Janssen Vaccines & Prevention B.V.*

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled Phase 2b Study to Assess the Efficacy, Immunogenicity and Safety of an Ad26.RSV.preF-based Regimen in the Prevention of RT-PCR-confirmed RSV-mediated Lower Respiratory Tract Disease in Adults Aged 65 Years and Older

Protocol VAC18193RSV2001; Phase 2b
AMENDMENT 8

CYPRESS

VAC18193 (JNJ-64400141/JNJ-64213175)

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

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

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

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PROTOCOL AMENDMENTS

Protocol Version	Date
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Amendment 3	08 May 2020
Amendment 4	25 August 2020
Amendment 5	04 February 2021
Amendment 6	26 May 2021
Amendment 7	21 September 2021
Amendment 8	16 February 2023

Amendments below are listed beginning with the most recent amendment.

Amendment 8 (16 February 2023)

The primary reason for the amendment: The primary reason for this amendment is to remove Revaccination Subcohort D as additional data with a Month 48 revaccination timepoint are not expected to provide novel insights on the kinetics of the immune response after revaccination with the Ad26/protein preF RSV vaccine. Additional changes were made, as listed below.

Applicable Section(s)	Description of Change(s)
Rationale: Revaccination Subcohort D is removed as additional data with a Month 48 revaccination timepoint are not expected to provide novel insights on the kinetics of the immune response after revaccination with the Ad26/protein preF RSV vaccine.	
SYNOPSIS Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Revaccination Subcohorts 1D and 2D (N=240) 1.2 Overall Rationale for the Study 2 OBJECTIVES, ENDPOINTS, AND HYPOTHESIS 3.1 Overview of Study Design 4.2 Exclusion Criteria 5 INTERVENTION ALLOCATION AND BLINDING 8 PRESTUDY AND CONCOMITANT THERAPY 9 STUDY EVALUATIONS 9.1.1 Overview 9.1.5 Revaccination Subcohorts 9.2.1.1.1 ARI Surveillance Assessment 9.2.2 Immunogenicity Evaluations 9.2.4.1 Adverse Events 10.1 Completion 11.1 Analysis Sets 11.9.2 Revaccination Subcohorts 11.2.4 Revaccination Subcohorts 11.12 Planned Analyses 12.3.1 All Adverse Events 12.3.2 Serious Adverse Events 16.1 Study-specific Design Considerations	Removal of Revaccination Subcohort D.

Rationale: To align the thrombosis with thrombocytopenia syndrome (TTS) wording across the RSV vaccine (VAC18193) program and with the TTS Adjudication Committee (TTSAC) and RSV TTS Charter.

Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Revaccination Subcohort 1A (N=120) Schedule of Activities – Revaccination Subcohort 2A (N=120) Schedule of Activities – Revaccination Subcohort 1B (N=135) Schedule of Activities – Revaccination Subcohort 2B (N=135) Schedule of Activities – Revaccination Subcohorts 1C and 2C (N=240) 9.2.4.1 Adverse Events 12.3.1 All Adverse Events 12.3.4.1 Thrombosis with Thrombocytopenia Syndrome	Updates were made to align the TTS wording across the RSV vaccine (VAC18193) program and with the TTSAC and RSV TTS Charter. Language referring to laboratory diagnostic tests for the follow-up and assessment of potential adverse events of special interest (AESIs) was added.
Rationale: To align with the most recent Janssen protocol template.	
12.3.2 Serious Adverse Events 13 PRODUCT QUALITY COMPLAINT HANDLING	Updates were made in alignment with the latest Janssen protocol template.
Rationale: Minor textual changes, clarifications and corrections have been made.	
Throughout the protocol.	

Amendment 7 (21 September 2021)

The primary reason for the amendment: The primary reason for this amendment is to facilitate a specific group of participants to co-participate in another clinical study (including interventional studies), if the other clinical study meets prespecified criteria. It concerns potential participants for revaccination subcohorts C and D who are currently not participating in RSV ARI follow-up.
Additional changes were made, as listed below.

Applicable Section(s)	Description of Change(s)
Rationale: To allow flexibility on co-participating in another clinical study (including interventional studies).	
4.2 Exclusion Criteria	A note has been added to clarify in which situations co-participation in another clinical study may be allowed.

Rationale: To change the end date of the third RSV season.	
Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Assessments for Participants with an ARI Episode 3.1 Overview of Study Design	The end of third RSV season date was changed from 30 April 2022 to 15 April 2022.
Rationale: The immunogenicity analyses for the revaccination subcohorts were revised to allow similar immunogenicity analyses for all revaccination subcohorts.	
SYNOPSIS 11.9.2 Revaccination Subcohorts	Geometric mean ratios and corresponding 95% confidence intervals between Day 15 post first vaccination and Day 15 post second vaccination (dependent on the revaccination subcohort) within the group receiving active study vaccine on Day 1, will be calculated for the different assays.
Rationale: It was clarified that all cases of thrombocytopenia observed, not limited to symptomatic cases, should be considered as potential thrombosis with thrombocytopenia syndrome (TTS) cases and therefore must be reported as a potential adverse event of special interest (AESI).	
9.2.4.1 Adverse Events 12.3.1 All Adverse Events 12.3.4.1 Thrombosis with Thrombocytopenia Syndrome	The term symptomatic thrombocytopenia was adjusted to the more inclusive term thrombocytopenia.
Rationale: It was clarified that Exclusion Criterion 22 (‘Participant has a history of TTS or heparin-induced thrombocytopenia and thrombosis (HITT)’ must be verified prior to each planned revaccination in the revaccination subcohorts.	
Schedule of Activities – Revaccination Subcohort 1A (N=120) Schedule of Activities – Revaccination Subcohort 2A (N=120) Schedule of Activities – Revaccination Subcohort 1B (N=135) Schedule of Activities – Revaccination Subcohort 2B (N=135) Schedule of Activities – Revaccination Subcohorts 1C and 2C (N=240) Schedule of Activities – Revaccination Subcohorts 1D and 2D (N=240)	In the footnotes to the Schedules of Activities for the revaccination subcohorts, Exclusion Criterion 22 was added to the list of selected eligibility criteria that are to be verified prior to each planned revaccination in the revaccination subcohorts.
Rationale: Minor textual changes, clarifications and corrections have been made.	
Throughout the protocol	

Amendment 6 (26 May 2021)

The primary reason for the amendment: This amendment has been created to provide information and guidance for investigators on signs and symptoms and on medical management should very rare events of thrombosis with thrombocytopenia syndrome (TTS) occur, as observed in another Ad26-based vaccine program (Ad26.COV2.S, COVID-19 vaccine). The Ad26/protein preF RSV vaccine uses the same Ad26 vector as Ad26.COV2.S, but has different transgene inserts. To date, no cases of TTS have been reported in Janssen's Ad26/protein preF RSV vaccine clinical studies nor in any other Ad26-based non-COVID-19 vaccine programs from Janssen. Nonetheless, TTS will be followed in this protocol as adverse event of special interest (AESI).

Applicable Section(s)	Description of Change(s)
Rationale: Following observation of very rare events of TTS after vaccination with Janssen's Ad26-based COVID-19 vaccine, TTS will be followed as an AESI in the Revaccination Subcohorts of this study.	
SYNOPSIS Schedule of Activities – Revaccination Subcohort 2A (N=120) Schedule of Activities – Revaccination Subcohort 1B (N=135) Schedule of Activities – Revaccination Subcohort 2B (N=135) Schedule of Activities – Revaccination Subcohorts 1C and 2C (N=240) Schedule of Activities – Revaccination Subcohorts 1D and 2D (N=240) ABBREVIATIONS 1.1 Background 2.1 Objectives and Endpoints 3.1 Overview of Study Design 4.2 Exclusion Criteria 8 PRESTUDY AND CONCOMITANT THERAPY 9.1.1 Overview 9.1.5 Revaccination Subcohorts 9.2.4.1 Adverse Events 10.2 Discontinuation of Study Vaccine/Withdrawal from the Study 11.11 Safety Analyses 12 ADVERSE EVENT REPORTING 12.2 Special Reporting Situations 12.3.1 All Adverse Events 12.3.4 Adverse Events of Special Interest REFERENCES Attachment 13	In the Revaccination Subcohorts, TTS is to be reported to the sponsor as an AESI, within 24 hours of awareness. A potential AESI is defined as thrombotic events or symptomatic thrombocytopenia.
Rationale: The objective on safety in terms of SAEs was erroneously removed in protocol amendment 5.	

Applicable Section(s)	Description of Change(s)
SYNOPSIS 2.1 Objectives and Endpoints	To re-add the objective on safety in terms of SAEs during the study.
Rationale: To change the end date of the second RSV season.	
Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Assessments for Participants with an ARI Episode 3.1 Overview of Study Design	The end of second RSV season date was changed from 30 April 2021 to 17 May 2021.
Rationale: Clarification on SAE collection in the Revaccination subcohorts.	
SYNOPSIS 2.1 Objectives and Endpoints 3.1 Overview of Study Design 9.1.1 Overview 9.1.5 Revaccination Subcohorts 9.2.4.1 Adverse Events 12.3.1 All Adverse Events	Added clarification on the collection of SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs leading to discontinuation from the study, and (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products in the Revaccination Subcohorts.
Rationale: To allow flexibility on when to stop the follow-up of ARIs for the Revaccination Subcohorts C and D.	
SYNOPSIS Schedule of Activities – Revaccination Subcohorts 1C and 2C (N=240) Schedule of Activities – Revaccination Subcohorts 1D and 2D (N=240) 2.1 Objectives and Endpoints 3.1 Overview of Study Design 9.1.1 Overview 9.1.5 Revaccination Subcohorts 9.2.1.1.1 ARI Surveillance Assessment 9.2.4.1 Adverse Events 12.3.1 All Adverse Events 12.3.2 Serious Adverse Events	For the Revaccination Subcohorts C and D, ARI follow-up will be stopped at the end of the third RSV season at the latest.
Rationale: The option for caregivers to complete the eDiary on behalf of the participant has been removed.	
SYNOPSIS 9.1.1 Overview	Caregivers are no longer allowed to complete the eDiary.
Rationale: To correct the footnote on the timing of the post-vaccination visits in the Schedule of Activities for the Revaccination Subcohorts.	

Applicable Section(s)	Description of Change(s)
Schedule of Activities – Revaccination Subcohort 1A (N=120) Schedule of Activities – Revaccination Subcohort 2A (N=120) Schedule of Activities – Revaccination Subcohort 1B (N=135) Schedule of Activities – Revaccination Subcohort 2B (N=135) Schedule of Activities – Revaccination Subcohorts 1C and 2C (N=240) Schedule of Activities – Revaccination Subcohorts 1D and 2D (N=240)	For the Revaccination Subcohorts, the visit day is relative to the actual day of vaccination in the first RSV season. The timing of the visit day is determined by the visit window relative to the last vaccination.
Rationale: New section on the process for protocol clarification communications was added to align with the most recent Jansen protocol template.	
17.1 Protocol Clarification Communications ABBREVIATIONS	New section on protocol clarification communications was added.
Rationale: To align the guidance on study conduct during the COVID-19 pandemic with the most recent Jansen protocol template.	
18 Appendix 1: Guidance on Study Conduct during a natural disaster GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC	The guidance on study conduct during the COVID-19 pandemic was updated.
Rationale: Minor textual changes, clarifications and corrections have been made.	
Throughout the protocol	

Amendment 5 (04 February 2021)

The primary reasons for the amendment: Follow-up of participants from Cohort 1 has been extended through a third RSV season to further evaluate durability of efficacy. Furthermore, additional Revaccination Subcohorts were added. Participants in these subcohorts will be revaccinated at different yearly intervals after the first vaccination to determine the optimal time for revaccination, and to explore the relative contribution of each component of the vaccine (Ad26.RSV.preF and RSV preF protein) to the immune response after revaccination.

Applicable Section(s)	Description of Change(s)
Rationale: Follow-up of participants from Cohort 1 is extended through a third RSV season to further evaluate durability of efficacy if analyses at the end of the second RSV season indicate a trend for durable efficacy or if results on durability are inconclusive at that time. Furthermore, additional Revaccination Subcohorts are implemented to assess the safety and immunogenicity of revaccination with active study vaccine administered at 2, 3, or 4 years after the first study vaccination to determine the optimal time for revaccination, and to explore the relative contribution of each component (Ad26.RSV.preF and RSV preF protein) to the immune response after revaccination.	
SYNOPSIS Schedule of Activities – Cohort 1 Schedule of Activities – Revaccination Subcohort 1A (N=120) Schedule of Activities – Revaccination Subcohort 2A (N=120) Schedule of Activities – Revaccination Subcohort 1B (N=135) Schedule of Activities – Revaccination Subcohort 2B (N=135) Schedule of Activities – Revaccination Subcohorts 1C and 2C (N=240) Schedule of Activities – Revaccination Subcohorts 1D and 2D (N=240) 1.2 Overall Rationale for the Study 2.1 Objectives and Endpoints 3.1 Overview of Study Design 3.2 Study Design Rationale 4.1 Inclusion Criteria 4.2 Exclusion Criteria 5 INTERVENTION ALLOCATION AND BLINDING 6 DOSAGE AND ADMINISTRATION 7 STUDY VACCINE COMPLIANCE 8 PRESTUDY AND CONCOMITANT THERAPY 9.1.1 Overview 9.1.2 Visit Windows 9.1.4 Post-Vaccination Follow-up After Vaccination on Day 1 9.1.5 Revaccination Subcohorts 9.2.1.1 Patient-Reported Outcomes	Follow-up of participants from Cohort 1 during a third RSV season is added, and additional Revaccination Subcohorts are implemented. Participants in these additional subcohorts will be revaccinated at 2, 3, or 4 years after the first study vaccination. Additional study visits and additional procedures and assessments are included for these participants.

