaccination of additional participants will be halted until this 24-hour sentinel safety evaluation is completed. Refer to Section 4.1 for further details.

  Prior to progression to Cohort 2, an internal DRC will review blinded[a] Day 8 safety data following administration of the first vaccination to all Cohort 1 participants. Refer to Section 4.1 for further details.

  There are pre-specified rules for all participants, that if met would result in pausing of further vaccinations, preventing exposure of new participants to study vaccine until the Data Review Committee (DRC) reviews all safety data (see Committee Structure in Appendix 3).

  Study vaccinations will be discontinued in participants for the reasons described in Section 7.1.

  Temporary contraindications to study vaccination are described in Section 5.5.

3. OBJECTIVES AND ENDPOINTS

The current study has an adaptive design to determine a combination of vaccine components for further clinical development in adults aged ≥60 years based on safety and immunogenicity. The selected RSV.preF-based vaccine formulation should improve immune responses to RSV B subtypes with no adverse effect on immune responses to RSV A subtypes compared to the Ad26/protein preF RSV vaccine.

[a] The DRC will review blinded data first but may review unblinded data if deemed necessary.

INITIAL SAFETY COHORT OBJECTIVE (COHORT 1): *To determine in small numbers of participants aged 60 years and older the safety of a vaccine formulation comprising a combination of Ad26.RSV A.preF and/or Ad26.RSV B.preF2 and/or RSV A preF and/or RSV B preF proteins before progression to vaccine components selection in a larger number of participants for further assessment of the safety and immunogenicity*

Objectives	***Endpoints***
PRIMARY	
• To assess the safety and reactogenicity of various combinations of RSV vaccine components	• Serious adverse events (SAEs) and adverse events of special interest (AESIs) from first dose administration until 6 months after vaccination • Solicited local and systemic adverse events (AEs) for 7 days after vaccine administration • Unsolicited AEs from the time of vaccine administration through the following 28 days

VACCINE COMPONENTS SELECTION OBJECTIVE (COHORTS 1 and 2): *To select an optimal RSV.preF based vaccine based on assessment of the safety and immunogenicity in participants aged 60 years and older receiving a vaccine formulation comprising a combination of Ad26.RSV A.preF and/or Ad26.RSV B.preF2 and/or RSV A preF and/or RSV B preF proteins.*

Objectives	***Endpoints***
PRIMARY	
• To assess the safety and reactogenicity of various combinations of RSV vaccine components	• SAEs and AESIs from first dose administration until 6 months after vaccination • Solicited local and systemic AEs for 7 days after vaccine administration • Unsolicited AEs from the time of vaccine administration through the following 28 days
• To assess humoral immune responses elicited by various combinations of RSV vaccine components	• RSV neutralization antibody titers
SECONDARY	
• To assess humoral and cellular immune responses elicited by various combinations of RSV vaccine components using other immunological assays	• F protein binding antibodies (pre-F and/or post-F), and antigen-specific T-cell responses*
EXPLORATORY	
• To further explore vaccine-elicited immune responses after single vaccination with various combinations of RSV vaccine components	• Exploratory endpoints may include the following, but are not limited to: RSV neutralization antibody titers against additional A and/or B strains, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, antibody-dependent cell-mediated cytotoxicity [ADCC], antibody-dependent cell-mediated phagocytosis [ADCP], antibody isotyping, antibody sequencing for repertoire), including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum samples, transcriptome analysis and sequencing of the T-cell receptor (TCR) and/or B-

Objectives	*Endpoints*
	cell receptor (BCR) or heavy/light chain (VH/VL) characterization, evaluation of the cellular immune response and the functional and memory immune response by intracellular cytokine staining (ICS)*, cellular phenotyping and memory B-cell ELISpot*
• To assess the durability of the immune response in selected groups	• Endpoints may include the following, but are not limited to: RSV neutralization antibody titers against RSV subtype A and B, RSV neutralization antibody titers against additional A and/or B strains, RSV F protein binding antibodies (pre-F and/or post-F), antigen-specific T-cell responses*, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, ADCC, ADCP, antibody isotyping, antibody sequencing for repertoire), including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum, transcriptome analysis and sequencing of the TCR and/or BCR or VH/VL characterization, evaluation of the cellular immune response and the functional and memory immune response by ICS*, cellular phenotyping and memory B-cell ELISpot*

* Only applicable for participants with blood draws for cellular responses.

EXPANDED SAFETY COHORT OBJECTIVE (COHORT 3): *To determine the safety and immunogenicity of the selected RSV.preF based vaccine in an expanded cohort of participants aged 60 years and older, comparing the formulation of the selected combination of RSV vaccine components (2x1 mL formulation, based on Cohort 1 and 2 results) and the formulation to be used for future clinical development (1x1 mL formulation); and to assess durability of the selected RSV.preF based vaccine and determine the effect of revaccination.*

Objectives	*Endpoints*
PRIMARY	
• To assess the safety and reactogenicity of the selected RSV.preF-based vaccine formulation (based on Cohort 1 and 2 results), compared to the formulation to be used for future clinical development	• SAEs and AESIs from first administration until 6 months after the last vaccination • Solicited local and systemic AEs for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
SECONDARY	
• To assess immune responses to the selected RSV.preF-based vaccine formulation (based on Cohort 1 and 2 results), compared to the formulation to be used for future clinical development	• RSV neutralization antibody titers
• To assess the durability of the immune response to the selected RSV.preF-based vaccine formulation in groups with and without revaccination	• RSV neutralization antibody titers

Objectives	*Endpoints*
EXPLORATORY	
• Additional exploratory analyses may be performed to further investigate humoral and cellular vaccine-elicited immune responses to the selected RSV.preF-based vaccine formulation and durability	• Endpoints may include the following, but are not limited to: RSV neutralization antibody titers against additional A and/or B strains, F protein binding antibodies (pre-F and/or post-F), and antigen-specific T-cell responses*, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, ADCC, ADCP, antibody isotyping, antibody sequencing for repertoire), including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum, transcriptome analysis and sequencing of the TCR and/or BCR or VH/VL characterization, evaluation of the cellular immune response and the functional and memory immune response by ICS*, cellular phenotyping and memory B-cell ELISpot*
• To further assess immune responses to the selected RSV.preF-based vaccine formulation (based on Cohort 1 and 2 results), the formulation to be used for future clinical development, and the current Ad26/protein preF RSV vaccine	• Endpoints may include the following, but are not limited to: RSV neutralization antibody titers, RSV neutralization antibody titers against additional A and/or B strains, F protein binding antibodies (pre-F and/or post-F), and antigen-specific T-cell responses*, anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, ADCC, ADCP, antibody isotyping, antibody sequencing for repertoire), including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum, transcriptome analysis and sequencing of the TCR and/or BCR or VH/VL characterization, evaluation of the cellular immune response and the functional and memory immune response by ICS*, cellular phenotyping and memory B-cell ELISpot*

* Only applicable for participants with blood draws for cellular responses.

REVACCINATION AND DURABILITY COHORT OBJECTIVE (COHORT 4): *To assess durability of the selected RSV.preF based vaccine, to determine the effect of revaccination; and to determine the safety and immunogenicity of the selected formulation for future clinical development in a cohort of participants aged 60 years and older*

Objectives	*Endpoints*
PRIMARY	
• To assess immune responses, including durability to the selected RSV.preF-based vaccine formulation (formulation for future clinical development) in groups with and without revaccination	• RSV neutralization antibody titers
SECONDARY	
• To assess the safety and reactogenicity of the selected RSV.preF-based vaccine formulation (formulation for future clinical development)	• SAEs and AESIs from first administration until 6 months after the last vaccination • Solicited local and systemic AEs for 7 days after each vaccine administration • Unsolicited AEs from the time of each vaccine administration through the following 28 days
EXPLORATORY	
• Additional exploratory analyses may be performed to further investigate humoral and cellular vaccine-elicited immune responses to the selected RSV.preF-based vaccine formulation and durability	• Endpoints may include the following, but are not limited to: RSV neutralization antibody titers against additional A and/or B strains, F protein binding antibodies (pre-F and/or post-F), anti-F protein antibody specificity and functionality characterization, adenovirus neutralization antibody titers, molecular antibody characterization (eg, avidity, Fc cell interaction, ADCC, ADCP, antibody isotyping, antibody sequencing for repertoire), and nasal antibodies to RSV, including but not limited to immunoglobulin (Ig)A and IgG, chemokines and cytokines in serum and/or nasal samples, transcriptome analysis and sequencing of the TCR and/or BCR or VH/VL characterization

Refer to Section 8 for evaluations related to endpoints.

HYPOTHESIS

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

Data will be analyzed descriptively.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled Phase 1/2a study to evaluate safety and immunogenicity of various Ad26.RSV.preF and/or RSV preF protein combinations followed by expanded safety evaluation and durability/revaccination evaluation of the selected RSV.preF-based vaccine formulation in participants aged ≥60 years in stable health.