Applicable Section(s)	Description of Change(s)
9.2.1.1.1 ARI Surveillance Assessment 9.2.1.2 Lawton-Brody Instrumental Activities of Daily Living (IADL) Scale 9.2.2 Immunogenicity Evaluations 9.2.4.1 Adverse Events 9.2.4.3 Physical Examination 10.1 Completion 10.3 Contraindications to Vaccination 11.1 Analysis Sets 11.2.4 Revaccination Subcohorts 11.4.1 Primary Efficacy Endpoints 11.4.2 Secondary Efficacy Endpoints 11.4.3 Exploratory Efficacy Endpoints 11.4.3.1 Analysis 11.9.2 Revaccination Subcohorts 11.11 Safety Analyses 11.12 Planned Analyses 12.3.1 All Adverse Events 12.3.2 Serious Adverse Events 14.3 Storage and Handling 16.1 Study-specific Design Considerations Attachment 1	
Rationale: Clarification that collection of ARI data will be ceased for that particular episode if a participant has tested positive for SARS-CoV-2.	
SYNOPSIS 9.1.1 Overview	Added clarification that collection of ARI data by the study site will be ceased for that particular episode if a participant has tested positive for SARS-CoV-2 (by a local test that is FDA-approved or by central laboratory PCR).
Rationale: Clarification that paper safety diaries may be used if designated by the sponsor.	
SYNOPSIS Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Cohort 2 (N=2,000) Schedule of Activities – Revaccination Subcohort 1A (N=120) Schedule of Activities – Revaccination Subcohort 2A (N=120) Schedule of Activities – Revaccination Subcohort 1B (N=135)	Added clarification that paper safety diaries may be used at the sponsor's discretion.

Applicable Section(s)	Description of Change(s)
Schedule of Activities – Revaccination Subcohort 2B (N=135) Schedule of Activities – Revaccination Subcohorts 1C and 2C (N=240) Schedule of Activities – Revaccination Subcohorts 1D and 2D (N=240) 3.1 Overview of Study Design 4.1 Inclusion Criteria 9.1.1 Overview	
Rationale: Clarification that in each case of portal/eDevice down time, PRO data can only be collected upon sponsor approval via interview using paper versions of the questionnaires.	
9.2.1.1 Patient-Reported Outcomes	Added clarification in case of portal/eDevice down time, PRO data can be collected upon sponsor approval via interview using paper versions of the questionnaires.
Rationale: Clarification that site monitoring can include both on-site monitoring visits as well as video site monitoring.	
17.6 Data Quality Assurance/Quality Control 17.8 Monitoring	Added clarification that site monitoring can be performed by using video site monitoring.
Rationale: Minor textual changes, clarifications and corrections have been made.	
Throughout the protocol	

Amendment 4 (25 August 2020)

The primary reason for the amendment: A subcohort of participants will receive a second vaccination with active study vaccine to further characterize the immune responses to vaccination.

Applicable Section(s)	Description of Change(s)
Rationale: Addition of a Revaccination Subcohort to assess safety and immunogenicity in a subcohort of participants, who will be given a second vaccination with active study vaccine at 12 months after the first immunization.	
SYNOPSIS Schedule of Activities – Cohort 1 Schedule of Activities – Revaccination Subcohort Schedule of Activities – Assessments for Participants with an ARI Episode 1.2 Overall Rationale for the Study 2.1 Objectives and Endpoints 3.1 Overview of Study Design	A revaccination at 12 months after the first vaccination (ie, Day 365 visit) is added for a separate subcohort of Cohort 1 (Revaccination Subcohort). Additional study procedures and assessments are added for these participants and clarifications are added regarding the open-label character of this revaccination.

Applicable Section(s)	Description of Change(s)
3.2 Study Design Rationale 4.2 Exclusion Criteria 5 INTERVENTION ALLOCATION AND BLINDING 6 DOSAGE AND ADMINISTRATION 7 STUDY VACCINE COMPLIANCE 8 PRESTUDY AND CONCOMITANT THERAPY 9.1.1 Overview 9.1.2 Visit Windows 9.1.4 Post-Vaccination Follow-up After Vaccination on Day 1 9.1.5 Revaccination Subcohort 9.1.6 Early Withdrawal – Early Exit Visit 9.2.2 Immunogenicity Evaluations 9.2.4 Safety Evaluations 10.3 Contraindications to Vaccination 11.1 Analysis Sets 11.2.4 Revaccination Subcohort 11.4.1 Primary Efficacy Endpoints 11.9.2 Revaccination Subcohort 11.12 Planned Analyses 12.3.1 All Adverse Events 12.3.2 Serious Adverse Events 14.3 Storage and Handling 16.1 Study-specific Design Considerations	
Rationale: Clarification in SAE reporting	
SYNOPSIS Schedule of Activities – Cohort 1 Schedule of Activities – Revaccination Subcohort 2.1 Objectives and Endpoints 3.1 Overview of Study Design 9.1.1 Overview 12.3.1 All Adverse Events 12.3.2 Serious Adverse Events	The paragraphs on SAE collection are reordered for clarity. Where needed, a sentence on SAE reporting for the Revaccination Subcohort is added.

Applicable Section(s)	Description of Change(s)
Rationale: Actualization of past due dates mentioned in the protocol, including the end of the first NH RSV season, and addition of VAC18193RSV2005 as an ongoing study.	
1.1 Background 3.1 Overview of Study Design Schedule of Activities – Cohort 1	Ongoing study VAC18193RSV2005 was added to the Ad26.RSV.preF and RSV preF Protein Clinical Data overview table. Due to progression of the ongoing study past some milestone dates, the tense of these milestones is actualized.
Rationale: Addition of MA-ARI form as a new attachment, for alignment with ICF.	
9.1.1 Overview Attachment 12	Addition of MA-ARI form as Attachment 12.
Rationale: Added video call as an option for virtual visits.	
18 Appendix 1: Guidance on Study Conduct during the COVID-19 Pandemic	
Rationale: Minor textual changes, clarifications and corrections have been made.	
Throughout the protocol	

Amendment 3 (8 May 2020)

The primary reason for the amendment: The Month 12 study vaccination is removed to determine if a single dose of the vaccine can give durable efficacy against RSV-mediated LRTD during a second RSV season.

Applicable Section(s)	Description of Change(s)
Rationale: The Month 12 vaccination is removed as it was decided to prioritize the assessment of durability of protection after a single vaccination.	
SYNOPSIS Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Cohort 2 (N=2,000) 1.2 Overall Rationale for the Study 2.1 Objectives and Endpoints 3.1 Overview of Study Design 9.1.1 Overview 9.1.2 Visit Windows 9.1.4 Day 365 (Week 52) 9.1.5 Post-vaccination Follow-up 9.1.7.1 Patient-Reported Outcomes 9.1.7.1.1 ARI Surveillance Assessment 9.1.10.3 Physical Examination	The Month 12 study vaccination and related assessments are removed. The post-vaccination follow-up visits in the second season are renamed relative to the first vaccination. The assessment period is clarified as ‘during each RSV season’ or ‘both RSV seasons’ as applicable.

Applicable Section(s)	Description of Change(s)
10.3 Contraindications to Vaccination 11.2.2 Immuno Subset 11.9.1 Immuno Subset 11.12 Planned Analyses 16.1 Study-Specific Design Considerations	
10.1 Completion 10.2 Discontinuation of Study Vaccine/Withdrawal from the Study	Due to the removal of the Month 12 vaccination, the definition of the study completion and discontinuation of study vaccine/withdrawal from the study changed.
SYNOPSIS Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Assessments for Participants with an ARI Episode 9.1.1 Overview 9.1.4 Day 365 (Week 52) 9.1.7.2 Lawton-Brody Instrumental Activities of Daily Living (IADL) Scale 9.1.10.3 Physical Examination 11.4.1 Primary Efficacy Endpoints Attachment 1	A new baseline has been added on Day 365 for the physical examination (except height measurement), RiiQ, Lawton-Brody IADL, and MRU assessments.
Rationale: By removing the second vaccination, the SAE follow-up has changed in the second RSV season of the study.	
SYNOPSIS Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Assessments for Participants with an ARI Episode 2.1 Objectives and Endpoints 3.1 Overview of Study Design 9.1.1 Overview 9.1.10.1 Adverse Events 12.3.1 All Adverse Events 12.3.2 Serious Adverse Events	From the Day 365 visit until the end of the second RSV season, SAEs associated with ARIs will be collected. During the entire study, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected.
Rationale: To update to background section with the latest clinical information.	
1.1 Background	The background section has been updated with the latest clinical information of the latest Investigator's Brochure (Edition 10, issued 4 December 2019).

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that the RiiQ and PGI-H questionnaires at the end of each RSV season can be completed by the participant in the eDiary or by telephone contact.	
SYNOPSIS Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Cohort 2 (N=2,000) 3.1 Overview of Study Design 9.1.5 Post-vaccination Follow-up	The RiiQ and the PGI-H at the end of the RSV season will be completed by the participant in the eDiary or by telephone contact. If completed by telephone interview, the study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
Rationale: To allow collection of clinical assessments on paper before entering in eDevice on the same day as the assessments.	
Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Cohort 2 (N=2,000) Schedule of Activities – Assessments for Participants with an ARI Episode 17.4 Source Documentation	The sponsor's strong preference is that the results of the clinical assessment are entered directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.
Rationale: To include a Clinical Evaluation Committee (CEC) review to determine if the ARIs are URTIs or LRTIs and the severity of the ARIs.	
SYNOPSIS 11.4.3 Exploratory Efficacy Endpoints	The CEC review will assess, independently and based on CRF/eDiary data, the location of the ARI (upper or lower respiratory tract infection) and the ARI severity. The CEC assessment, as well as other information based on MRU, presence of clinically relevant disease, use of therapeutic interventions, RiiQ, clinical assessment, Lawton-Brody IADL, and change in frailty will be used to evaluate the severity of the RSV-positive ARIs, and will be used to explore the relation with the case definitions.
Rationale: To explore the relationship between G-ELISA and RT-PCR-confirmed RSV infection.	
SYNOPSIS 2.1 Objectives and Endpoints 9.2.2 Immunogenicity Evaluations 11.4.3 Exploratory Efficacy Endpoints	As there is no established cut-off in G-ELISA fold-rise for serology confirmation of RSV in older adults, the objectives related to serologic confirmation of RSV are conditional on finding a cut-off that is sufficiently sensitive and specific.
Rationale: To collect information on influenza vaccination at the end of each RSV season.	
Schedule of Activities – Cohort 1 (N=5,800)	A check for seasonal influenza vaccination has been added to the assessments at the end of each RSV season.

Applicable Section(s)	Description of Change(s)
Rationale: To include bacterial panel testing for the detection of other respiratory pathogens in the midturbinate nasal swabs.	
9.1.7.5 Diagnosis of RSV and Other Respiratory Infections 9.2.2 Immunogenicity Evaluations	The midturbinate nasal swab may also be used to perform bacterial panel testing.
Rationale: To add the end of RSV season visits to the visit windows table.	
9.1.2 Visit Windows	Visits 3 and 6, ie, the end of RSV season visits, are added to the visit windows table.
Rationale: To correct that participants should store their eDevice at home at the end of the first RSV season.	
9.1.5 Post-vaccination Follow-up	Participants who were provided an eDevice to complete assessments at home during the first RSV season will be instructed to store their eDevice at a safe place at home in preparation of the second season.
Rationale: To avoid confusion between the RiiQ v2 questionnaire and the RiiQ subset, the term RiiQ subset has been removed from this protocol.	
SYNOPSIS Schedule of Activities – Assessments for Participants with an ARI Episode 3.1 Overview of Study Design 9.1.1 Overview 9.1.7 Efficacy Evaluations 17.4 Source Documentation Attachment 4 Attachment 5 Attachment 11	The term 'RiiQ subset' has been split into the RiiQ Symptom scale (Attachment 5) and the RiiQ Impact on Daily Activities Scale (Attachment 11). Additionally, the naming has been adjusted as needed in the protocol.
Rationale: For health and safety reasons due to the Coronavirus Disease 2019 (COVID-19), participants may not be able to come to the study site for scheduled procedures.	
Appendix 1	Appendix 1 has been added to provide guidance to the investigator for managing study-related procedures during the COVID-19 pandemic.
Rationale: Minor textual changes, clarifications and corrections have been made.	
Throughout the protocol	

Amendment 2 (20 March 2020)

The primary reason for the amendment: The primary reason for this amendment is to shorten the ARI surveillance to minimize participant-participant contact and participant-site contact due to safety concerns related to increasing incidence of COVID-19 cases in US, where older adults are the highest risk group.