The study design includes 4 cohorts: an initial dose escalation safety cohort (Cohort 1 in a total of 132 participants), an extension of Cohort 1 for vaccine components selection (Cohort 2 in a total

of 528 participants), an expanded safety cohort (Cohort 3 in a total of 400 participants), and a revaccination/durability cohort (Cohort 4 in a total of 540 participants). Data from Cohorts 1 and 2 will be combined to select the components of the RSV.preF-based vaccine formulation to be used in Cohorts 3 and 4, and further clinical development. Overall, the total number of participants will be approximately1,600.

The study duration will be approximately 1,095 days (3 years) per participant in Cohorts 1 and 2; 365 days (1 year) per participant in Cohort 3, Arms 10 and 13; and 5 years per participant in Cohort 3, Arms 11a, 11b, and 12 and Cohort 4. The study comprises a maximum 28-day screening period, administration of study vaccine (active or placebo), a minimum 28-day follow-up period after vaccination, and a follow-up period up to 3 years after vaccination for Cohorts 1 and 2; 1 year after vaccination for Cohort 3, Arms 10 and 13; and up to 5 years after the first vaccination for Cohort 3, Arms 11a, 11b and 12, and Cohort 4. The end of the study is defined as the last participant's last visit.

After vaccination with study vaccine on Day 1, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. Any unsolicited AEs, solicited local (injection site) or systemic AEs, and vital signs (sitting systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) will be documented by study site personnel following this observation period. In addition, participants will record temperature and solicited signs and symptoms in a participant diary beginning on the evening of the day of vaccination and on a daily basis for 7 days post-vaccination.

Blood will be collected from all participants to assess immune responses pre-vaccination and at the timepoints indicated in the Schedule of Activities.

An internal DRC will be commissioned for this study to evaluate safety and reactogenicity data. If any of the pre-specified study vaccination pausing rules is met, further study vaccination will be paused and a DRC meeting will be convened (See Section 6.9). Refer to Committees Structure in Appendix 3.

Initial Safety Cohort (Cohort 1)

In the initial safety cohort, participants will be randomized progressively to 1 of 4 groups with additional safety checks in place in a sentinel subgroup before extending enrollment to the next group (Table 5). Sentinel participants in the same group will be enrolled at the same site. Vaccine components evaluated in Cohorts 1 and 2 will be administered as 2 IM injections of 1 mL in the same deltoid muscle.

- Group 1: Initially, 4 sentinel participants will be enrolled: 2 participants in Arm 1a, 1 participant in Arm 1b, and 1 participant in Arm 1c. (Note: The 2:1:1 distribution in the sentinel participants is applied to facilitate further randomization). Enrollment will be paused to allow for 24-hour safety assessments in these 4 sentinel participants by the principal investigator(s) (PI), the sponsor's study responsible physician/scientist (SRP/S), and the sponsor's medical leader (ML). In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 14 participants will be randomized in a 5:1:1 ratio and

vaccinated. Seven days after vaccination available safety data will be reviewed by the PI(s), SRP/S, ML, and the sponsor's medical safety officer (MSO) before proceeding to Group 2.

- Group 2: Initially, 12 sentinel participants will be enrolled; 2 participants in Arms 2, 3, 4, 5, and 6; 1 participant in Arm 1b; and 1 participant in Arm 1c. (Note: The 2:2:2:2:2:1:1 distribution in the sentinel participants is applied to facilitate further randomization). Enrollment will be paused to allow for 24-hour safety assessments in the 12 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 54 participants will be randomized in a 5:5:5:5:5:1:1 ratio and vaccinated. Seven days after vaccination, available safety data will be reviewed by the PI(s), SRP/S, ML, and MSO before proceeding to Group 3.
- Group 3: Initially, 6 sentinel participants will be enrolled; 2 participants in Arms 7 and 8; 1 participant in Arm 1b; and 1 participant in Arm 1c. (Note: The 2:2:1:1 distribution in the sentinel participants is applied to facilitate further randomization). Enrollment will be paused to allow for 24-hour safety assessments in these 6 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 24 participants will be randomized in a 5:5:1:1 ratio and vaccinated. Seven days after vaccination, available safety data will be reviewed by the PI(s), SRP/S, ML, and MSO before proceeding to Group 4.
- Group 4: Initially, 4 sentinel participants will be enrolled; 2 participants in Arm 9; 1 participant in Arm 1b; and 1 participant in Arm 1c. (Note: The 2:1:1 distribution in the sentinel participants is applied to facilitate further randomization). These sentinel participants will be dosed at least 1 hour apart. Enrollment will be paused to allow 24-hour safety assessments in the 4 sentinel participants by the PI(s), SRP/S, and ML. In the absence of any clinical safety concerns over the 24-hour assessment, the remaining 14 participants will be randomized in a 5:1:1 ratio and vaccinated.

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

Progression to Cohort 2 will be based on acceptable safety in the initial safety cohort (Cohort 1), as determined by DRC review of Day 8 safety data in all Cohort 1 participants. If there are clinically relevant safety findings in any of the study arms in Cohort 1, further evaluation of these study arms will not be continued in Cohort 2.

Table 5: Study Design: Initial Safety Cohort (Cohort 1)

Group	Arm	N	Vaccine Components 2×1 mL Formulation Day 1				
			Ad26.RSV-A.preF	Ad26.RSV-B.preF2	RSV-A preF protein	RSV-B preF protein	Placebo
1	1a	12		1×10^{11} vp		150µg	
	1b	3	1×10^{11} vp		150µg		
	1c	3					Placebo
2	2	12			150µg	150µg	
	3	12	2.5×10^{10} vp	2.5×10^{10} vp	150µg	150µg	
	4	12	5×10^{10} vp	5×10^{10} vp	150µg	150µg	
	5	12	1×10^{11} vp		300µg		
	6	12	1×10^{11} vp		150µg	150µg	
	1b	3	1×10^{11} vp		150µg		
	1c	3					Placebo
3	7	12	1×10^{11} vp	5×10^{10} vp	150µg	150µg	
	8	12	1.5×10^{11} vp		300µg		
	1b	3	1×10^{11} vp		150µg		
	1c	3					Placebo
4	9	12	1×10^{11} vp	1×10^{11} vp	150µg	150µg	
	1b	3	1×10^{11} vp		150µg		
	1c	3					Placebo
COHORT 1 TOTAL		**132**					

N number of participants; vp virus particles

Vaccine Components Selection Cohort (Cohorts 1 and 2)

The safety and immunogenicity data obtained from Cohort 1 will be combined with those obtained in Cohort 2 to support vaccine components selection. In Cohort 2, approximately 528 participants will be randomized in parallel to 1 of 11 arms (in a 1:1:1:1:1:1:1:1:1:1:1 ratio to Arms 1a to 9; Table 6). No pauses for safety assessments during enrollment are planned.

For a subset of the participants, additional cellular immunogenicity assessments will be performed. This subset will be referred to as the Cellular Immuno Subset and will consist of approximately 50 active study vaccine participants per arm (all participants in Cohort 1 and approximately 38 participants per arm in Cohort 2). The Cellular Immuno Subset will be recruited in study sites that have PBMC collection capability.

Participants in Cohorts 1 and 2 will continue follow-up up to 3 years post vaccination.

Based on safety and immunogenicity results available at the time of primary analysis, the sponsor will decide on the optimal vaccine composition to be used in the expanded safety cohort (Cohort 3), the revaccination/durability cohort (Cohort 4), and further clinical development. Additional factors such as manufacturability and ease of administration may be taken into account to select the optimal vaccine formulation for the expanded safety phase.

Table 6: Study Design: Supporting Vaccine Components Selection Cohort (Cohort 2)

Arm	N	Vaccine Components in 2×1 mL Formulation Day 1				
		Ad26.RSV-A.preF	Ad26.RSV-B.preF2	RSV-A preF protein	RSV-B preF protein	Placebo
1a	48		1×10^{11} vp		150µg	
1b	48	1×10^{11} vp		150µg		
1c	48					Placebo
2	48			150µg	150µg	
3	48	2.5×10^{10} vp	2.5×10^{10} vp	150µg	150µg	
4	48	5×10^{10} vp	5×10^{10} vp	150µg	150µg	
5	48	1×10^{11} vp		300µg		
6	48	1×10^{11} vp		150µg	150µg	
7	48	1×10^{11} vp	5×10^{10} vp	150µg	150µg	
8	48	1.5×10^{11} vp		300µg		
9	48	1×10^{11} vp	1×10^{11} vp	150µg	150µg	
COHORT 2 TOTAL	**528**					

N number of participants; vp virus particles
Notes: Data from Cohort 1 and Cohort 2 will be pooled for safety and immunogenicity analysis.

Expanded Safety Cohort (Cohort 3)

In the expanded safety cohort, approximately 400 participants will be randomized in parallel to 1 of 5 arms (in a 6:3:3:2:2 ratio to Arms 10, 11a, 11b, 12, and 13; Table 7). No pauses in enrollment for safety assessments are planned. Participants will receive either the selected 2×1 mL formulation based on the results from Cohorts 1 and 2, the selected 1 mL formulation for future clinical development, placebo, or the current Ad26/protein preF RSV vaccine (1×10^{11} vp Ad26.RSV-A.preF/150 µg RSV-A preF protein).

Vaccine components evaluated in Cohorts 1 and 2 will be administered as 2 IM injections of 1 mL in the same deltoid muscle. However, once the optimal composition is selected, manufacturing formulation will be adjusted to ensure the administration of a single 1 mL vaccine dose in subsequent cohorts. Participants in Arms 11a and 11b will receive the selected vaccine in a 1 mL formulation and a second injection with placebo (1 mL) for blinding purposes. Cohort 3 thus will compare the 2×1 mL formulation of the selected combination of RSV vaccine components from Cohorts 1 and 2 (Arm 10) with the 1 mL formulation to be used for future clinical development (Arms 11a and 11b) with follow-up for 1 year post-vaccination in a double-blind placebo-controlled fashion. Participants in Arm 13 will receive the current Ad26/protein preF RSV vaccine (1×10^{11} vp Ad26.RSV-A.preF/150 µg RSV-A preF protein) in a 1 mL formulation and a second injection with placebo (1 mL) for blinding purposes. Participants in Arms 11a, 11b and 12 will continue the study to assess durability and the effect of revaccination with follow-up up to 5 years post first vaccination. The timing of revaccination (at least 12 months relative to the first dose) will be based on Ad26/protein preF RSV vaccine clinical data.

For a subset of the participants, additional cellular immunogenicity assessments will be performed. This subset will be referred to as the Cellular Immuno Subset and will consist of approximately 240 participants: 40 participants per arm in Arms 10, 12 and 13, and 60 participants per arm in Arms 11a and 11b. The Cellular Immuno Subset will be recruited in study sites that have PBMC collection capability.

Table 7: Study Design: Expanded Safety Cohort (Cohort 3)

Arm	N	Day 1	Day X*
10**	150	Selected 2×1 mL formulation (based on Cohort 1 and 2 results)	-
11a	75	Selected formulation for future clinical development (1 mL) + placebo (1 mL)	Selected formulation for future clinical development
11b	75	Selected formulation for future clinical development (1 mL) + placebo (1 mL)	Placebo
12	50	Placebo (2×1 mL)	Selected formulation for future clinical development
13**	50	1×10^{11} vp Ad26.RSV-A.preF/150 µg RSV-A preF protein (1 mL) + placebo (1 mL)	-
COHORT 3 TOTAL	**400**		

* Timing of revaccination to be defined based on Ad26/protein preF RSV vaccine clinical data (Studies VAC18193RSV1004, VAC18193RSV2001, and VAC18193RSV3001)
** Arms 10 and 13 will be completed after 1 year of follow-up

Revaccination and Durability Cohort (Cohort 4)

In the revaccination and durability cohort, approximately 540 participants will be randomized in parallel to 1 of 3 arms (in a 5:5:2 ratio to Arms 14, 15 and 16; Table 8). No pauses in enrollment for safety assessments are planned. Participants in Arms 14 and 15 will receive the selected formulation for future clinical development on Day 1 and participants in Arm 16 will receive placebo on Day 1. Participants in Arm 14 (revaccination arm) and Arm 16 will receive the selected formulation at the same revaccination timepoint as participants in Arm 11a and 12 of Cohort 3. Participants in Arm 15 will receive placebo at the same revaccination timepoint as participants in Arm 11b of Cohort 3.

Table 8: Study Design: Revaccination and Durability Cohort (Cohort 4)

Arm	N	Day 1	Day X[a]
14	225	Selected formulation for future clinical development	Selected formulation for future clinical development
15	225	Selected formulation for future clinical development	Placebo
16	90	Placebo	Selected formulation for future clinical development
COHORT 4 TOTAL	**540**		

[a] Timing of revaccination to be defined based on Ad26/protein preF RSV vaccine clinical data (Studies VAC18193RSV1004, VAC18193RSV2001, and VAC18193RSV3001)

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

4.2. Scientific Rationale for Study Design

For the study rationale, refer to Section 2.1.

Dose Selection

The rationale behind the selection of the doses is described in Section 4.3, Justification for Dose.

Blinding, Control, Study Phase/Periods, Intervention Groups

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

Biomarker Collection

For all participants, additional biomarker analysis may be performed to explore potentially informative biomarkers related to vaccine-elicited immune responses.

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. Written consent/assent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

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

See Section 2.3 for Benefit-Risk Assessment.

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

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

4.3. Justification for Dose

Ad26.RSV-A.preF at dose levels of 5×10^{10} vp and 1×10^{11} vp (Phase 1/2a study VAC18193RSV1004), and at dose levels of 1×10^{11} vp, 1.3×10^{11} vp, and 1.6×10^{11} vp (Phase 2a study VAC18193RSV2005), combined with RSV-A preF protein showed an acceptable safety and reactogenicity profile in a population aged 60 years and older. Ad26.RSV-A.preF administered

alone at dose levels of 5×10^{10} vp and 1×10^{11} vp and RSV-A preF protein administered alone at a dose level of 150 µg has also been evaluated in study VAC18193RSV1004 and did not reveal any safety concerns. The Ad26/protein preF RSV vaccine containing a combination of 1×10^{11} vp Ad26.RSV-A.preF and 150 µg RSV-A preF protein has been evaluated in the Phase 2b study VAC18193RSV2001 and showed efficacy in preventing RSV-mediated LRTD.

Based on encouraging nonclinical immunogenicity and efficacy data, and available clinical data on the reactogenicity, immunogenicity, and efficacy of Ad26.RSV-A.preF and RSV-A preF protein, a range of vaccine formulations including Ad26.RSV-B.preF2 and RSV-B preF protein components was selected to be evaluated in the current study. As RSV preF protein at a dose level of 300 µg and Ad26 up to a dose level of 2×10^{11} vp will be evaluated for the first time in the current study, the safety and reactogenicity profile will be monitored closely. These dose levels have been evaluated in a nonclinical toxicity study and were shown to be well tolerated with no adverse vaccine-related findings observed.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit or contact for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant's assessment at that study site, in the time frame specified in the clinical trial agreement.

Participant Study Completion Definition

A participant will be considered to have completed the study if the participant has completed assessments at the Month 12 visit (Cohort 3, Arms 10 and 13), Month 36 visit (Cohort 1 and 2) or Month 60 visit (Cohort 3, Arms 11a, 11b, 12, and Cohort 4).

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before administration of the study vaccine.[a] Refer to Section 5.4 for conditions under which the repeat of any screening procedures are allowed.

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

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

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

5.1. Inclusion Criteria

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

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

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

3. aged 60 years or older on the day of signing the ICF and expected to be available for the duration of the study.

4. before randomization, a participant must be:

   - postmenopausal (postmenopausal state is defined as no menses for 12 months without an alternative medical cause); and
   - not intending to conceive by any methods.

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

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

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

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

[a] Participants can be enrolled with Grade 1 or Grade 2 values for vital signs measurements (refer to Appendix 6).

[b] For the FDA toxicity grading tables, refer to Appendix 6.

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

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

5.2. Exclusion Criteria

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

1. history of malignancy within 5 years before screening not in the following categories:
   a. Participants with squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix may be enrolled at the discretion of the investigator.
   b. Participants with a history of malignancy within 5 years before screening, with minimal risk of recurrence per investigator's judgment, can be enrolled.
2. known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine components (including any of the constituents of the study vaccine) (IB Ad26/protein preF RSV vaccine 2021, IB VAC18195 2021).

   Note: participants with egg allergies can be enrolled.
3. abnormal function of the immune system resulting from:
   a. Clinical conditions (eg, autoimmune disease or immunodeficiency) expected to have an impact on the immune response elicited by the study vaccine.

      Participants with autoimmune disease (eg, autoimmune-mediated thyroid disease, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis, and Type 1 diabetes) that is stable and inactive without the use of systemic immunomodulators and glucocorticoids may be enrolled at the discretion of the investigator.
   b. Chronic or recurrent use of systemic corticosteroids within 2 months before administration of study vaccine and during the study. A substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent.

      Note: Ocular, topical, intra-articular, or inhaled steroids are allowed.
   c. Administration of antineoplastic and immunomodulating agents, eg, cancer chemotherapeutic agents, or radiotherapy within 6 months before administration of study vaccine and during the study.

      Note: Topical immunomodulating agents may be allowed upon sponsor approval.

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

5. per medical history, participant has HIV type 1 or type 2 infection.

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

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

   Note: Locally administered monoclonal antibodies (for example, intra-ocular) may be allowed upon sponsor approval. The investigator is encouraged to contact the sponsor to discuss eligibility of participants on immunoglobulin treatment.

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

9. received or plans to receive:

   a. Licensed live attenuated vaccines within 28 days before or after planned administration of study vaccination

   b. Other licensed (not live) vaccines within 14 days before or after planned administration of study vaccination.

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

   a. Live attenuated SARS-CoV-2 vaccine within 28 days before or after planned administration of the first or subsequent study vaccines.

   b. Non-live SARS-CoV-2 vaccine within 14 days before or after planned administration of the first or subsequent study vaccines.