Applicable Section(s)	Description of Change(s)
Rationale: To change the ARI surveillance period in the first NH RSV season to 20 March 2020 due to the coronavirus disease 2019 (COVID-19) pandemic.	
SYNOPSIS Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Assessments for Participants with an ARI Episode 3.1 Overview of Study Design 8 PRESTUDY AND CONCOMITANT THERAPY 9.1 Study Procedures	The ARI surveillance period is shortened to 20 March 2020 instead of the earlier defined date for the end of the first NH RSV season (ie, 30 April). For the first NH RSV season, if possible, participants who have an ongoing ARIs, where an ARI Day 3-5 visit including the collection of a nasal swab or sputum sample has occurred, should continue collecting daily temperature monitoring, RiiQ™ and PGI questionnaires on their eDevices until their symptoms resolve or return to baseline for 2 days. If possible, sites should collect ARI Day 29 visit data, but excluding procedures that require on-site visit (ie, serology and clinical assessment), over the telephone.
Rationale: To allow a separate unscheduled visit to follow-up on SAEs at the end of the first season visit (Visit 3).	
Schedule of Activities – Cohort 1 (N=5,800) Schedule of Activities – Assessments for Participants with an ARI Episode	When the window for the end of season visit at the end of the first NH RSV season (as defined in the protocol) is not coinciding with at least 6 months SAE follow-up, a separate SAE safety follow-up call should be conducted 6 months after vaccination and captured as an unscheduled visit.
Rationale: To add an unplanned interim analysis due to the COVID-19 pandemic.	
SYNOPSIS 11.12 Planned Analyses	Due to the increasing incidence of COVID-19 cases, it is becoming increasingly difficult to conduct ARI surveillance, without putting staff or study participants at risk. As the RSV season is nearing a close, a decision has been made to stop ARI surveillance.
Rationale: To move the secondary objective on serologic confirmation of RSV to the exploratory objectives.	
SYNOPSIS 2.1 Objectives and Endpoints 11.4.3 Exploratory Efficacy Endpoints	The secondary objective on serologic confirmation of RSV is moved to the exploratory objectives.
Rationale: Minor textual changes, clarifications and corrections have been made.	
Throughout the protocol	

Amendment 1 (11 October 2019)

The primary reason for the amendment: The primary reason for this amendment is to remove duplicates in the ePRO assessments captured via the electronic devices (ie, the participant eDiary and the site's eDevice) in participants with an ARI episode.

Applicable Section(s)	Description of Change(s)
Rationale: To align time points for assessments through the participant eDiary and the site's eDevice in participants with an ARI episode.	
SYNOPSIS Overview of Study Design; Schedule of Activities – Assessments for Participants with an ARI Episode; Section 3.1 Overview of Study Design; Section 9.1.1 Overview; Section 9.2.1.1.3 Patient Global Impression Scores	Completion of the PGI-H, PGI-S, PGI-C, and Return to Usual Health question on the site's eDevice at the ARI Days 3-5 visit has been removed from the protocol, because these assessments will already be completed by the participant in the eDiary during the ARI episode.
Schedule of Activities – Assessments for Participants with an ARI Episode; Section 9.2.1.1.3 Patient Global Impression Scores	The eDiary assessments on ARI Day 29 have been removed from the participant's device, because these assessments will already be completed by the participant on the site's eDevice during the ARI Day 29 visit.
Rationale: To align the analysis methods related to vaccine efficacy across the primary, secondary and exploratory endpoints.	
SYNOPSIS Statistical Methods; Section 11.1 Analysis Sets	"Any participant with RT-PCR-confirmed RSV-mediated LRTD (according to Case Definition #3) with onset within 14 days after vaccination will be excluded from the PPE population" has been changed to: "Any participant with an RT-PCR-confirmed RSV-mediated ARI with onset within 14 days after vaccination will be excluded from the PPE population".
SYNOPSIS Statistical Methods; Section 11.4.1.1 Analysis; Section 11.4.2.1 Analysis; Section 11.4.3.1 Analysis	A Poisson model will be fitted for all of these endpoints. In addition, for some endpoints an exact binomial confidence interval (rather than a score-based exact confidence interval) will be calculated.
Rationale: To collect influenza vaccination information for use in the analysis of ARIs.	
Schedule of Activities – Assessments for Participants with an ARI Episode	For participants with an ARI episode, a check for seasonal influenza vaccination has been added to the assessments of the ARI Day 3-5 and ARI Day 29 visits.
Rationale: To clarify the rescreening process for screen failed participants.	
Section 9.1.3 Screening/Randomization and Vaccination (Day 1)	The possibility for rescreening has been added to the protocol. If a participant is a screen failure but at some point in the future is expected to meet the eligibility criteria, the participant may be rescreened on one occasion only. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.

Applicable Section(s)	Description of Change(s)
Rationale: To aid completion of screening procedures, the possibility to split screening into 2 visits has been added.	
Section 9.1.3 Screening/Randomization and Vaccination (Day 1)	Screening may be split into 2 visits after consultation with the sponsor. Every effort should be made for split visits to occur within 3 to 5 days.
Rationale: Minor textual changes, clarifications and corrections have been made.	
Throughout the protocol	

SYNOPSIS

A Randomized, Double-blind, Placebo-controlled Phase 2b Study to Assess the Efficacy, Immunogenicity and Safety of an Ad26.RSV.preF-based Regimen in the Prevention of RT-PCR-confirmed RSV-mediated Lower Respiratory Tract Disease in Adults Aged 65 Years and Older

A human adenovirus-vectored vaccine candidate and a pre-fusion conformation-stabilized respiratory syncytial virus (RSV) fusion (F) protein that have shown promise in preclinical animal models of RSV will be assessed in this study:

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

The active study vaccines used in the current study are Ad26.RSV.preF and RSV preF protein each administered alone as a single injection, and Ad26.RSV.preF/RSV preF protein mixture administered as a single injection.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives and Endpoints

Objectives	*Endpoints*
PRIMARY	
• To demonstrate the efficacy of active study vaccine in the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed RSV-mediated lower respiratory tract disease (LRTD) according to Case Definition #1[a], when compared to placebo	• First occurrence[b] of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #1
• To demonstrate the efficacy of active study vaccine in the prevention of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #2[a], when compared to placebo	• First occurrence of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #2
• To demonstrate the efficacy of active study vaccine in the prevention of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #3[a], when compared to placebo	• First occurrence of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #3
SECONDARY	
• To assess the efficacy of active study vaccine in the prevention of any RT-PCR-confirmed RSV disease when compared to placebo	• First occurrence of any RT-PCR-confirmed RSV disease
• In the Immuno Subset and in subgroups of this subset (eg, participants at increased risk of severe RSV disease), to evaluate the immunogenicity of active study vaccine	• Characterization of the humoral and cellular immune responses with emphasis on neutralizing and binding antibodies and antigen-specific cytokine production by T cells

[a] Clinical case definitions for RSV-mediated LRTD are presented in Section "Efficacy Evaluations" below.

[b] First occurrence of the considered endpoint is defined as the first episode of the considered endpoint in a given RSV season (regardless of RSV A or B strain, unless otherwise specified).

Objectives	*Endpoints*
• In the Safety Subset and in subgroups of this subset (eg, participants at increased risk of severe RSV disease), to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) during 7 days after vaccination, and in terms of unsolicited AEs during 28 days after vaccination	• Occurrence, severity, duration and relationship to vaccination of solicited local and systemic AEs during 7 days after vaccination and of unsolicited AEs during 28 days after vaccination
• In the Revaccination Subcohorts, to evaluate the safety and reactogenicity in terms of solicited local and systemic AEs during 7 days after revaccination with active study vaccine administered at 1, 2, or 3 years after the first vaccination, and in terms of unsolicited AEs during 28 days after revaccination	• Occurrence, severity, duration and relationship to vaccination of solicited local and systemic AEs during 7 days after revaccination at 1, 2, or 3 years after the first vaccination and of unsolicited AEs during 28 days after revaccination at 1, 2, or 3 years after the first vaccination
• To evaluate safety in terms of serious adverse events (SAEs) during the RSV season[a] • To evaluate safety in terms of adverse events of special interest (AESIs) during 6 months after revaccination[a]	• Occurrence and relationship to vaccination of SAEs during the RSV season • Occurrence and relationship to vaccination of AESIs during 6 months after revaccination
• To evaluate safety in terms of SAEs during the acute respiratory infection (ARI) follow-up periods[b]	• Occurrence and relationship to vaccination of SAEs during the ARI follow-up periods
EXPLORATORY	
• Explore the relationship between G-ELISA and RT-PCR-confirmed RSV infection. Provided a cut-off for G-ELISA fold-rise is found that is sufficiently sensitive and specific, the following objectives will be explored:	• Fold-rise in G-ELISA between ARI Day 3-5 and ARI Day 29. – First occurrence of any serology and/or RT-PCR-confirmed RSV disease

[a] For participants who will not receive a revaccination, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later). In addition, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation, and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the entire study for all participants.

For Revaccination Subcohort A, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from the time of revaccination at Month 12 until the end of the second RSV season, or until 6 months after revaccination, whichever comes later. For Revaccination Subcohort 2A, all SAEs and AESIs will also be collected from the time of revaccination on Day 730 until 6 months after revaccination. For the other Revaccination Subcohorts (B and C), SAEs and AESIs will be collected from the time of revaccination until 6 months thereafter. In addition, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation, and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the entire study for all participants. For the participants in the Revaccination Subcohort C, these (S)AEs will be collected retrospectively for the time period between the last end of the RSV season visit and the revaccination upon the day of revaccination.

[b] For participants who will not receive a revaccination, SAEs associated with ARIs and complications related to ARIs that classify as SAEs will be collected from the Day 365 (Month 12) visit until the end of the second RSV season, from the end of the second RSV season until the Day 730 (Month 24) visit, and from the Day 730 (Month 24) visit until the end of the third RSV season.

For all Revaccination subcohorts, collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season for Subcohort A, on Day 730 (Month 24) for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

Objectives	*Endpoints*
– To assess the efficacy of active study vaccine in the prevention of any serology and/or RT-PCR-confirmed RSV disease when compared to placebo – To assess the efficacy of active study vaccine in the prevention of serology-confirmed RSV-mediated LRTD according to each case definition, when compared to placebo – To assess the efficacy of active study vaccine in the prevention of any serology-confirmed RSV disease when compared to placebo To assess the efficacy of active study vaccine in the prevention of any serology and/or RT-PCR-confirmed RSV-mediated LRTD according to each case definition, when compared to placebo	– First occurrence of serology-confirmed RSV-mediated LRTD according to each case definition First occurrence of any serology-confirmed RSV disease First occurrence of any serology and/or RT-PCR-confirmed RSV-mediated LRTD
• If vaccine efficacy (VE) is demonstrated: – To explore the efficacy of active study vaccine during the second and third RSV season in the prevention of RT-PCR-confirmed RSV-mediated LRTD according to each of the 3 case definitions in each RSV season, respectively, when compared to placebo. To explore the efficacy of active study vaccine over 2 and 3 RSV seasons in the prevention of RT-PCR-confirmed RSV-mediated LRTD according to each of the 3 case definitions, when compared to placebo The objectives assessed during the first year, might also be explored during the second and third year and over the 3-year period	• First occurrence of RT-PCR-confirmed RSV-mediated LRTD during the second and third RSV season according to each of the 3 case definitions • First occurrence of RT-PCR-confirmed RSV-mediated LRTD over 2 and over 3 RSV seasons according to each of the 3 case definitions • For objectives considering the VE during the second and third season, the first occurrence of the considered endpoint in the second and third season will be assessed • For objectives considering VE over 3 RSV seasons, the first occurrence of the considered endpoint over 3 seasons will be assessed
• To assess the effect of active study vaccine on the level of RSV infection when compared to placebo	• Assessment of the RSV viral load by quantitative RT-PCR
• To explore the efficacy of active study vaccine in the prevention of any RT-PCR-confirmed RSV disease caused by an RSV A strain and any RT-PCR-confirmed RSV disease caused by an RSV B strain when compared to placebo	• First occurrence of any RT-PCR-confirmed RSV disease caused by an RSV A strain or RSV B strain, respectively
• To explore the effect of active study vaccine on the potential complications of RSV disease and of any respiratory disease	• First occurrence of potential complications of respiratory disease (eg, pneumonia, new onset, worsening, or an exacerbation of congestive heart failure (CHF), asthma, and chronic obstructive pulmonary disease (COPD) linked to any respiratory disease and linked to any RT-PCR-confirmed RSV disease

Objectives	*Endpoints*
• In the Revaccination Subcohorts, to evaluate humoral and cellular immunogenicity following a revaccination administered at 1 (humoral only), 2, or 3 years after the first vaccination	• Characterization of the humoral and cellular immune response following a revaccination at 1 (humoral only), 2, or 3 years after the first vaccination, with emphasis on neutralizing and binding antibodies
• To evaluate the immune response biomarkers in study participants as correlates of risk of RSV disease and as correlates of protection induced by the vaccine	• Assessment of the correlation of humoral immune responses with emphasis on neutralizing and binding antibodies with the risk of RSV disease and protection induced by the vaccine
• To explore biomarkers for the diagnosis of RSV infection and RSV disease severity	• Assessment of blood samples collected during ARI episodes for biomarkers that correlate with RSV infection and RSV disease severity
• To explore the efficacy of active study vaccine against other respiratory diseases	• Midturbinate nasal swabs may be tested for the presence of other respiratory pathogens
• To explore the effect of active study vaccine on hospitalization in the overall populations and in subgroups	• First occurrence of hospitalization linked to any respiratory disease and linked to any RT-PCR confirmed RSV disease
• To explore the impact of active study vaccine on the course of respiratory disease and general health status	• Daily symptom severity reported by participants using the Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)[a], patient global impression scales, temperature logs, Medical Resource Utilization (MRU) and oxygen saturation in participants with an ARI (RSV-confirmed or any cause)
• To explore the impact of the baseline frailty and functioning in Instrumental Activities of Daily Living (IADL) on the incidence, severity, and duration of RT-PCR confirmed RSV-mediated LRTD	• Assessment of RSV incidence (by RT-PCR), RSV severity (per RiiQ questionnaire), and duration of ARI episode(s) in relation to the baseline frailty score and baseline Lawton-Brody IADL
• In Revaccination Subcohorts 2A and 2B, to explore the relative contribution of each component of the active vaccine on safety and reactogenicity in terms of solicited local and systemic AEs during 7 days after revaccination, and in terms of unsolicited AEs during 28 days after revaccination	• Occurrence, severity, duration, and relationship to vaccination of solicited local and systemic AEs during 7 days after revaccination and of unsolicited AEs during 28 days after revaccination
• In Revaccination Subcohorts 2A and 2B, to explore the relative contribution of each component of the active vaccine on humoral and cellular immunogenicity following revaccination	• Characterization of the humoral and cellular immune response following revaccination, with emphasis on neutralizing and binding antibodies

Hypothesis

The study is designed to test the primary hypothesis of VE in the Per-protocol Efficacy (PPE) population.