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

11. received an RSV vaccine in a previous RSV vaccine study at any time prior to randomization.

12. received or plans to receive an Ad26-vectored vaccine at any time prior to randomization until 28 days after the last study vaccination (for exclusion criteria related to SARS-CoV-2 vaccines; please refer to Exclusion Criterion 10).

13. has taken any disallowed therapies as noted in Section 6.8, Concomitant Therapy, before vaccination.

14. received an investigational drug or used an invasive investigational medical device within 30 days or received an investigational vaccine within 6 months before the planned administration of the study vaccine or is currently enrolled or plans to participate in another investigational study during this study.

    Note: Participation in an observational clinical study (ie, without intervention) or in the observational phase of interventional studies is allowed upon approval of the sponsor or its delegate.

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

16. had major surgery (per the investigator's judgment) within 4 weeks before vaccination, or will not have fully recovered from surgery at time of vaccination (in the opinion of the investigator), or has major surgery planned during the time the participant is expected to participate in the study.

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

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

19. 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.

20. cannot communicate reliably with the investigator.

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

22. who have significant scarring, tattoos, abrasions, cuts, or infections over the deltoid region of both arms that, in the investigator's opinion, could interfere with evaluation of injection site local reactions.

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of

additional medical records) after screening but before the first dose of study vaccine is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Section 5.4, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3.

5.3. Lifestyle Considerations

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

1. refer to Section 6.8 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 (eg, contraceptive requirements).

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 the criteria for participation in this study (screen failure) may be rescreened once. Individuals who are rescreened will be assigned a new participant number and will undergo the informed consent process, and then restart a new screening phase.

5.5. Criteria for Temporarily Delaying Administration of Study Vaccine

The following events constitute a temporary contraindication to study vaccination:

- Clinically significant acute illness at the time of vaccination. This does not include minor illnesses, such as diarrhea or mild upper respiratory tract infection.

- Fever (body temperature ≥38.0°C [≥100.4°F]) within 24 hours prior to the planned time of vaccination.

- Medically indicated vaccinations, including SARS-CoV-2 vaccine boosters

If any of these events occur at the scheduled time for vaccination, randomization at a later date within the screening window (allowed window up to 10 days) is permitted at the discretion of the investigator and after consultation with the sponsor. If randomization cannot occur within the screening window, rescreening is required. If any of these events occur at the scheduled time for the second vaccination, the vaccination can be rescheduled, as long as this is in agreement with the allowed windows (refer to the Schedule of Activities).

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

6. STUDY VACCINE(S) AND CONCOMITANT THERAPY

6.1. Study Vaccine(s) Administered

The investigational medicinal products (IMPs) to be administered to participants in this study are Ad26/protein preF RSV vaccine, Ad26.RSV-B.preF2 mixed with RSV-B preF protein, RSV-A preF protein mixed with RSV-B preF protein, Ad26/protein preF RSV vaccine mixed with RSV-B preF protein, Ad26/protein preF RSV vaccine mixed with Ad26.RSV-B.preF2 and RSV-B preF protein. All IMPs will be administered IM into the deltoid muscle according to the schedules shown in Table 5, Table 6, Table 7, and Table 8. Various dose levels will be evaluated:

- Ad26.RSV-A.preF (JNJ-64400141) will be used at a dose level of 2.5×10^{10} vp, 5×10^{10} vp, 1×10^{11} vp, or 1.5×10^{11} vp.
- RSV-A preF protein (JNJ-64213175) will be used at a dose level of 150 µg or 300 µg.
- Ad26.RSV-B.preF2 (JNJ-86051823) will be used at a dose level of 2.5×10^{10} vp, 5×10^{10} vp or 1×10^{11} vp.
- RSV-B preF protein (JNJ-78991172) will be used at a dose level of 150 µg.

Placebo will be 0.9% saline.

For Cohorts 1 and 2, and Arm 10 in Cohort 3, study vaccine will be prepared in a 2×1 mL formulation. Each component will be provided in a separate vial and components will be mixed according to treatment assignment. The total 2 mL volume will be divided into 2 injections of 1 mL, which will be administered IM in the same deltoid muscle. Arms 11a and 11b in Cohort 3 will be used to evaluate the formulation of the selected vaccine for future clinical development in comparison to the initial formulations administered as 2 separate injections of 1 mL. On Day 1, the participants in Arms 11a and 11b will receive the selected vaccine in a 1 mL formulation and a second injection with placebo (1 mL) for blinding purposes; participants in Arm 13 will receive the current Ad26/protein preF RSV vaccine (1×10^{11} vp Ad26.RSV-A.preF/150 µg RSV-A preF protein) in a 1 mL formulation and a second injection with placebo (1 mL) for blinding purposes. The participants in Cohort 4 will receive the selected vaccine in the 1 mL formulation for future clinical development. Full details of vaccine preparation, including mixing of components, are provided in the Investigational Product Preparation Instructions.

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

All study vaccines will be manufactured and provided under the responsibility of the sponsor. Refer to the IB's for a list of excipients (IB Ad26/protein preF RSV vaccine 2021 and IB VAC18195 2021).

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

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

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

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

Accountability

The investigator is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the participant must be documented on the intervention 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 as indicated on 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 intervention 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 intervention return form.

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

Study vaccine must be dispensed under the supervision of the investigator or a qualified member of the study site personnel. Study vaccine will be supplied only to participants participating in the study. Study vaccine may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study vaccine from, nor store it at, any site other than the study sites agreed upon with the sponsor.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Study Vaccine Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Participants will be randomly assigned to a vaccination group, as described in Section 4.1, based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks.

Sites will be split into 2 categories based on their PBMC collection capabilities for enrolment in the Cellular Immuno Subset.

For Cohorts 2 and 3, sites collecting PBMC samples will randomize participants in the Cellular Immuno Subset of the respective cohort in a ratio as described in Section 4.1. These sites may enroll participants without PBMC sampling on the same day once their daily PBMC capacity has been reached. PBMC samples will be collected for all participants in Cohort 1 and for 38 participants per arm in Cohort 2. In Cohort 3 PBMC samples will be collected for approximately 240 participants: 40 participants per arm in Arms 10, 12, and 13, and 60 participants per arm in Arms 11a and 11b. When the Cellular Immuno Subset has been completed for a cohort, the sites will continue randomizing the remaining participants without PBMC sampling. Sites with no PBMC sample collection capabilities will randomize participants that are not part of the Cellular Immuno Subset. Separate randomization lists will be used for the Cellular Immuno Subset and for the participants that are not part of the Cellular Immuno Subset.

The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study vaccine kit 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.

Blinding

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

For the sponsor, unblinding (at the participant level) of Cohort 1 and 2 will occur at the time of the primary analysis (Section 9.5). From the primary analysis onwards, group level results of Cohort 1 and 2 may be shared as needed, however, efforts will be made to preserve the blinding to the individual participant allocation. Sponsor unblinding (at the participant level) of Cohort 3 will occur at the time of the interim analysis when all participants in Cohort 3 have completed their 28-day post-first vaccination visit (Section 9.5). From this interim analysis onwards, group level results from Cohort 3 may be shared as needed, however, efforts will be made to preserve the blinding to the individual participant allocation (for participants in Arms 11a, 11b, and 12). Sponsor unblinding (at the participant level) of Cohort 4 will occur at the time of the interim analysis when all participants in Cohort 4 have completed their 28 days post-first vaccination visit (Section 9.5). From this interim analysis onwards, group level results from Cohort 4 may be shared as needed, however, efforts will be made to preserve the blinding to the individual participant allocation.

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

Under normal circumstances, the blind must not be broken for a cohort until all participants in that cohort have completed the study and the database is finalized for the cohort, except for Cohort 3: the blind will be broken for participants in Arms 10 and 13 once all participants in these arms have completed their last visit after 1 year of follow-up post-vaccination. The investigator may, in an emergency, determine the identity of the randomization group by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

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

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified (Section 9.5), the randomization codes and, if required, the translation of randomization codes into vaccine and control groups will be disclosed to the sponsor and only for those participants included in the interim analysis.

Participants who withdraw will not be replaced.

6.4. Study Vaccine Compliance

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

6.5. Dose Modification

Not applicable.

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

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

6.7. Treatment of Overdose

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

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

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

6.8. Concomitant Therapy

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

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

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

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

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

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

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

Use of systemic corticosteroids[a] must be documented throughout the study. Antineoplastic and immunomodulating agents administered parenterally, eg, cancer chemotherapeutic agents or systemic corticosteroids, or radiotherapy are prohibited throughout the study. If the use of systemic corticosteroids, antineoplastic or immunomodulating agents or any therapy described in Exclusion Criterion 7 becomes medically indicated during the study for any participant, the sponsor should be notified.

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

6.9. Study Pausing Rules

For Cohort 1, randomization and vaccination of participants will be suspended during review of the 24-hour data following the first administration of study vaccine to sentinel participants in each group (see Section 4.1).

If a study vaccination is considered to raise significant safety concerns (and a specific set of pausing criteria have been met), further vaccination of participants will be paused. The concerned data will be reviewed by the DRC, after which the DRC will recommend whether the pause can be lifted or not, or whether other steps are needed.

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

The DRC will review blinded data first but has the right to request the randomization codes and review unblinded data if deemed necessary. The DRC will make recommendations regarding the continuation of the study to the sponsor study team. The sponsor study team will communicate conclusions regarding study continuation to the investigator, the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), and applicable health authorities as appropriate.

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

The occurrence of any of the following events will lead to a pause in further study vaccination. This list is only applicable for concerned AEs that occur up to 4 weeks after each vaccination and to concerned SAEs and AESIs.

1. Death of a participant, considered related to study vaccine or if the causal relationship to the study vaccine cannot be excluded; OR

   Note: All cases of death will be sent for DRC information. Upon their review, DRC may then decide whether a study pause is required.

2. One or more participants per cohort experience an SAE, AESI (ie, confirmed TTS), or a Grade 4 (solicited or unsolicited) adverse event or a persistent (upon repeat testing) Grade 4 laboratory abnormality that is determined to be related to study vaccine (in Cohorts 1 and 2 only); OR

3. One or more participants per cohort experience anaphylaxis or generalized urticaria within 24 hours of vaccination, clearly not attributable to other causes than vaccination with study vaccine; OR

4. Two or more participants per cohort experience a Grade 3 or 4 unsolicited AE of the same type (as per medical judgment of the sponsor), that is determined to be related to study vaccine, that persists for 72 hours or longer; OR

5. Two or more participants per cohort (in Cohorts 1 and 2 only) experience a persistent (upon repeat testing) Grade 3 or 4 laboratory abnormality related to the same laboratory parameter and considered related to study vaccine, that persists for 72 hours or longer; OR

6. Two or more participants per cohort experience a Grade 3 or 4 solicited AE of the same type, determined to be related to study vaccine, that persists for 72 hours or longer.

For number 2 and number 5: to assess abnormal laboratory values, the test must be repeated at least once, within 48 hours of the site becoming aware of the abnormal value.

For number 4, number 5, and number 6: after each DRC review of similar AEs, the Committee 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 pausing rules, the investigator should notify the sponsor's medical monitor or designee (AND fax or email serious adverse event form to Global Medical Safety Operations, if applicable), immediately and no later than 24 hours after becoming aware of any related adverse event of Grade 3 or above AND update the eCRF with relevant information on the same day the adverse event information is collected. A thorough analysis of all Grade 3 (or above) cases will be carried out by the sponsor's medical monitor or designee, irrespective of whether the criteria for pausing the study are met. Based on the pausing criteria, the sponsor's medical monitor or designee then decides whether a study pause is warranted. All sites will be notified immediately in case of a study pause. The sponsor's medical monitor or designee is responsible for the immediate notification of DRC members and coordination of a DRC meeting in case of a study pause.

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

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

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

7. DISCONTINUATION OF STUDY VACCINATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Vaccination

Study vaccinations will be withheld for the reasons listed below. These participants must not receive any further doses of study vaccine but should remain on study for follow-up with assessments of safety and immunogenicity as indicated in the as indicated in the Schedule of Activities. Additional unscheduled visits may be performed for safety/reactogenicity reasons, if needed. In case of questions, the investigator is encouraged to contact the sponsor.

- Any related adverse event, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, requires discontinuation from study vaccine
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- Anaphylactic reaction following vaccination

- Serious adverse event or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Administration of antineoplastic and immunomodulating agents or radiotherapy prior to 14 days after the second study vaccination
- Withdrawal of consent
- 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
- Participant previously experienced TTS, including CVST or HIT

Study vaccine assigned to the participant who discontinued study vaccination may not be assigned to another participant.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion,) as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 3). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

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

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

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

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

Over the entire study, the total blood volume to be collected from each participant will be:

- In Cohort 1 and the participants in Cohort 2 that are part of the Cellular Immuno Subset: approximately 648 mL;
- In the remaining participants in Cohort 2: approximately 228 mL;
- In participants in Cohort 3, Arms 10 and 13 that are part of the Cellular Immuno Subset: approximately 456 mL;
- In the remaining participants in Cohort 3, Arms 10 and 13: approximately 156 mL;
- In participants in Cohort 3, Arms 11a, 11b and 12 that are part of the Cellular Immuno Subset: approximately 1,084 mL;
- In the remaining participants in Cohort 3, Arms 11a, 11b and 12 and all participants in Cohort 4: approximately 364 mL.

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

Visit Windows

Windows are allowed for the following visits as indicated in Table 9, Table 10, and Table 11:

Table 9: Visit Windows: Cohort 1 and 2

Clinic Visit #	Visit Day	Visit Window	Primary Purpose
3	8	+ 3 days	7 days post study vaccination, Safety visit
4	15	+ 3 days	14 days post study vaccination, Immunogenicity and Safety visit
5	29	+ 7 days	28 days post study vaccination, Immunogenicity and Safety visit
6	85	+ 7 days	3 months post study vaccination, Immunogenicity and Safety visit
7	183	± 14 days	6 months post study vaccination, Immunogenicity and Safety visit
8	365	± 1 month	1 year post study vaccination, Immunogenicity visit
9	730	± 1 month	2 years post study vaccination, Immunogenicity visit
10	1095	± 1 month	3 years post study vaccination, Immunogenicity visit

Table 10: Visit Windows: Cohort 3 (Arms 10 and 13)

Clinic Visit #	Visit Day	Visit Window	Primary Purpose
3	8	+ 3 days	7 days post study vaccination, Safety visit
4	15	+ 3 days	14 days post study vaccination, Immunogenicity and Safety visit
5	29	+ 7 days	28 days post study vaccination, Immunogenicity and Safety visit
6	85	+ 7 days	3 months post study vaccination, Immunogenicity and Safety visit
7	183	± 14 days	6 months post study vaccination, Immunogenicity and Safety visit
8	365	± 1 month	1 year post study vaccination, Immunogenicity visit

Table 11: Visit Windows: Cohort 3 (Arms 11a, 11b and 12) and Cohort 4

Clinic Visit #	Visit Day	Visit Window	Primary Purpose
3	8	+ 3 days	7 days post first study vaccination, Safety visit
4	15	+ 3 days	14 days post first study vaccination, Immunogenicity and Safety visit
5	29	+ 7 days	28 days post first study vaccination, Immunogenicity and Safety visit
6	85	+ 7 days	3 months post first study vaccination, Immunogenicity and Safety visit
7	183	± 14 days	6 months post first study vaccination, Immunogenicity and Safety visit
8	X	± 1 month	Vaccination 2
9	X+7	+ 3 days	7 days post second study vaccination, Safety visit
10	X+14	+ 3 days	14 days post second study vaccination, Immunogenicity and Safety visit
11	X+28	+ 7 days	28 days post second study vaccination, Immunogenicity and Safety visit
12	X+84	+ 7 days	3 months post second study vaccination, Immunogenicity and Safety visit
13	X+183	± 14 days	6 months post second study vaccination, Immunogenicity and Safety visit
14	730	± 1 month	2 years post first study vaccination, Immunogenicity visit
15	1095	± 1 month	3 years post first study vaccination, Immunogenicity visit
16	1460	± 1 month	4 years post first study vaccination, Immunogenicity visit
17	1825	± 1 month	5 years post first study vaccination, Immunogenicity visit

* Timing of revaccination to be defined based on Ad26/protein preF RSV vaccine clinical data (Studies VAC18193RSV1004, VAC18193RSV2001, and VAC18193RSV3001)

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

Screening

The study will include a screening phase of up to 28 days. If possible, screening may also be performed prior to randomization on the day of vaccination. In that case, Visits 1 and 2 will coincide on Day 1. Screening must be completed, and all eligibility criteria must be fulfilled prior to randomization and vaccination.

Sample Collection and Handling

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

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

For samples collected using a central laboratory, 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 (IB Ad26/protein preF RSV vaccine 2021, IB VAC18195 2021)
- Study site investigational product and procedures manual
- Laboratory manual
- Investigational Product Preparation Instructions
- IWRS Manual
- Electronic data capture (eDC) Manual/eCRF completion guidelines
- Sample ICF
- Participant diaries and instructions for use
- Thermometer
- Ruler (to measure diameter of any erythema and swelling)
- Laboratory kits
- Contact Information page(s)
- Study protocol
- Wallet card

8.1. Immunogenicity Assessments

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

Possible immunogenicity evaluations may include (but are not limited to) the assays summarized in Table 12.