- The null hypothesis is that the VE for each of the 3 primary endpoints is ≤0%
- The alternative hypothesis is that the VE for at least one of the primary endpoints is >0%

[a] The Respiratory Infection Intensity and Impact Questionnaire used in this study is the RiiQ™ Version 2, 2018 (hereafter referred to as RiiQ).

OVERVIEW OF STUDY DESIGN

This is a multi-center, randomized, double-blind, placebo-controlled Phase 2b proof-of-concept study to establish VE of the study vaccine during the RSV season after single vaccination. A target of up to 5,800 participants (Cohort 1)[a] will be enrolled and randomized in parallel in a 1:1 ratio to 1 of 2 groups to receive active study vaccine (Group 1) or placebo (Group 2).

Cohort 1 will contain the following subsets:

- Safety Subset (N=700): approximately 350 active study vaccine participants and 350 placebo participants who have given informed consent for the additional study procedures for assessment of safety.
- Immuno Subset (N=200 from selected study sites): approximately 100 active study vaccine participants and 100 placebo participants who have given informed consent for the additional study procedures for assessment of immunogenicity.

Under Amendment 4 (dated 25 August 2020), a subcohort of Cohort 1 participants will be implemented. This Revaccination Subcohort (N=240) will consist of approximately 120 participants from Group 1 who received active study vaccine on Day 1 and 120 participants from Group 2 who received placebo on Day 1, and who have given informed consent for the additional study procedures. Participants in this Revaccination Subcohort will receive a revaccination with active study vaccine on Day 365 (Month 12, 1 year after the first vaccination) to assess the safety and immunogenicity of a second vaccination.

Under Amendment 5 (dated 04 February 2021), additional Revaccination Subcohorts will be implemented. Participants in these additional Revaccination Subcohorts will receive a revaccination with active study vaccine at 2, or 3 years after the first vaccination to assess the safety and immunogenicity of revaccination with Ad26.RSV.preF/RSV preF protein mixture or with the individual vaccine components as indicated in the table below.

Under Amendment 8 (dated 16 February 2023), Revaccination Subcohort D (ie, participants who would have received a revaccination with the Ad26.RSV.preF/RSV preF protein mixture at 4 years after the first vaccination) will be removed as additional data with a Month 48 revaccination timepoint are not expected to provide novel insights on the kinetics of the immune response after revaccination with the Ad26.RSV.preF/RSV preF protein mixture.

Note: Participants can be enrolled in both the Safety and the Immuno Subset. Participants in Revaccination Subcohorts A and B cannot have participated in the Safety or the Immuno Subset.

Cohort/Group/ Subcohort	**Day 1 Vaccination**	**Day 365 (Month 12) Revaccination**	**Month 24 Revaccination**	**Month 36 Revaccination**
		(Amendment 4)	**(Amendment 5)**	
Cohort 1[a,b] N=5,800				
Group 1 N=2,900	Active vaccine mixture			
	Safety Subset[c] (N 350)			
	Immuno Subset[c] (N 100)			

[a] In case 5,500 or more participants are enrolled from the Northern Hemisphere, no additional participants from the Southern Hemisphere will be enrolled.

Cohort/Group/ Subcohort	Day 1 Vaccination	Day 365 (Month 12) Revaccination	Month 24 Revaccination	Month 36 Revaccination
		(Amendment 4)	(Amendment 5)	
Revaccination Subcohort 1A[c] (N=120)	Active vaccine mixture	Active vaccine mixture		
Revaccination Subcohort 1B[c] (N=135)	Active vaccine mixture		Active vaccine mixture	
Revaccination Subcohort 1C[c,d] (N=120)	Active vaccine mixture			Active vaccine mixture
Group 2 N=2,900	Placebo *Safety Subset*[c] *(N 350)* *Immuno Subset*[c] *(N 100)*			
Revaccination Subcohort 2A[c] (N=120)	Placebo	Active vaccine mixture	Ad26.RSV.preF alone (N=40)	
			RSV preF protein alone (N=40)	
			Active vaccine mixture (N=40)	
Revaccination Subcohort 2B[c] (N=135)	Placebo		Active vaccine mixture	Ad26.RSV.preF alone (N=45)
				RSV preF protein alone (N=45)
				Active vaccine mixture (N=45)
Revaccination Subcohort 2C[c,d] (N=120)	Placebo			Active vaccine mixture

Active vaccine mixture refers to Ad26.RSV.preF (1×10^{11} vp)/RSV preF protein (150 µg) administered as a single injection.
Ad26.RSV.preF alone refers to Ad26.RSV.preF at a dose of 1×10^{11} vp.
RSV preF protein alone refers to RSV preF protein at a dose of 150 µg.

[a] If 5,500 or more participants are enrolled from the NH, no additional participants from the SH will be enrolled. In addition, if the number of participants enrolled in the NH is less than 5,500 but 18 or more RT PCR confirmed RSV mediated LRTD events (using Case Definition #2) are observed in the NH before opening sites in the SH, no sites will be opened in the SH and the study will be performed as a NH study only.

[b] The study progression beyond the first year is dependent on results obtained at the end of the first NH RSV season.

[c] Participants who provided separate informed consent.

[d] The study will continue with Revaccination Subcohort C depending on the 28 day post second vaccination analysis results from Revaccination Subcohort B.

LRTD= lower respiratory tract disease, NH= Northern Hemisphere, SH= Southern Hemisphere, vp= viral particles

After administration of study vaccine, participants who experience any symptoms suggesting an ARI[a] should contact the study site and start completing the eDiary ARI assessment on a daily basis (preferably in the evening) and/or the study site should contact the participant if any ARI symptoms are recorded in the eDiary. To help participants remember to report symptoms of a possible ARI, written instructions will be provided, and an eDiary reminder will be sent to the participant's eDevice twice per week during all 3 RSV seasons, as well as between the second and third RSV season. The reminder will ask participants if they

[a] An ARI is defined as the occurrence of at least one upper respiratory tract infection (URTI) or lower respiratory tract infection (LRTI) symptom that the participant reports that is different or worse than he or she usually experiences. See Attachment 1.

have experienced any ARI symptoms, or for participants that have one or more of these symptoms at baseline, if they have experienced any additional ARI symptoms or a worsening of their baseline symptoms. Participants continue to receive daily reminders during an ARI episode until they report 2 consecutive days without any symptoms of an ARI beyond those present at baseline. The daily eDiary ARI assessment will then end and twice weekly reminders to complete the eDiary ARI surveillance assessment will resume.

All ARIs, all complications related to ARIs, and concomitant medications associated with ARIs will be captured on the ARI form for all participants.

For participants in the Revaccination Subcohorts, follow-up of ARIs will stop at the end of the second RSV season for Subcohort A, at the Day 730 (Month 24) visit for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

Procedures for Participants who Experience an ARI Episode

When any participant experiences any symptom of ARI, the following will take place:

- Participants should contact the site as soon as possible to notify the site of any symptoms suggesting an ARI (such as rhinitis, nasal congestion, sore throat, cough, etc.), or the site will contact the participants if ARI symptoms are recorded in the eDiary. During this telephone or telemedicine contact, the site may confirm if the reported symptoms qualify as an ARI episode, in order to determine whether to proceed with the ARI procedures. The participant will then be reminded to:

  Complete the RiiQ Symptom Scale (Attachment 5) and the RiiQ Impact on Daily Activities Scale (Attachment 11, as part of the Combined Impact Assessment), and thermometer readings every evening (preferably), beginning on the evening of the day of symptom onset (ARI Day 1) until the ARI episode resolves. The eDiary will also ask participants to complete the Patient Global Impression of Health (PGI-H), the Patient Global Impression of Severity (PGI-S), the Patient Global Impression of Change (PGI-C), and the Return to Usual Health question, as part of the Combined Impact Assessment. (Note that the PGI-C and the Return to Usual Health question will not be completed on ARI Day 1). A resolved ARI episode is defined as 2 consecutive days with no symptoms listed on the RiiQ Symptom Scale, or, for participants who have RiiQ symptoms present at baseline (assessed pre-vaccination for the first RSV season, at the Day 365 [Month 12] visit for the second RSV season [pre-vaccination if applicable], and at the Day 730 [Month 24] visit for the third RSV season), 2 consecutive days where all symptoms on the RiiQ Symptom Scale have returned to the severity level reported at baseline.

  If a participant is unable to complete the eDiary, a study staff member can collect information on the participant's symptoms and temperature, by contacting the participant by telephone or telemedicine (or visit the participant at home), reading the questions aloud to the participant and entering the participant's responses on the site's eDevice on the participant's behalf.

  Collect a midturbinate nasal swab at home on the day of symptom onset or the day thereafter (ARI Days 1-2). If the participant requires it, the participant's caregiver can assist the participant to collect the midturbinate nasal swabs.

  Ensure the midturbinate nasal swabs collected at home are provided to the study staff within 4 days (preferably) after collection.

  Come to the site between 2 and 4 days after symptom onset (ARI Days 3-5), or, if a site visit is not feasible, a member of the study staff can visit the participant at home (or at the hospital, if needed) during this time frame.

- Between 2 and 4 days after symptom onset (ARI Days 3-5), a midturbinate nasal swab, a sputum sample (in participants with a productive cough, when possible) and a blood sample for seroconfirmation and exploration of biomarkers that correlate with RSV infection and RSV disease severity will be taken by a qualified member of the study staff, and vital signs, including body

temperature, blood pressure, heart rate, respiratory rate and oxygen saturation, will be measured. A clinical assessment, including a targeted physical examination, will be completed by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. The participant's functional status will also be evaluated by the Lawton-Brody IADL questionnaire. The MRU questionnaire will be completed based on clinical interview. The participant will complete all 4 scales of the RiiQ v2 questionnaire on the site's eDevice and provide the study staff member the midturbinate nasal swab collected by the participant at home.

- At ARI Day 29 (±7 days), participants will be asked to return to the site where a blood sample will be drawn for seroconfirmation and exploration of biomarkers that correlate with RSV infection and RSV disease severity. A qualified member of the study staff will measure vital signs, including body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation. A clinical assessment (including a targeted physical examination) will be performed by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent, and the Lawton-Brody IADL assessment and MRU questionnaire will be completed based on interview with the participant. Participants will complete all 4 scales of the RiiQ questionnaire, and each of the PGI scales and the Return to Usual Health question on the site's eDevice.

For all medically attended ARIs, including those resulting in hospitalization, a standard question list will be provided, with the aim to collect additional information on any other diagnostics (eg, chest x-rays, spirometry, pulmonary function tests, etc.) or interventions during the clinical course of the ARI.

For participants who experience symptoms suggesting an ARI episode, RT-PCR assay of the midturbinate nasal swabs and sputum sample (when available), taken after symptom onset will be used to determine whether the infection was caused by RSV[a]. If at least one of these samples is positive for RSV, the collected information will be applied against the clinical case definitions for RSV-mediated LRTD. For participants hospitalized with symptoms of an ARI, confirmation of RSV infection using a Food and Drug Administration (FDA)-approved RT-PCR test at the local (hospital) laboratory will also be obtained.

Site staff and participants will remain blinded as to the outcome of RT-PCR test results until study unblinding, but participants and their routine health care professional (HCP) can obtain external diagnostics, including RSV RT-PCR, as medically needed.

Collection of ARI data by the study site will be ceased for that particular episode if a participant has tested positive for SARS-CoV-2 (by a local test that is FDA-approved or by central laboratory PCR).

At the end of the first and third RSV season, the study-site personnel will contact the participants by telephone or telemedicine contact and read aloud the questions of the Lawton-Brody IADL questionnaire to the participant and record the participant's responses on the site's eDevice. The RiiQ questionnaire and the PGI-H will be completed by the participant in the eDiary or by telephone or telemedicine interview. At the end of the second RSV season visit, the Lawton-Brody IADL questionnaire will be collected on-site by interview with the participant and recorded on the site's eDevice; the RiiQ and the PGI-H will be completed by the participant on the site's eDevice.

At the end of the first RSV season, each study participant will also be invited to complete an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. In general, the IDMC will monitor safety data on an ongoing basis to ensure the continuing safety of the participants. In

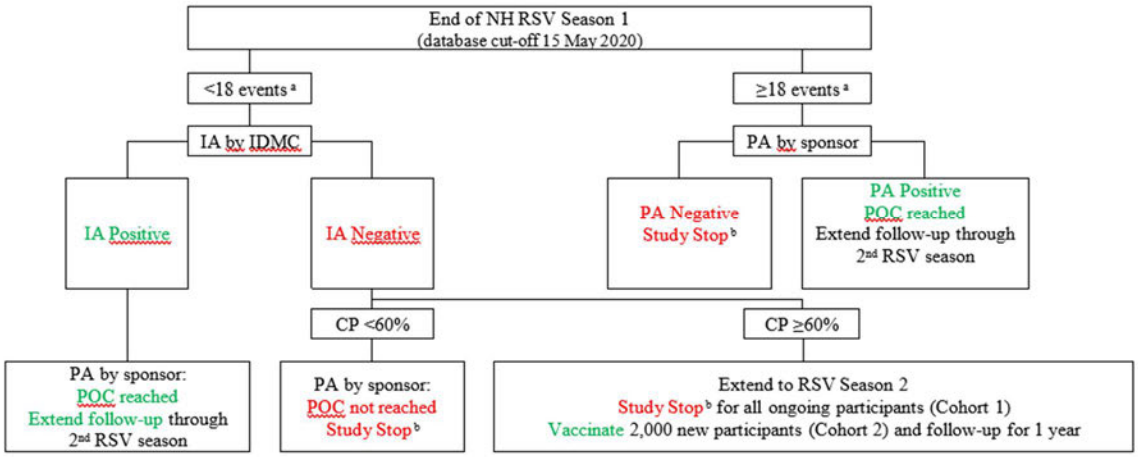
[a] For some secondary and exploratory endpoints, the determination will be made by serology.

addition, the IDMC will formally monitor the efficacy endpoints at the time points specified under Section "Planned Analyses" below.

During the interim analyses (IAs), as outlined in Figure 1 and Figure 2, the IDMC will evaluate in an unblinded fashion whether superiority is established for at least one of the primary endpoints or whether futility (conditional power <60%) is shown for all 3 multiple primary endpoints (only at the end of the RSV season[a] in the event of <18 RT-PCR-confirmed RSV-mediated LRTD events are observed).

The IDMC responsibilities, authorities, and procedures will be documented in its charter.

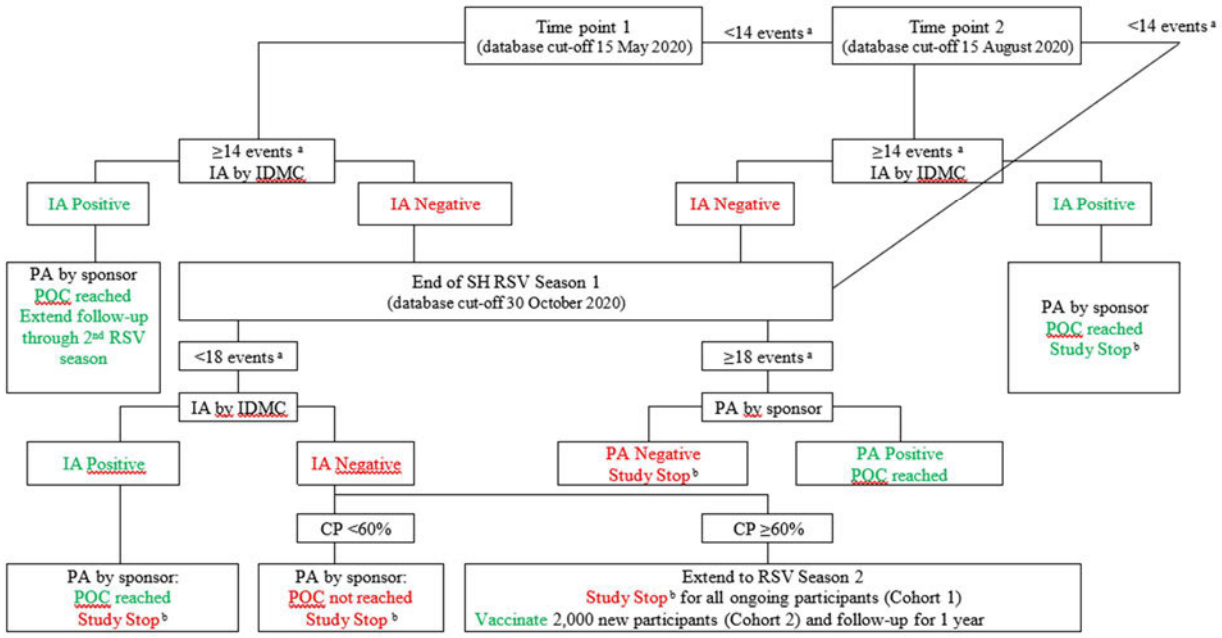
Figure 1: Flow Chart for the Primary Analysis in Case the Study is Performed at the Northern Hemisphere Only



[a] Number of RT-PCR-confirmed RSV-mediated LRTD cases (based on Case Definition #2)
[b] The study will stop at the end of the RSV season or 6 months after vaccination on Day 1, whichever comes later.
CP =conditional power, IA =interim analysis, IDMC =Independent Data Monitoring Committee, LRTD =lower respiratory tract disease, NH =Northern Hemisphere, PA =primary analysis, POC =proof of concept

[a] The end of the first RSV season is defined as the end of the NH RSV season in case the study is performed at the NH only and as the end of the SH RSV season in case the study is performed at both hemispheres.

Figure 2: Flow Chart for the Primary Analysis in Case the Study is Performed at the Northern and Southern Hemisphere



[a] Number of RT-PCR-confirmed RSV-mediated LRTD cases (based on Case Definition #2).
[b] The study will stop at the end of the RSV season or 6 months after vaccination on Day 1, whichever comes later.
If the number of participants enrolled in the NH is <5,500 but ≥18 RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed in the NH before opening sites in the SH, no sites will be opened in the SH and the study will be performed as a NH study only.
CP =conditional power, IA =interim analysis, IDMC =Independent Data Monitoring Committee, LRTD =lower respiratory tract disease, NH =Northern Hemisphere, PA =primary analysis, POC =proof of concept, SH =Southern Hemisphere

PARTICIPANT POPULATION

Participants will be adult men and women, aged ≥65 years on the day of signing the Informed Consent Form (ICF). All participants will be in good or stable health (on the basis of physical examination, medical history, and vital signs measurement performed on Day 1).

Participants aged ≥65 years are generally considered at high risk for severe disease. Participants in this age range with chronic heart disease (CHF, coronary artery disease [eg, angina pectoris, ischemic cardiomyopathy, history of myocardial infarct (MI), history of coronary artery bypass graft or coronary artery stent]) and chronic lung disease (eg, asthma and COPD) are generally at even higher risk for severe RSV disease; hereafter, this population will be referred to as “increased risk”. Participants at increased risk for severe RSV disease due to these underlying medical conditions will be enrolled in the study. Randomization will be set up to ensure enrollment of 350 participants at increased risk for severe RSV disease in the Safety Subset and 50 participants at increased risk for severe RSV disease in the Immuno Subset. Participants with severe chronic cardiac and lung diseases will be excluded from the study.

DOSAGE AND ADMINISTRATION

The active study vaccines used in this study are Ad26.RSV.preF and RSV preF protein each administered alone as a single injection in the deltoid muscle, and an Ad26.RSV.preF/RSV preF protein mixture administered as a single injection in the deltoid muscle. All injections will be 1 mL in volume.

- Ad26.RSV.preF (JNJ-64400141) will be supplied at a concentration of 2×10^{11} vp (viral particles)/1 mL in single-use vials. Dose levels of 1×10^{11} vp will be used.
- RSV preF protein (JNJ-64213175) will be supplied at a concentration of 0.3 mg/1 mL in single-use vials. Dose levels of 150 µg will be used.
- Placebo for Ad26.RSV.preF and RSV preF protein.

On Day 1, an unblinded pharmacist, or other qualified individual, who will have no other study function will prepare the appropriate vial and/or syringe, labeled with the participant's identification number, and provide the syringes for Ad26.RSV.preF/RSV preF protein and placebo in a blinded manner to the blinded study vaccine administrator who will perform the injection.

The blinding for study vaccination received on Day 1 will be maintained for site and participants until the database lock for the final analysis of the considered cohort, except for the participants in Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination prior to re-randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re-randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

EFFICACY EVALUATIONS

This is a proof-of-concept study to test VE. The vaccine is not expected to be 100% efficacious.

VE will be evaluated based on the first occurrence of RT-PCR-confirmed RSV-mediated LRTD (cases defined according to the 3 primary endpoint definitions) in the active vaccine group compared to the placebo group in the PPE population. The case definitions are defined as follows:

Case Definition #1	Case Definition #2	Case Definition #3
≥3 symptoms of LRTI (new onset or worsening)	≥2 symptoms of LRTI (new onset or worsening)	≥2 symptoms of LRTI, *OR* ≥1 symptom of LRTI *combined with* ≥1 systemic symptom (new onset or worsening)

LRTI =lower respiratory tract infection

To meet the primary endpoint according to the respective case definitions the following criteria will be taken into account:

- symptoms reported by participants on the RiiQ Symptom Scale and body temperature during the full ARI episode OR
- clinical assessment terms reported by a qualified study staff member during the ARI Days 3-5 clinical visit

  in combination with

- confirmation of RSV by RT-PCR in one or more of the midturbinate nasal swabs, or in the sputum sample (when available)

Of note, on the day of the ARI Days 3-5 clinical visit, the case definitions can be met by symptoms reported by participants on the RiiQ or by signs and symptoms reported by the qualified study staff member. Case definitions cannot be met by a combination of symptoms reported by the participant with signs and symptoms reported by the qualified study staff member.

Confirmation of RSV infection by RT-PCR (midturbinate swabs and sputum sample, when available) will be performed at the central laboratory. For participants hospitalized with symptoms of an ARI, confirmation of RSV infection using an FDA-approved RT-PCR test at the local (hospital) laboratory will also be used for the analysis of case definitions if results from the central laboratory are not available. One positive sample (defined as any sample with a value above the limit of detection) is sufficient.

As a sensitivity analysis, the analysis of the primary endpoint will be repeated, but participants with RSV infection and a co-infection with at least one other respiratory virus (ie, confirmed using an FDA approved RT-PCR test in one or more of the midturbinate nasal swabs, or in the sputum sample, when available) will not be considered as a case for that episode, as the etiology of the symptoms will be indeterminate.

As an additional sensitivity analysis, the analysis of the primary endpoint will be repeated, taking into account only the RT-PCR test results from the central laboratory (ie, excluding the local test results for hospitalized participants).

Presence and severity of symptoms will be collected using participant responses to the RiiQ Symptom Scale and temperature readings participants report in the eDiary each day throughout each ARI episode. On the day of the ARI Days 3-5 clinical visit, signs and symptoms will also be collected by qualified study staff in a clinical assessment.

Symptoms (new onset or worsening) occurring at the same day will be counted. When during ARI Days 3-5, symptoms are reported more than once per day by the participant (eg, on the site's eDevice and in the participant eDiary), the worst severity from the RiiQ will be taken into account. On the day of the ARI Days 3-5 clinical visit, signs and symptoms collected during the clinical assessment by a qualified study staff member will be considered separately from the symptoms reported by the participant on the site's eDevice or in the participant eDiary. A new onset of a symptom is a symptom that is reported during the ARI episode and that was not reported at baseline (defined by pre-dose assessment on the day of vaccination for the first RSV season, the Day 365 [Month 12] visit for the second RSV season [pre-vaccination if applicable], and at the Day 730 [Month 24] visit for the third RSV season). Worsening of a symptom is defined as a symptom that is reported at baseline (defined by pre-dose assessment on the day of vaccination for the first RSV season, at the Day 365 visit for the second RSV season [pre-vaccination if applicable], and at the Day 730 visit for the third RSV season) that worsens in severity during the ARI episode compared to baseline.

First occurrence of a considered endpoint is defined as the first episode of the considered endpoint in a given RSV season (regardless A or B strain, unless otherwise specified).

RT-PCR assay of the midturbinate nasal swabs, and a sputum sample (when available), taken after symptom onset will be used to determine whether the infection was caused by RSV. For RSV positive cases, the RSV subtype, viral load and presence of other respiratory pathogens will also be determined from the midturbinate nasal swabs. Samples from RSV negative ARI episodes may also be assessed for the presence of other respiratory pathogens.

IMMUNOGENICITY EVALUATIONS

Blood will be collected from all participants for humoral immunogenicity assessments before vaccination (Day 1), and 14 days and 1 year after vaccination. These samples will be used for humoral immunogenicity assessments for participants experiencing an ARI episode during the RSV season.

For participants in the Immuno Subset (approximately 100 active study vaccine participants and 100 placebo participants), blood will be collected for analysis of humoral and cellular immune responses before vaccination on Day 1 and at 14 days, 84 days, 24 weeks, 1 year, 18 months, 24 months, and 30 months after vaccination on Day 1.