Table 12: Summary of Immunogenicity Assays

Assay	Purpose
Primary Endpoints*	
RSV neutralization assay	Analysis of neutralizing antibodies against the RSV A2 strain
	Analysis of neutralizing antibodies against an RSV B strain
Secondary Endpoints	
F protein antibodies (ELISA; pre-F and/or post-F)	Analysis of antibodies binding to RSV F protein in prefusion and/or post-fusion form
IFN-γ ELISpot**	T-cell IFN-γ responses to RSV F protein peptides
Exploratory Endpoints	
RSV neutralization assay	Analysis of neutralizing antibodies against additional A and/or B strains
F protein antibody specificity characterization	Pre- and post-F specificity by binding or functional assays as ELISA, and/or competition ELISA. Adsorption of serum or plasma with pre-F and post-F protein before any antibody assay, epitope mapping, functional VNAs
G and/or N protein antibodies (ELISA)	Analysis of antibodies binding to RSV G and/or N protein
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics may include, but not limited to, ADCC, ADCP, avidity, Fc cell interaction, other respiratory viral neutralizing or binding assays, Ig isotype, and antibody assessments for antibody repertoire
ICS and/or cellular phenotyping and/or cellular function characterization**	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 markers), cellular phenotyping by extracellular markers for several immune cells including but not limited to B-cells and T-cells, and B-cell memory ELISpot for B-cell memory formation analysis
Transcriptome analysis	Regulation of genes (clusters), expression patterns, that for example could predict specific immune responses after vaccination
Chemokine/cytokine analysis	Levels of chemokines and cytokines in serum
Sequencing of T-cells and/or B-cells	Including but not limited to sequencing of TCR and BCR including VH/VL (heavy/light chain) characterization

* Analysis of neutralizing antibodies against the RSV A2 and RSV B strain is a primary endpoint in the vaccine components selection cohort (Cohorts 1 and 2) and in the revaccination and durability cohort (Cohort 4), and a secondary endpoint in the expanded safety cohort objective (Cohort 3).

** Only applicable for participants with blood draws for cellular responses.

ADCC: antibody dependent cell mediated cytotoxicity; ADCP: antibody dependent cell mediated phagocytosis; BCR: B cell receptor; ELISA: enzyme linked immunosorbent assay; ELISpot: enzyme linked immunospot; F: fusion; ICS: intracellular cytokine staining; IFN γ: interferon gamma; IL 2: interleukin 2, Ig: immunoglobulin; PBMC: peripheral blood mononuclear cell; RSV: respiratory syncytial virus; TCR: T cell receptor; VH: heavy chain variable domain; VL: light chain variable domain; VNA: virus neutralizing antibody

8.2. Safety Assessments

Key safety assessments will include the monitoring of AEs, vital signs, physical examinations (all cohorts), and safety laboratory assessments (Cohorts 1 and 2 only).

Details regarding the DRC are provided in Committees Structure in Appendix 3.

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and Appendix 4.

Any clinically significant abnormalities 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.

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

8.2.1. Physical Examinations

A physical examination, including height and body weight, will be carried out pre-vaccination during the screening period and, if deemed necessary by investigator, also on Day 1. At all other visits, an abbreviated, symptom-directed examination will be performed if deemed necessary by the investigator based on any clinically relevant issues, clinically relevant symptoms, and medical history. Symptom-directed physical examination may also be performed if deemed necessary by the investigator.

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

8.2.2. Vital Signs

Body temperature (oral route preferred), heart rate (beats per minute), respiratory rate (breaths per minute), and systolic and diastolic blood pressure (mm Hg) will be assessed.

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

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

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

Participants will utilize a diary to record body temperature measurements post-vaccination (see Section 8).

8.2.3. Clinical Safety Laboratory Assessments

For participants in Cohorts 1 and 2, blood samples for serum chemistry and hematology will be collected at screening, on Day 1, and 7 days after vaccination (or at the exit visit if early exit is within 7 days after vaccination and the participant terminates from the study without withdrawing consent) as noted in Appendix 2: Clinical Laboratory Tests. 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.

8.3. Adverse Events, Serious Adverse Events, Adverse Events of Special Interest and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, AESIs (including potential AESIs, refer to Section 8.3.6) and PQCs, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

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

Further details on AEs, SAEs, AESIs, and PQCs can be found in Appendix 4.

8.3.1. Time Period and Frequency for Collecting Adverse Event, Serious Adverse Event and Adverse Event of Special Interest Information

All Adverse Events

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

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

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

All other unsolicited AEs and special reporting situations, whether serious or non-serious, will be reported for each vaccination from the time of vaccination until 28 days post-vaccination. Unsolicited AEs with the onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded as such.

All SAEs and AEs leading to discontinuation from the study (regardless of the causal relationship) and all AESIs are to be reported from the moment of vaccination until 6 months post vaccination. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All COVID-19 cases will be collected for all participants for the duration of the study.

See Section 7.2 for procedures associated with withdrawal of consent.

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

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately, but no later than within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor immediately, but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

AESIs

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

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events and Adverse Events of Special Interest

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

Solicited Adverse Events

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 diary (see Section 8).

After vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events.

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

Solicited Local (Injection Site) AEs

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

Solicited Systemic AEs

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

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

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

Unsolicited Adverse Events

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

For details regarding AESIs, refer to Section 8.3.6.

8.3.3. Follow-up of Adverse Events, Serious Adverse Events and Adverse Events of Special Interest

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

Adverse events, and the special reporting situation of pregnancy, will be followed by the investigator as specified in Appendix 4.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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 Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. If a participant becomes pregnant during the study, a determination regarding study vaccination discontinuation must be made by the investigator in consultation with the sponsor.

Follow-up information regarding the outcome of the pregnancy will be required.

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

8.3.6. Adverse Events of Special Interest

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

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

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

Specific requirements for the AESI are described below.

8.3.6.1. Thrombosis with Thrombocytopenia Syndrome

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

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

- Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Section 10.7, Appendix 7,

  and/or

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

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

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

For either a thrombotic event or thrombocytopenia, complete blood count including platelet count and a coagulation profile available from participant's medical records should be entered in the eCRF. In case these results are not available at the time of the event report in the eCRF, the study site is required to obtain a complete blood count including platelet count and a coagulation profile. Tests should be performed at the local laboratory. Repeat testing may be requested for confirmation upon sponsor discretion.

Aliquots of serum samples collected for immunogenicity test can be reconverted for participant's safety purposes upon sponsor request.

Refer to Appendix 2, Table 20 for a non-exhaustive list of required tests.

In addition, the sponsor requires additional blood samples to be obtained as soon as possible after the potential AESI onset, either during an ad hoc unscheduled visit or the next scheduled visit, whichever comes first. Refer to Appendix 2, Table 21 for a non-exhaustive list of laboratory tests

that may be requested by the sponsor in case of potential AESI reporting for which these additional samples may be used.

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

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

If an event meets the criteria for an SAE (Section 10.4.1), it should be reported using the same process as for other SAEs.

Treatment and Follow-up Recommendation

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

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics and Pharmacogenomics

Genetics and pharmacogenomics are not evaluated in this study.

8.6. Biomarkers

Blood will be drawn at selected timepoints during the study for evaluation of biomarkers (may include, but not limited to RNA-seq including TCR and BCR sequencing) related to vaccine immunogenicity, as indicated in the Schedule of Activities. Analyses of biomarkers may be conducted at the sponsor's discretion and may be reported separately from this study.

8.7. Medical Resource Utilization and 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.

9.1. Statistical Hypotheses

No formal hypothesis will be tested.

9.2. Sample Size Determination

9.2.1. Initial Safety Cohort (Cohort 1)

The number of participants chosen for the initial safety cohort will provide a preliminary safety assessment. Participants receiving placebo and participants receiving the Ad26/protein preF RSV vaccine as used in studies VAC18193RSV2001 and VAC18193RSV3001 are included for blinding and safety purposes and will provide additional control specimens for immunogenicity assays.

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

Table 13 provides the probability of observing at least one AE in a group of the considered sample size given several true AE rates.

Table 13: 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=2	N=3	N=4	N=12
0.5	1.0%	1.5%	2.0%	5.8%
1	2.0%	3.0%	3.9%	11.4%
2.5	4.9%	7.3%	9.6%	26.2%
10	19.0%	27.1%	34.3%	71.8%
25	43.8%	57.8%	68.4%	96.8%
50	75.0%	87.5%	93.8%	100%

AE = adverse event; N = number of participants.

9.2.2. Vaccine Components Selection Cohort (Cohorts 1 and 2)

The objective is to compare immunomarker levels, including virus neutralizing antibody (VNA) levels, of the various combinations of vaccine components (Arms 1a, and Arms 2 to 9) to Arm 1b (1×10^{11} vp Ad26.RSV-A.preF/150 µg RSV-A preF protein), based on the estimated geometric mean titer (GMT) ratios and corresponding 95% confidence intervals (CIs). With a sample size of 55 evaluable participants per arm, and assuming a standard deviation for RSV-A2 VNA of 1.3[a] on the $\log_2$ scale, the precision of the estimated GMTs will be ~0.36 on the $\log_2$ scale. To account for approximately 10% dropout, a sample size of 60 participants per arm will be used.

[a] Based on Day 29 VNA results from study VAC18193RSV1004: Cohort 2, Groups 14+17 and Cohort 3, Groups 19+20

Table 14 shows the estimated 95% CIs for several GMT ratios, assuming a standard deviation for RSV-A2 VNA of 1.3 on the $\log_2$ scale for 55 participants for immunogenicity evaluation per arm.