Humoral immune responses in the Revaccination Subcohorts will be assessed in approximately 240 participants in Revaccination Subcohorts A and C, and in approximately 270 participants in Revaccination Subcohort B at the time points indicated in the Schedules of Activities for Revaccination Subcohorts. Cellular immune responses will be assessed in all participants (at certified sites) in Revaccination Subcohort 2A after the third vaccination and in Revaccination Subcohort B after the second and third vaccination. Cellular immune responses will be assessed in a subset of approximately 100 participants (approximately 50 per group) in Revaccination Subcohort C.

Immunogenicity assessments may include, but are not limited to, the assays summarized below.

Humoral Assays	Purpose
Secondary endpoints	
RSV neutralization A	Analysis of neutralizing antibodies to an A strain
F protein antibodies (ELISA; pre F and/or post F)	Analysis of antibodies binding to RSV F protein in pre fusion and/or post fusion form
Exploratory endpoints	
RSV strain cross neutralization	Analysis of cross neutralizing antibodies to B and/or a different A strain(s)
F protein antibody specificity characterization	Pre and post F specificity by binding or functional assays such as ELISA, and/or competition ELISA. Adsorption of serum with pre F and post F protein before any antibody assay, epitope mapping, functional VNAs
G protein antibodies (ELISA)	Analysis of antibodies binding to RSV G protein
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to, ADCC, ADCP, avidity, other respiratory viral neutralizing or binding assays, Ig isotype, functional VNAs to other respiratory viruses, and antibody assessments for antibody repertoire
Transcriptomic analysis	RNA transcriptomic analysis maybe conducted in the revaccination subcohorts to assess regulation of genes (clusters) and expression patterns

ADCC =antibody dependent cell mediated cytotoxicity, ADCP =antibody dependent cellular phagocytosis, ELISA =enzyme linked immunosorbent assay, F =fusion, G =glycoprotein, Ig =immunoglobulin, RNA =ribonucleic acid; VNA =virus neutralizing antibody
Note: Antibody analyses might be performed in nasosorption samples and serum.
The abovementioned assays might be performed on samples of the Revaccination Subcohorts to assess exploratory endpoints.

Cellular Assays	Purpose
Secondary endpoints	
IFN γ ELISpot	T cell IFN γ responses to RSV F protein peptides
Exploratory endpoints	
ICS	Analysis of T cell responses to RSV F protein peptide stimulated PBMC (including, but not limited to, $CD4^+/CD8^+$, IL 2, IFN γ, TNF α, activation markers and memory)
Chemokine/cytokine analysis	Levels of chemokines and cytokines in nasosorption samples or produced by antigen stimulated PBMC
Sequencing of B cells	Including but not limited to sequencing of BCR (B cell receptor) or VH/VL (heavy/light chain characterization) for specificity

ELISpot =enzyme linked immunospot, F =fusion; ICS =intracellular cytokine staining, IFN γ =interferon gamma, IL 2 =interleukin 2, PBMC =peripheral blood mononuclear cells, TNF α =tumor necrosis factor alpha

Nasosorption samples using synthetic absorptive matrix (SAM) will be taken from Immuno Subset participants prior to vaccination (Day 1) and at the 14 days post-vaccination visit and will be used for immunogenicity assessments including, but not limited to immunogenicity assessments of antigen specific immunoglobulins (IgG and IgA), microbiome and pathogen analysis.

Blood samples collected between 2 and 4 days after symptom onset (ARI Days 3-5) and at 28 days after symptom onset (ARI Day 29) from participants who experience ARI episodes will be assayed by serology (including but not limited to RSV virus neutralizing antibodies [VNAs] or ELISA specific to RSV protein G [glycoprotein] as available and applicable) for RSV exposure confirmation. These samples will also be used for exploration of biomarkers that correlate with RSV infection and RSV disease severity (including but not limited to RT-PCR for RSV, RNA transcriptomics to assess regulation of genes [clusters] and expression patterns, cytokine/chemokine analysis as available and applicable). Additionally, these samples might be used for other pathogen exposure seroconfirmation.

MEDICAL RESOURCE UTILIZATION

Baseline MRU will be collected from all participants prior to vaccination. MRU data will be collected from all participants with an ARI episode, using the MRU Questionnaire completed during study visits at ARI Days 3-5 and ARI Day 29 (±7 days) of each ARI episode.

SAFETY EVALUATIONS

Adverse Events

All participants

All participants will be closely observed for a minimum of 30 minutes after vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator.

For all participants, SAEs will be collected from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later).[a]

For all participants, some subsets of SAEs will be collected for additional study periods[a]:

- ARIs and complications related to ARIs that classify as SAEs will be captured and will be reported as SAEs in the electronic case report form (eCRF) for the duration of the second RSV season, between the second and the third RSV season, and for the duration of the third RSV season.
- From the time of vaccination (Day 1) until the end of the study period for each participant, SAEs classified as related to the study vaccine, SAEs resulting in death, and (S)AEs leading to discontinuation from the study will be collected.
- During the entire study, (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated ICF is obtained onwards until the end of the study period for each participant.

The (S)AE listing in the eCRF will not be updated based on the RSV RT-PCR results and will remain listed on the eCRF as ARIs.

Safety Subset and Revaccination Subcohorts

Additional procedures will be carried out in the Safety Subset following vaccination on Day 1 and in the Revaccination Subcohorts following revaccination on Day 365 (Month 12)/Day 730 (Month 24)/Day 1,095 (Month 36), as described below:

- Solicited local (at the injection site) AEs, solicited systemic AEs, and body temperatures will be recorded in the eDiary (or a paper diary, if designated by the sponsor), beginning on the evening of the vaccine

[a] The windows for SAE collection in the Revaccination Subcohorts are described below under "Safety Subset and Revaccination Subcohorts".

dosing day and on a daily basis for the following 7 days. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.

- Any unsolicited, solicited local or systemic AEs will be documented in the eCRF by study-site personnel following the 30-minutes observation period. In addition, vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period.
- All other (unsolicited) AEs and special reporting situations will be reported from the time of vaccination through the following 28 days. Safety Subset participants will be contacted by telephone or telemedicine contact at 28 days (+3 days) after vaccination to collect information on unsolicited AEs; for participants in the Revaccination Subcohorts, this information will be collected at the 28-day (+3 days) post-revaccination visit.
- All ARIs and all complications related to ARIs will be reported as AEs in the eCRF from the time of vaccination through the following 28 days.

For Revaccination Subcohort A, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from the time of revaccination at Month 12 until the end of the second RSV season, or until 6 months after revaccination, whichever comes later. For Revaccination Subcohort 2A, all SAEs and AESIs will also be collected from the time of revaccination on Day 730 until 6 months after revaccination. For Revaccination Subcohorts B and C, all SAEs and AESIs will be collected from the time of revaccination until 6 months thereafter. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season for Subcohort A, on Day 730 (Month 24) for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

For all Revaccination Subcohorts, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs leading to discontinuation from the study, and (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be collected during the entire study for all participants. For the participants in the Revaccination Subcohort C, these (S)AEs will be collected retrospectively for the time period between the last end of the RSV season visit and the revaccination upon the day of revaccination.

Other Safety Evaluations

Vital Signs

- Heart rate, respiratory rate, supine systolic blood pressure and supine diastolic blood pressure
- Body temperature
- Oxygen saturation (SpO_2)

Physical Examination

A full physical examination, including body weight, will be carried out before each vaccination. Height will be measured on Day 1 only.

STATISTICAL METHODS

Sample Size Determination

Efficacy

Under the following assumptions:

- a VE for Case Definition #2 of 70%

- and an incidence of Case Definition #2 of 0.75% in placebo recipients during the RSV season, assuming vaccination occurs before the RSV season
- 3 primary endpoints which are nested
- a 1-sided α of 5% (total; corrections are performed for multiple endpoints and for IAs
- 10% of exclusions (due to drop-out, major protocol deviations, etc.

Simulations performed in R show that for a Northern Hemisphere (NH) only study, 2,750 participants per vaccination group result in 80% total power to demonstrate VE >0 for Case Definition #2 at the end of the RSV season, resulting in a total sample size of 5,500 participants. The end of the first RSV season is then defined as the end of the NH RSV season.

In case recruitment is not completed in the NH (and <18 RT-PCR-confirmed RSV-mediated LRTD events [using Case Definition #2] are observed in the NH before opening sites in the Southern Hemisphere [SH]), enrollment will continue in the SH. As there is the possibility to have an early IA during the NH or SH RSV season, an additional 150 participants per vaccination group is needed to have 80% total power to demonstrate VE >0 for Case Definition #2 at the end of the RSV season. The end of the first RSV season is defined as the end of the SH RSV season in case the study is performed at both hemispheres. So, if recruitment is spread over 2 hemispheres, the total sample size will be 5,800 participants.

With respect to Case Definitions #1 and #3, further simulations showed that the power to obtain a significant result for any case definition, after multiplicity correction that control the type I error at 5%, tended to be similar or better than for Case Definition #2 alone, without multiplicity correction.

Immuno Subset

Immunogenicity will be assessed in the Immuno Subset, ie, approximately 200 participants, of whom ~100 are active study vaccine participants. Approximately 25% of participants in the Immuno Subset in each region will be at increased risk of severe RSV disease.

The table below shows the actual distance from the mean to the limits of 95% CI around the actual value at Day 15 for different assays, accounting for 10% of exclusions with the current sample size for the Immuno Subset.

Distance from the Mean to the Limits of 95% CI for Pre-F ELISA, VNA, and ELISpot.

		Pre-F ELISA (SD=1.3)		**VNA (SD=1.5)**		**ELISpot (SD=1.2)**	
	N (Active Group)	**Distance[a] from Mean to Limits 95%CI**	**95%CI if Observed Mean is eg, 6,000**	**Distance[a] from Mean to Limits 95%CI**	**95%CI if Observed Mean is eg, 6,500**	**Distance[a] from Mean to Limits 95%CI**	**95%CI if Observed Mean is eg, 400**
All	100	0.272	(4,969;7,245)	0.314	(5,229;8,080)	0.251	(336;476)
Increased Risk	25	0.576	(4,025;8,944)	0.665	(4,099;10,306)	0.532	(277;578)

CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, ELISpot = enzyme-linked immunospot, SD = standard deviation, VNA = virus neutralization assay

[a] Calculated on the $\log_2$-scale.

Safety Subset

With ~350 active study vaccine participants in the Safety Subset, the observation of 0 events in the database would be associated with 95% confidence that the true rate is <1%. For SAEs, which are captured in all participants, the observation of 0 events in the database would be associated with 95% confidence that the true rate is <0.1%.

In addition, a cap will be installed to ensure that 350 participants in the Safety Subset (~175 in each group) are at increased risk for severe RSV disease. With 175 active study vaccine participants at increased risk of severe RSV disease in the Safety Subset, the observation of 0 events (solicited or unsolicited) in the database would be associated with 95% confidence that the true rate in participants at increased risk of severe RSV disease is <1.7%.

SAEs will be captured in all participants. Outside the Safety Subset and Immuno Subset, no cap is installed on the number of participants at increased risk of severe RSV disease. It is expected that participants at increased risk for severe RSV disease will represent approximately 30% of the overall population. Assuming that 30% of the participants in the overall population are at increased risk of severe RSV disease (~870 participants), the observation of 0 events in participants at increased risk of severe RSV disease would be associated with 95% confidence that the true rate is <0.4%.

The following table shows the probabilities of observing at least one AE in one of the arms at given true AE rates in the Safety Subset (overall population and participants at increased risk of severe RSV disease).

	Probability of Observing at Least One Adverse Event in N Participants			
True Adverse	**Overall**		**Increased Risk**	
Event Rate	**N=350**	**N=2,900**	**N=175**	**N=870[a]**
0.1%	30%	95%	16%	58%
0.5%	83%	100%	58%	99%
1%	97%	100%	83%	100%
2.5%	>99.9%	100%	99%	100%

[a] Approximate number

Revaccination Subcohorts

Immunogenicity

Immunogenicity will also be assessed in participants of the Revaccination Subcohorts, which consist of ~120 participants (Revaccination Subcohorts A and C) or ~135 participants (Revaccination Subcohort B) who received active study vaccine on Day 1 and ~120 participants (Revaccination Subcohorts A and C) or ~135 participants (Revaccination Subcohort B) who received placebo on Day 1 for a total of ~750 participants. All participants in the Revaccination Subcohorts will receive a second vaccination with active study vaccine: on Day 365 (Month 12) (Revaccination Subcohort A), on Day 730 (Month 24) (Revaccination Subcohort B), or on Day 1,095 (Month 36) (Revaccination Subcohort C).

The geometric mean of the titer ratios (GMRs) between Day 15 post first vaccination and Day 15 post second vaccination within a group, as well as the ratio of Day 15 post second vaccination between the 2 groups (active study vaccine versus placebo on Day 1), for the different assays will be calculated.

The table below shows the actual distance from the mean to the limits of 95% CI around the ratio between Day 15 post first vaccination and Day 15 post second vaccination within a group for the different assays. The calculations consider an exclusion rate of 10% from the sample size of revaccinated participants (~108 participants per group for Revaccination Subcohorts A and C, and ~120 participants per group for Revaccination Subcohort B).

Distance From the Mean to the Limits of 95% CI Around the Ratio Between Day 15 Post First Vaccination and Day 15 Post Second Vaccination Within a Group for Pre-F ELISA, VNA, and ELISpot

Revaccination Subcohort	Assay	N (per group)	Distance[a] from Mean to Limits 95%CI	95%CI if Observed Ratio is 1
A and C	Pre-F ELISA (SD=1.3)	120	0.248	(0.84;1.19)
	VNA A2 (SD=1.5)	120	0.286	(0.82;1.22)
	ELISpot (SD=1.2)*	50	0.341	(0.79; 1.27)
B	Pre-F ELISA (SD=1.3)	135	0.235	(0.85; 1.18)
	VNA A2 (SD=1.5)	135	0.271	(0.83; 1.21)
	ELISpot (SD=1.2)	135	0.217	(0.86;1.16)

CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, ELISpot = enzyme-linked immunospot (assay), SD = standard deviation, VNA = virus neutralization assay
[a] Calculated on the $\log_2$-scale assuming a correlation of 0.5 between the 2 timepoints.
*: No PBMC samples are taken for Revaccination Subcohort A.

The table below shows the actual distance from the mean to the limits of 95% CI around the Day 15 post second vaccination ratio between the 2 groups, for the different assays. The calculations consider an exclusion rate of 10% from the sample size of revaccinated participants (~108 participants per group for Revaccination Subcohorts A and C, and ~120 participants per group for Revaccination Subcohort B).

Distance From the Mean to the Limits of 95% CI Around the Ratio on Day 15 Post Second Vaccination Between the Two Groups for Pre-F ELISA, VNA and ELISpot

Revaccination Subcohort	Assay	N (per group)	Distance[a] from Mean to Limits 95%CI	95%CI if Observed Ratio is 1
A and C	Pre-F ELISA (SD=1.3)	120	0.349	(0.79;1.27)
	VNA (SD=1.5)	120	0.402	(0.76;1.32)
	ELISpot (SD=1.2)*	50	0.476	(0.72; 1.39)
B	Pre-F ELISA (SD=1.3)	135	0.331	(0.79;1.26)
	VNA A2 (SD=1.5)	135	0.381	(0.77; 1.30)
	ELISpot (SD=1.2)	135	0.305	(0.81; 1.24)

CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, ELISpot = enzyme-linked immunospot (assay), SD = standard deviation, VNA = virus neutralization assay
[a] Calculated on the $\log_2$-scale.
*: No PBMC samples are taken for Revaccination Subcohort A.

Safety

With ~240 active study vaccine participants in Revaccination Subcohorts A and C, and ~270 active study vaccine participants in Revaccination Subcohort B, the observation of 0 events in the database would be associated with 95% confidence that the true rate is <1.5%.

The table below shows the probabilities of observing at least 1 AE in one of the arms at given true AE rates in the Revaccination Subcohorts.

True Adverse Event Rate	Revaccination Subcohorts A and C		Revaccination Subcohort B	
	Overall	Per Group	Overall	Per Group
	N=240[a]	N=120[a]	N=270 [a]	N=135[a]
0.1%	21%	11%	24%	13%
0.5%	70%	45%	74%	49%
1%	91%	70%	93%	74%
2.5%	>99.9%	95%	100%	97%

[a] Approximate number

Analysis Sets

- The Full Analysis Set (FAS) will include all randomized participants with a documented vaccine administration, regardless of the occurrence of protocol deviations. The FAS is the primary safety population. The analysis of solicited and unsolicited AEs after the Day 1 vaccination will be restricted to a subset of the FAS (ie, the Safety Subset).[a] The analysis of solicited and unsolicited AEs after revaccination on Day 365 (Month 12)/Day 730 (Month 24)/Day 1,095 (Month 36) will be restricted to participants of the Revaccination Subcohorts that are part of the FAS.
- The Per-protocol Immunogenicity (PPI) population will include all randomized and vaccinated participants for whom immunogenicity data are available. Samples taken after a participant experienced a major protocol deviation expecting to impact the immunogenicity outcomes will be excluded from the PPI. The analysis of immunogenicity will focus on 2 subsets of the PPI, ie, the Immuno Subset and the Revaccination Subcohorts.

  In addition, for participants who experience a natural RSV infection (based on RT-PCR, or other sources), samples taken after the natural infection will not be taken into account in the assessment of the immunogenicity.

  The PPI population is the primary immunogenicity population. For key tables, sensitivity immunogenicity analyses will also be performed on the FAS, including participants for whom immunogenicity measures are available. Excluded samples might be taken into account as well in the sensitivity analysis.
- The Per-protocol Efficacy (PPE) population will include all randomized and vaccinated participants excluding participants with major protocol deviations expecting to impact the efficacy outcomes. Any participant with an RT-PCR-confirmed RSV-mediated ARI with onset within 14 days after vaccination will be excluded from the PPE population. Participants who discontinue within 14 days after vaccination will be excluded from the PPE population as well.

  The PPE population is the primary efficacy population. Sensitivity efficacy analyses will also be performed on the FAS. For exploratory efficacy analyses focusing on data from the second RSV season only, the participants of Revaccination Subcohort A will be additionally excluded. For analyses focusing on data from the third RSV season, participants of Revaccination Subcohorts A and B will be excluded. For exploratory efficacy analyses focusing on data over 2 RSV seasons, the second RSV season data will be excluded for the participants of Revaccination Subcohort A. For analyses focusing on data over 3 RSV seasons, second and third RSV season data will be excluded for the participants of Revaccination Subcohort A, and third RSV season data will be excluded for participants of Revaccination Subcohort B. Participants who develop major protocol deviations expecting to impact the efficacy outcomes and

[a] The specification of this subset for analysis of solicited and unsolicited AEs does not preclude the investigator from reporting an AE in any participant if he/she considers the event to be of clinical relevance and/or related to the study vaccine.

occurring up to the considered RSV season will be **additionally** excluded from the PPE when focusing on data including the second or third RSV season.

Planned Analyses

Recruitment Completed in the Northern Hemisphere Only (Target Sample Size ≥5,500)

If participants are only enrolled in the NH and if by the end of the first NH RSV season (database cut-off of 15 May 2020) ≥18 RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed, the study will be unblinded for the sponsor and the primary analysis will be performed by the sponsor.

If, by the end of the first NH RSV season, <18 RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed, an IA will be performed by the IDMC. The IDMC will evaluate in an unblinded fashion if superiority is established for at least one of the primary endpoints.

- In the event of superiority, the sponsor will be notified. The database used for the IDMC analysis will be unblinded for the sponsor and the primary analysis will be performed by the sponsor.
- If superiority is not demonstrated, the IDMC will evaluate the conditional power to demonstrate proof of concept (under the original assumptions of incidence and VE) if 2,000 new participants are added to the study. If the conditional power is <60%, the database used for the IDMC analysis will be unblinded for the sponsor and the primary analysis will be performed by the sponsor. If the conditional power is ≥60%, 2,000 new participants (Cohort 2) will be added to the study who will be followed up for one RSV season. The ongoing participants from Cohort 1 will be stopped at the end of RSV season or 6 months after last vaccination whatever comes later.

Recruitment Spread Over the Northern and the Southern Hemisphere (Target Sample Size up to 5,800)

If the number of participants enrolled in the NH is <5,500 and <18 RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed in the NH before opening sites in the SH[a], additional participants will be enrolled in the SH up to a total sample size (NH and SH combined) of 5,800 participants. In that case, a single IA may be performed during the NH or SH RSV season. This "early" IA will be performed by the IDMC at the earliest of those 2 predetermined time points (15 May 2020 or 15 August 2020) where ≥14 events (RT-PCR-confirmed RSV-mediated LRTD cases per Case Definition #2) are observed. If the early IA is performed, the IDMC will evaluate in an unblinded fashion if superiority is established for at least one of the primary endpoints. The IDMC will notify the sponsor of the outcome. In the event of superiority, the database used for the IDMC analysis will be unblinded for the sponsor and the primary analysis will be performed by the sponsor. If superiority is not shown at the IA or if the number of RT-PCR-confirmed RSV-mediated LRTD cases (using Case Definition #2) is <14 at the second time point (15 August 2020), the primary analysis will be performed at the end of the SH RSV season (database cut-off of 30 October 2020) in a similar way as in a NH study only.

The IA plan is outlined in Figure 1 in case the study is performed in the NH only, and in Figure 2 in case the study is performed in the NH and SH.

[a] If the number of participants enrolled in the NH is less than 5,500 and 18 or more RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed in the NH before opening sites in the SH, no sites will be opened in the SH and the study will be performed as a NH study only.

Additional Analyses

If in a NH+SH study VE is demonstrated at the early IA, an additional analysis will be performed at the end of the RSV season. This will count as supportive information.

If VE is demonstrated at the end of the first NH RSV season, the study will continue and the ongoing participants from Cohort 1 will be followed up for a second RSV season. If this is the case, additional analyses will be performed at the end of the second RSV season to evaluate if there is a trend for durable efficacy. If analyses at the end of the second RSV season indicate a trend for durable efficacy or in case results on durability are inconclusive, the study will continue and the ongoing participants from Cohort 1 will be followed up for a third RSV season. If this is the case, additional analyses will be performed at the end of the third RSV season to further evaluate durability of efficacy.

Analysis 28 Days Post Second Vaccination in Revaccination Subcohorts A, B, and C

This analysis will be done for each Revaccination Subcohort (A, B, and C) and will include safety and immunogenicity data from the considered Revaccination Subcohort. The analysis will be performed on unblinded data. Data collected up to the time of the 28-day post second vaccination visit for the last participant in the considered Revaccination Subcohort will be included in the analysis.

The blind will be maintained at the participant/site level, with respect to the vaccination received on Day 1 until the database lock for the final analysis of the considered cohort, except for the participants in Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination prior to re-randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re-randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

End of Season 2 Analysis

This analysis will include all efficacy, safety, and immunogenicity data collected up to the time of the end of the second RSV season. If the number of RSV-positive cases observed during the second season is low, the efficacy analysis might be restricted to a listing of major efficacy endpoints in RSV-positive participants during the second RSV season. In case no RSV cases are reported, then the end of Season 2 analysis might be restricted to only safety and immunogenicity.

This analysis might be split in 2 parts given the availability of the data. The first part will include all efficacy, safety, and immunogenicity data collected until the end of the second RSV season and the second part will include additional safety data collected between the end of the second RSV season and the end of the SAE safety follow-up.

Analysis of Revaccination Subcohorts A and B, when Revaccination Subcohorts 2A and 2B have reached the 28 Days Post Third Vaccination Timepoint

This analysis will be done separately for each Revaccination Subcohort (A and B) and will include safety and immunogenicity data from the considered Revaccination Subcohort. The analysis will be performed on unblinded data. Data collected up to the time of the 28-day post third vaccination visit for the last participant in the considered Revaccination Subcohort will be included in the analysis.

The blind will be maintained at the participant/site level, with respect to the vaccination received on Day 1 until the database lock for the final analysis of the considered cohort, except for the participants in Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination prior to re-randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re-randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

End of Efficacy Study Analysis

This analysis will include all efficacy, safety, and immunogenicity data collected until the end of the third RSV season. Efficacy data collected up to the end of the third season visit for the last participant will be included in the analysis.

The end of efficacy study analysis will be performed on unblinded data.

Final Analysis of Revaccination Subcohorts (A, B, and C).

This analysis will be done for each Revaccination Subcohort (A, B, and C) and will include safety and immunogenicity data from the considered Revaccination Subcohort. The analysis will be performed on unblinded data. Data collected up to the last visit for the last participant in the considered Revaccination Subcohort will be included in the analysis.

Early Stop ARI Surveillance in 2020

Due to the increasing incidence of COVID-19 cases, it is becoming increasingly difficult to conduct ARI surveillance, without putting staff or study participants at risk. As the first RSV season is nearing a close, a decision has been made to stop ARI surveillance for the first RSV season under Amendment 2.

Unplanned Snapshot Interim Analysis

An unplanned snapshot IA may be performed to allow for early decision making on capacity planning for the Ad26 SARS-CoV2, which is being developed for the prophylactic immunization against SARS-CoV-2 infection, and Ad26.RSV.preF vaccines. This is especially important for the production capacity in 2020 and 2021. The results of this unplanned snapshot IA will only be shared with select members of upper management not involved in the conduct of the study. This will be described in more detail in a separate charter.

Since this unplanned snapshot IA will only be used for internal decision making, will not further affect the conduct of the study, and it is not expected that the number of events will drastically change for the primary analysis, no type I error adjustment will be applied. The success of the study will solely depend on the results of the primary analysis.

Efficacy Analyses

Primary Efficacy Endpoints

Any analysis of the primary endpoints for VE will evaluate the number of participants with (at least one episode of) RT-PCR-confirmed RSV-mediated LRTD (cases defined according to the 3 primary endpoint definitions) in the active vaccine group compared to the placebo group in the PPE population. Time at risk will also be taken into account.

The α-levels for all efficacy analyses will be adjusted to account for the multiple endpoint approach and for multiple analyses. Both methods will be combined to come to one cut-off that will be used to define significance. The exact values depend on the number of cases already observed at the time of (interim) analysis.