Note: Per arm, immunogenicity data from the initial safety cohort (Cohort 1) will be combined with those from Cohort 2 to support vaccine components selection, as applicable.

Table 14: Estimated 95% CIs, by Observed GMT Ratio of VNA Levels.

N per Arm	Observed GMT Ratio	Corresponding 95% CI
55	1	[0.71; 1.41]
	1.2	[0.85; 1.69]
	1.5	[1.07; 2.11]

CI = confidence interval; GMT = geometric mean titer; N = number of participants.

9.2.3. Expanded Safety Cohort (Cohort 3)

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

Table 15 shows the probabilities of observing at least one AE in the expanded safety cohort with 150 participants per vaccine formulation, 50 participants receiving placebo, and 50 participants receiving 1×10^{11} vp Ad26.RSV-A.preF/ 150 µg RSV-A preF protein, at given true AE rates. This table shows that the current numbers give a reasonable probability to also observe less frequent events in the active arms in this cohort. Combining the 60 participants from Cohorts 1 and 2 and 150 participants from Cohort 3 for the selected vaccine formulation results in 210 participants for this formulation.

Table 15: Probability of Observing at Least One Adverse Event in the Expanded Safety Cohort (Cohort 3) at a Given True Adverse Event Rate

True AE Rate (%)	Probability of Observing at Least One AE in N Participants (%)			
	N=50	N=60	N=150	N=210
0.5	22.2%	26.0%	52.9%	65.1%
1	39.5%	45.3%	77.9%	87.9%
2.5	71.8%	78.1%	97.8%	99.5%
10	99.5%	99.8%	100.0%	100.0%
25	100.0%	100.0%	100.0%	100.0%
50	100.0%	100.0%	100.0%	100.0%

AE = adverse event; N = number of participants.

The observation of 0 events (eg, SAEs) is associated with 95% confidence that the true event rate is below the rates specified in Table 16 for the considered number of participants.

Table 16: Upper Limit of the 1-sided 95% CI if no Cases are Observed for Different Sample Sizes

Sample Size	N=50	N=60	N=150	N=210
Upper Limit 1-sided 95% CI	5.8%	4.9%	2.0%	1.4%

CI = confidence interval; N = number of participants.

9.2.4. Revaccination and Durability Cohort (Cohort 4)

The revaccination and durability cohort (Cohort 4) should provide sufficient data on the selected vaccine formulation to support future clinical development. To have approximately 150 participants available per arm for evaluating durability of immune response at end of the 5-year study period, and assuming a dropout rate of 10% per year, approximately 300 participants per arm are needed.

Corresponding arms of Cohort 3 and 4 will be combined (Arm 11a [Cohort 3] + Arm 14 [Cohort 4], and Arm 11b [Cohort 3] + Arm 15 [Cohort 4], respectively) for the evaluation of durability of the immune response. Having 75 participants in Arm 11a and 11b in Cohort 3 requires enrollment of 225 participants in Arms 14 and 15 in Cohort 4. Enrollment of 90 participants in Arm 16 (placebo) results in enrollment of in total 540 participants in Cohort 4. Placebo arms from Cohort 3 and 4, Arm 12 and Arm 16, respectively, will be combined in the analyses, as applicable.

Table 17 shows the probabilities of observing at least one AE for the selected formulation for future clinical development, at given true AE rates. This table shows that the current numbers give a reasonable probability to also observe less frequent events in the active arms in this cohort.

Table 17: Probability of Observing at Least One Adverse Event for the Selected Formulation for Future Clinical Development, at a Given True Adverse Event Rate

True AE Rate (%)	Probability of Observing at Least One AE in N Participants (%)				
	N=150	N=225	N=300	N=450	N=600
0.5	52.9%	67.6%	77.8%	89.5%	95.1%
1	77.9%	89.6%	95.1%	98.9%	99.8%
2.5	97.8%	99.7%	99.9%	100.0%	100.0%
10	100.0%	100.0%	100.0%	100.0%	100.0%
25	100.0%	100.0%	100.0%	100.0%	100.0%
50	100.0%	100.0%	100.0%	100.0%	100.0%

AE = adverse event; N = number of participants.

The observation of 0 events (eg, SAEs) is associated with 95% confidence that the true event rate is below the rates specified in Table 18 for the considered number of participants.

Table 18: Upper Limit of the 1-sided 95% CI if no Cases are Observed for Different Sample Sizes

Sample Size	N=150	N=225	N=300	N=450	N=600
Upper Limit 1-sided 95% CI	2.0%	1.3%	1.0%	0.7%	0.5%

CI = confidence interval; N = number of participants.

9.3. Populations for Analysis Sets

Vaccine assignment will follow the as-treated principle.

For purposes of analysis, the following populations are defined:

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

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

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

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to sponsor unblinding of the locked database for the primary analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The primary analysis will be performed when all participants in Cohort 1 and Cohort 2 have completed their 28-day post-vaccination visit or discontinued earlier.

Analysis populations are defined in Section 9.3. Planned analyses are defined in Section 9.5.

9.4.2. Participant Information

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

9.4.3. Immunogenicity Analyses

Immunogenicity data of corresponding arms from Cohort 1 and Cohort 2 will be combined in all analyses. Immunogenicity data of corresponding arms from Cohort 3 and Cohort 4 will be combined as applicable.

Continuous variables will be summarized descriptively. For continuous parameters, descriptive statistics of the actual values will be calculated at all timepoints, including geometric mean with 95% CI, median and quartiles, as applicable. Additionally, geometric mean fold rises from baseline and corresponding 95% CIs might be calculated.

For combined primary endpoint data of Cohort 1 and Cohort 2, geometric mean ratios between each active arm and Arm 1b will be calculated at all available timepoints, with corresponding 95% CI, as applicable. For Cohort 3, Arms 11a and 11b will be combined and the active arms will be compared to each other at all available timepoints up to 1 year after vaccination on Day 1, by means of geometric mean ratios with corresponding 95% CI. For durability and revaccination evaluation Arm 11a (Cohort 3) and Arm 14 (Cohort 4) will be combined, Arm 11b (Cohort 3) and Arm 15 (Cohort 4) will be combined, and Arm 12 (Cohort 3) and Arm 16 (Cohort 4) will be combined.

For immunogenicity analyses, baseline is considered as the last assessment pre-vaccination. Graphical representations of immunologic parameters will be made as applicable.

Geometric means per arm, and geometric mean ratios between active arms, with corresponding 95% CIs will be estimated via an analysis of variance (ANOVA) including all active arms, using log-transformed post-vaccination immune parameter response as dependent variable and study arm as independent variable. The means and differences in mean and CIs will be back-transformed (by exponentiation) to CIs around a GMT or geometric mean titer ratio (GMR). This analysis will be performed for all available assays and all time points, separately per assay. Data of the same arms form different cohorts will be combined, as applicable.

As a sensitivity analysis, the ANOVA may also be performed adjusting for the respective baseline titers, by including baseline titer as additional covariate.

For categorical variables, frequency tables will be presented.

9.4.4. Safety Analyses

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively by cohort and study arm, and by group (pooled over cohorts, as applicable). All safety analyses will be made on the FA Set.

Adverse Events

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

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe AE, an AESI, an SAE or a COVID-19 infection.

Solicited local (at injection site) and systemic AEs will be summarized descriptively. The number and percentages of participants with at least one solicited local (at injection site) or systemic adverse event will be presented. The frequencies by vaccine group as well as frequencies according to severity and duration will be described for solicited AEs. Frequencies of unsolicited AEs, separately for all and vaccination-related only, will be presented by System Organ Class and preferred term, while those of solicited AEs will be presented only by preferred term.

Clinical Laboratory Tests

Laboratory abnormalities will be determined according to the FDA toxicity grading tables (see Appendix 6), or in accordance with the normal ranges for the clinical laboratory parameter if no

grades are available. Any laboratory value shown as a "graded" value in the FDA table that is within laboratory normal ranges will not be graded for severity.

Vital Signs

Vital signs including temperature, heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

Physical Examinations

Physical examination findings pre-vaccination will be summarized per vaccine administration. A listing of the abnormalities will be made.

9.4.5. Other Analyses

Biomarker data analysis may be conducted at the sponsor's discretion and may be reported separately from this study.

9.5. Planned Analyses

The following analyses are planned:

- Primary analysis: 28 days post-vaccination safety and immunogenicity analysis. This analysis will be performed when all participants in Cohort 1 and Cohort 2 have completed their 28-day post-vaccination visit. Data from corresponding arms from the 2 cohorts will be combined. The goal of this analysis will be to select the vaccine formulation to be used in Cohort 3.
- Interim analyses:

  6-month post-vaccination safety and immunogenicity analysis for Cohorts 1 and 2. Available safety and immunogenicity data of all participants in Cohort 1 and Cohort 2 up to the Day 185 follow-up visit post-vaccination will be included in the analysis. This analysis may include immunogenicity data available from additional timepoints.

  1-year post-vaccination immunogenicity analysis for Cohorts 1 and 2. Immunogenicity data of all participants in Cohort 1 and Cohort 2 up to (and including) the 1-year follow-up visit post-vaccination will be included in the analysis.

  28 days post-vaccination safety and immunogenicity analysis for Cohort 3. This analysis will be performed when all participants in Cohort 3 have completed their 28-day post-vaccination visit.

  28 days post-vaccination safety and immunogenicity analysis for Cohort 4. This analysis will be performed when all participants in Cohort 4 have completed their 28-day post-vaccination visit.

  6-month post first vaccination safety and immunogenicity analysis for Cohorts 3 and 4. This interim analysis will include all safety and immunogenicity data from all participants in Cohorts 3 and 4, collected up to (and including) the 6-months follow-up visit post Day 1 vaccination.

28 days post revaccination safety and immunogenicity analysis for Cohorts 3 and 4. This interim analysis will include all safety and immunogenicity data from all participants in Cohorts 3 and 4, collected up to (and including) the 28-day post-revaccination visit.

Yearly follow-up analyses until 3 years post first vaccination in Cohorts 1 and 2 and until 5 years post first vaccination in Cohort 3 (Arms 11a, 11b and 12) and Cohort 4. These analyses will include immunogenicity and safety data up to the 2-year follow-up visit post Day 1 vaccination, the 3-year follow-up visit post Day 1 vaccination, the 4-year follow-up visit post-Day 1 vaccination (applicable for Cohort 3 [Arms 11a, 11b and 12] and Cohort 4 only), and 5-year follow-up visit post Day 1 vaccination (applicable for Cohort 3 [Arms 11a, 11b and 12] and Cohort 4 only).

- Final analysis: immunogenicity analysis and safety data up to study end. This analysis will be performed on unblinded data.

Additional interim analyses may be performed during the study for the purpose of informing future vaccine development-related decisions in a timely manner, or upon health authority request. If they occur, these unplanned interim analyses may replace or be combined with planned analyses, depending on the timing.

For any planned or additional analysis performed before the final analysis, the sponsor will be unblinded at the time of the analysis, while study site personnel and participants will remain blinded until the end of the study.

The statistical analysis plan will describe the planned interim analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

Ad26	adenovirus type 26
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
BCR	B-cell receptor
CI	confidence interval
COVID-19	coronavirus disease-2019
CTM	Clinical Trial Manager
CVST	cerebral venous sinus thrombosis
DNA	deoxyribonucleic acid
DRC	Data Review Committee
eCRF	electronic case report form
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
F protein	fusion protein
FA	Full Analysis
FDA	(United States) Food and Drug Administration
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GMR	geometric mean titer ratio
GMT	geometric mean titer
HITT	heparin-induced thrombocytopenia and thrombosis
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IWRS	interactive web response system
LLN	lower limit of normal
LRTD	lower respiratory tract disease
LTM	Local Trial Manager
MedDRA	Medical Dictionary for Regulatory Activities
ML	medical leader
MSO	medical safety officer
PBMC	peripheral blood mononuclear cell
PCC	protocol clarification communication
PI	principal investigator
post-F	post-fusion
PPI	Per-protocol Immunogenicity
PQC	Product Quality Complaint
pre-F	prefusion conformation-stabilized F protein
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SoA	Schedule of Activities
SRP	study responsible physician
SRS	study responsible scientist
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TTS	thrombosis with thrombocytopenia syndrome
VH	heavy chain variable domain
VL	light chain variable domain
VNA	virus neutralizing antibody
vp	viral particles

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central or local laboratory:

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Table 19: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Hemoglobin	Prothrombin time* Activated partial thromboplastin time*	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
Clinical Chemistry	Sodium Potassium Blood urea nitrogen (BUN) Creatinine Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)		

*At baseline only

Table 20: Protocol-Required Laboratory Tests After Potential AESI Reporting

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

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

Table 21: Laboratory Tests That May Be Requested by the Sponsor After Potential AESI Reporting

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

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

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

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

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

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 Clarification Communications

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

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

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

Protocol Amendments

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

During the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all

cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

- Completed investigator financial disclosure forms from all 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

Independent Ethics Committee or Institutional Review Board

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

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study vaccine

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

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

10.3.2. Financial Disclosure

Investigators and 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 study and for 1 year after completion of the study.

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

10.3.3. Informed Consent Process

Each participant must give 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

must 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 must be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

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

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

10.3.4. Data Protection

Privacy of Personal Data

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

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

The informed consent obtained from the participant includes information about, and where required per applicable regulations, 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.

The informed consent also provides information to address the lawful 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, or make requests concerning his or her personal data in accordance with applicable data protection law. 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.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand Ad26.RSV-A.preF, RSV-A preF protein, Ad26.RSV-B.preF2, and RSV-B preF protein, to understand RSV and other respiratory pathogens, and to develop tests/assays related to understand Ad26.RSV-A.preF, RSV-A preF protein, Ad26.RSV-B.preF2, and RSV-B preF protein, to understand RSV and other respiratory pathogens. The research may begin at any time during the study or the post-study storage period.

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

10.3.6. Committees Structure

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

Data Review Committee

An internal DRC will be established to evaluate safety and reactogenicity data, including interim safety and reactogenicity data of Cohort 1, to ensure the continuing safety of the participants enrolled in this study. Ad-hoc meetings will be convened in case any of the pre-specified study vaccination pausing rules are met. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. After the review, the DRC will make recommendations regarding the continuation of the study.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding Ad26.RSV-A.preF, RSV-A preF protein, Ad26.RSV-B.preF2, and RSV-B preF protein or the sponsor's operations (eg, patent

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

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Ad26.RSV-A.preF, RSV-A preF protein, Ad26.RSV-B.preF2, and RSV-B preF protein and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator 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 interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

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

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

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

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the eCRF. 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 must be available for review at the next scheduled monitoring visit.

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

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

10.3.10. Source Documents

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

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

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

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

10.3.11. Monitoring

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

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

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

10.3.12. On-Site Audits

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

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

10.3.13. Record Retention

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

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

responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

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

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: For time period of sponsor's AE collection, see All Adverse Events under Section 8.3.1.

Serious Adverse Event

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 must 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) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. Ad26.RSV-A.preF, RSV-A preF protein, Ad26.RSV-B.preF2, and RSV-B preF protein, the expectedness of an AE will be determined by whether or not it is listed in the IB (IB Ad26/protein preF RSV vaccine 2021, IB VAC18195 2021).

10.4.2. Attribution Definitions

Assessment of Causality

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

Related

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

Not Related

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

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

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

10.4.3. 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 (FDA 2007), included in Appendix 6, Toxicity Grading Scale.

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

Grade 1	Mild	Symptoms causing no or minimal interference with usual social and functional activities
Grade 2	Moderate	Symptoms causing greater than minimal interference with usual social and functional activities
Grade 3	Severe	Symptoms causing inability to perform usual social and functional activities and 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

The severity of solicited signs and symptoms will be graded in the diary by the participant based on the severity assessment provided in the diary and then verified by the investigator using the toxicity grading scale in Appendix 6. (Note: severity of the measured events will be derived from the diameter [for erythema and swelling] and the temperature measurements [for fever])

10.4.4. 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)
- Exposure to a sponsor study vaccine from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

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

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study vaccine, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory

infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

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

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

Serious Adverse Events

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

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

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

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

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

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

Adverse Events of Special Interest

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

10.4.6. Product Quality Complaint Handling

Definition

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

Procedures

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

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

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 4.

Definition of Woman of Childbearing Potential

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- **permanently sterile (for the purpose of this study)**

  Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.

  Has congenital abnormalities resulting in sterility.

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

10.6. Appendix 6: Toxicity Grading Scale

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

A: Tables for Clinical Abnormalities

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

[#] Revised by the sponsor.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°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 – 155	> 155	Hospitalization for malignant hypertension[#]
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	Hospitalization for malignant hypertension[#]
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	Hospitalization for hypotensive shock[#]
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.
** For oral temperature: no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.
[#] Revised by the sponsor.

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

[#] Revised by the sponsor.

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to	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

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.
***ULN is the upper limit of the normal range.

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

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

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

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

10.7. Appendix 7: Thrombotic Events to be Reported as Potential AESIs

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

- MedDRA PTs for large vessel thrombosis and embolism

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

- MedDRA PTs for more common thrombotic events

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

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

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

10.8. Appendix 8: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

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

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

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

If the participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing. study assessments, and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the Clinical Study Report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

Screening and Randomization

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

Site Visits

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

Vaccine Administration

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

Informed Consent Form

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

Source Data Verification/Monitoring

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

Site Audits

- During the COVID-19 pandemic and at the impacted sites, study site GCP audits with direct impact/engagement from the investigator and study site personnel would not be conducted in order to comply with national, local, and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study-related documents may take place with limited impact/engagement if possible.

10.9. Appendix 9: 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 intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Vaccines & Prevention B.V.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

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

Signature

User	Date	Reason
PPD [redacted]	22-Dec-2021 16:16:22 (GMT)	Document Approval