For each of the 3 primary endpoints the following will be performed: an exact Poisson regression will be fitted with the event rate, defined as the number of cases over the follow-up time (offset) as dependent variable and the vaccination group and age and being at increased risk for severe RSV disease (both as stratified) as independent variables. For cases, the follow-up time is defined as the time between vaccination and the occurrence of the first event (according to the considered endpoint), for non-cases, it is the time between vaccination and the end of season visit. However, for participants that discontinued before the end of the season and had an event (according to the considered endpoint), the follow-up time is defined as the time between vaccination and the occurrence of the first event and for participants that discontinued before

having an event, follow-up time is the time between vaccination and the date of last contact. Thus, all participants are included in the analysis according to their follow-up time. The exact p-value corresponding to vaccination group will be compared with the cut-off as described above.

If the p-value is below the cut-off for at least 1 of the 3 primary endpoints, proof of concept is demonstrated. The individual 2-sided CIs (1-2 × cut-off) for the VE (1-relative risk rate), measured by each of the 3 endpoints, will be calculated from the regression model described above.

The primary analysis will be performed on the PPE population, which will take cases into account with an onset at least 14 days after vaccination.

As a sensitivity analysis, the above model will be repeated based on the FAS (which also does not take into account the restriction on the onset [at least 14 days] and will count cases from vaccination on Day 1 onwards). Additional sensitivity analyses will include an exact binomial test, not taking into account the strata, based on the PPE population and the FAS. The VE (=1-relative risk) and the corresponding corrected 2-sided CI based on the exact binomial will be calculated as well.

The Clinical Evaluation Committee (CEC) review will assess, independently and based on CRF/eDiary data, the location of the ARI (upper or lower respiratory tract infection) and the ARI severity. The CEC assessment, as well as other information based on MRU, presence of clinically relevant disease, use of therapeutic interventions, RiiQ, clinical assessment, Lawton-Brody IADL, and change in frailty will be used to evaluate the severity of the RSV-positive ARIs, and will be used to explore the relation with the case definitions.

Secondary Efficacy Endpoints

For each of the secondary endpoints an exact Poisson regression will be fitted in a similar way as for the primary endpoint. The 95% 2-sided CI for the VE (1-relative risk rate) will be calculated from the regression model described above.

In addition, for each of the secondary endpoints, the proportion of participants with an event will be tabulated. The corresponding VE (1-relative risk) and the 95% 2-sided CI will be calculated without taking the strata into account based on an exact binomial test.

Exploratory Efficacy Endpoints

For endpoints that intend to explore VE, an exact Poisson regression model will be fitted in a similar way as for the primary endpoint. The 95% 2-sided CI for the VE (1-relative risk rate) will be calculated from the regression model described above.

For continuous endpoints, actual values will be summarized descriptively as well as changes from baseline (if meaningful). Categorical endpoints will be tabulated.

Immunogenicity Analyses

No formal statistical testing of the immunogenicity data is planned. All immunogenicity analyses will be performed on the PPI population. Key tables might be repeated for the FAS (including samples that are excluded from the PPI analysis).

Immuno Subset

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% CI for ELISA and RSV neutralization assay; median and quartiles for IFN-γ ELISpot and ICS) will be calculated for continuous immunologic parameters at all time points. For the humoral assays, geometric mean fold rises from baseline and corresponding 95% CIs might additionally be calculated. Baseline is considered as the last available assessment before the vaccination. Graphical representations of immunologic parameters will be made as applicable.

The impact of baseline factors on the humoral and cellular responses will be explored graphically or via descriptive statistics.

Revaccination Subcohorts

No formal hypothesis on immunogenicity will be tested for Revaccination Subcohorts. Descriptive statistics (geometric mean and 95% CI for ELISA and RSV neutralization assay, median and quartiles for IFN-γ ELISpot) will be calculated for continuous immunologic parameters at all time points. Geometric mean fold rises from baseline and corresponding 95% CIs might additionally be calculated. Geometric mean ratios and corresponding 95% CIs between Day 15 post first vaccination and Day 15 post second vaccination within the group receiving active study vaccine on Day 1 and the day of the second vaccination depending on the Revaccination Subcohort will be calculated for the different assays.

In addition, the GMT ratios with corresponding 95% CIs of Day 15 post second vaccination for the group receiving active study vaccine twice versus the group receiving placebo first and active study vaccine 1, 2, or 3 years later will also be calculated for the different assays. Therefore, an analysis of variance (ANOVA) model will be fitted with the respective titers as dependent variable and group as independent variable. The estimate and CIs obtained as such will be back transformed (by exponentiation) to a GMT ratio and the corresponding CI. As a sensitivity analysis, different variances between the groups will be allowed, therefore the CIs will be calculated via Welsh's ANOVA.

For Revaccination Subcohorts 2A and 2B that get a third vaccination with Ad26.RSV.preF/RSV preF protein mixture or with the individual vaccine components, no formal hypothesis is tested; descriptive statistics over time after the third vaccination will be calculated.

Graphical representations of immunologic parameters will be made as applicable.

The impact of baseline factors on the humoral responses will be explored graphically or via descriptive statistics.

Correlates of Risk

If VE is demonstrated, correlates of risk will be explored. More details with appropriate methods will then be provided in a separate SAP.

Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized.

Safety Analyses

No formal statistical testing of safety data is planned. Safety data by vaccination group and based on the FAS will be analyzed descriptively. The analysis of solicited and unsolicited AEs will be restricted to a subset of the FAS (ie, the Safety Subset). For SAEs, the complete FAS is considered. The impact of baseline factors (eg, being at increased risk for severe RSV disease) might be explored as well. Additionally, the analysis of solicited and unsolicited AEs and AESIs (if collected) will also be performed for each of the Revaccination Subcohorts and will be restricted to participants of the Revaccination Subcohorts that are part of the FAS.

Any ARI recorded as an (S)AE in the eCRF will be excluded from any AE analysis if the laboratory RT-PCR is subsequently found to be positive for RSV. ARIs arising from RSV infection will not be reported as (S)AEs in the Clinical Study Report as they are endpoints of the study and will be tabulated separately.

Patient-reported Outcomes

Patient reported outcomes will be descriptively analyzed.

SCHEDULE OF ACTIVITIES – COHORT 1 (N=5,800)*

Per Amendment 5, this schedule is for all participants in Cohort 1 who are not included in a Revaccination Subcohort. The procedures and assessments for participants in a Revaccination Subcohort (A, B, or C) are shown in separate schedules. Participants for Revaccination Subcohort B will be identified at the end of the second RSV season, and participants for Revaccination Subcohorts C will be identified at the end of the third RSV season.

Clinic Visit #	**1**	**2**	**2a ☎**	**2b**	**2c[a]**	**3 [a] ☎**	**4[b,c]**	**5[,a,b,c]**	**6[a,b,c]**	**7[b,c]**	**8[a,b,c]**	**9[b] ☎**
Visit Timing	**Vac 1**	**Vac 1 +14 d**	**Vac 1 +28 d**	**Vac 1 +84 d**	**Vac 1 +24 we**	**End 1st RSV Season[d]**	**Vac 1 + 365 d**	**Vac 1 +18 mo**	**End 2nd RSV Season[d]**	**Vac 1 +730 d**	**Vac 1 +30 mo**	**End of 3rd RSV Season[d]**
Visit Week	**0**	**2**	**4**	**12**	**24**		**52**	**76**		**104**	**130**	
Visit Day	**1**	**15[f]**	**29[f]**	**85[f]**	**169[f]**		**365**	**533[f]**		**730**	**912[f]**	
Visit Window		**+3 d**	**+3 d**	**±7 d**	**±14 d**	**+35 d**	**±2 mo**	**±14 d**	**-7/+14 d**	**±2 mo[kk]**	**±14 d**	**-7/+14 d**
Visit Type	Screening and **VACCINATION 1**	ALL PARTICIPANTS	SAFETY SUBSET ONLY	IMMUNO SUBSET ONLY	IMMUNO SUBSET ONLY	ALL PARTICIPANTS	**ALL PARTICIPANTS**	IMMUNO SUBSET ONLY	ALL PARTICIPANTS	**ALL PARTICIPANTS (except Revaccc. Subcohorts A+B)**	IMMUNO SUBSET ONLY	ALL PARTICIPANTS **(except Revaccc. Subcohorts A+B)**
Written informed consent [g]	❶						●		●			
Inclusion/exclusion criteria	❶											
Demographics	❶											
Medical history	❶											
Medical conditions of interest [h]	❶						●[j]			●[j]		
Pre-vaccination medications [i]	❶											
Check for seasonal influenza and SARS-CoV-2 vaccination	❶ ❷	❷				●	●		●	●		●
Physical examination [k]	❶						●			●		
Randomization [l]	❶											
Clinical assessment [m] (collected by study staff)	❶						●			●		
Lawton-Brody IADL [q]	❶					●[p]	●		●	●		●[p]
eDiary training and distribution [r]	●	●[s]					●			●		
RiiQ™ v2	❶[n]					●[o]	●[n]		●	●[n]		●[o]

* In case the study will only be conducted at the Northern Hemisphere (NH), a target number of 5,500 participants will be enrolled and randomized.

Clinic Visit #	1	2	2a ☎	2b	2c[a]	3[a] ☎	4[b,c]	5[a,b,c]	6[a,b,c]	7[b,c]	8[a,b,c]	9[b] ☎
Visit Timing	**Vac 1**	**Vac 1 +14 d**	**Vac 1 +28 d**	**Vac 1 +84 d**	**Vac 1 +24 we**	**End 1st RSV Season[d]**	**Vac 1 + 365 d**	**Vac 1 +18 mo**	**End 2nd RSV Season[d]**	**Vac 1 +730 d**	**Vac 1 +30 mo**	**End of 3rd RSV Season[d]**
Visit Week	**0**	**2**	**4**	**12**	**24**		**52**	**76**		**104**	**130**	
Visit Day	**1**	**15[f]**	**29[f]**	**85[f]**	**169[f]**		**365**	**533[f]**		**730**	**912[f]**	
Visit Window		**+3 d**	**+3 d**	**±7 d**	**±14 d**	**+35 d**	**±2 mo**	**±14 d**	**-7/+14 d**	**±2 mo[kk]**	**±14 d**	**-7/+14 d**
Visit Type	**Screening and VACCINATION 1**	**ALL PARTICIPANTS**	**SAFETY SUBSET ONLY**	**IMMUNO SUBSET ONLY**	**IMMUNO SUBSET ONLY**	**ALL PARTICIPANTS**	**ALL PARTICIPANTS**	**IMMUNO SUBSET ONLY**	**ALL PARTICIPANTS**	**ALL PARTICIPANTS (except Revacc. Subcohorts A+B)**	**IMMUNO SUBSET ONLY**	**ALL PARTICIPANTS (except Revacc. Subcohorts A+B)**
Patient Global Impression of Health (PGI-H)	❶[n]					●[o]	●[n]		●	●[n]		●[o]
MRU questionnaire (baseline version) [q]	❶						●			●		
Midturbinate nasal swab kit training and distribution	●	●[s]					●		●[ll]	●		
Thermometer training and distribution	●						●			●		
Verification of selected eligibility criteria [t]							●			●		
Vaccination	●											
30-minute post-vaccination observation [u]	●											
SAEs [v]		*Continuous from administration of study vaccine on Day 1 until the end of first RSV season (or 6 months after vaccination, whichever comes later), from the Day 365 visit until the end of the second RSV season, and from the Day 730 visit until the end of the third RSV season[e]*										
AEs and special reporting situations related to study procedures and non-investigational (concomitant) Janssen products	*Continuous until the end of the study*											
AEs leading to discontinuation (from study)		*Continuous until the end of the study*										
Concomitant medications [w,x]		*Continuous*										
ARI surveillance [y]		*Twice per week via the eDiary from vaccination on Day 1 until the end of the first RSV season, from the Day 365 visit until the end of the second RSV season, from the end of the second RSV season until the Day 730 visit, and from the Day 730 visit until the end of the third RSV season[z]*										
Experience Survey						●[aa]						
Humoral immunity sample, mL [bb] (non-Immuno Subset participants)	❶ 15[cc]	15[cc]					15			15		
IMMUNO SUBSET ONLY:												
- Humoral immunity sample, mL[dd]	❶ 15[cc]	15[cc]		15	15		15	15		15	15	
- Cellular immunity sample, mL [ee]	❶ 40	40		40	40		40	40		40	40	
- Nasosorption sample (SAM)	❶	●										

Clinic Visit #	1	2	2a ☎	2b	2c[a]	3[a] ☎	4[b,c]	5[a,b,c]	6[a,b,c]	7[b,c]	8[a,b,c]	9[b] ☎
Visit Timing	**Vac 1**	**Vac 1 +14 d**	**Vac 1 +28 d**	**Vac 1 +84 d**	**Vac 1 +24 we**	**End 1st RSV Season[d]**	**Vac 1 + 365 d**	**Vac 1 +18 mo**	**End 2nd RSV Season[d]**	**Vac 1 +730 d**	**Vac 1 +30 mo**	**End of 3rd RSV Season[d]**
Visit Week	**0**	**2**	**4**	**12**	**24**		**52**	**76**		**104**	**130**	
Visit Day	**1**	**15[f]**	**29[f]**	**85[f]**	**169[f]**		**365**	**533[f]**		**730**	**912[f]**	
Visit Window		**+3 d**	**+3 d**	**±7 d**	**±14 d**	**+35 d**	**±2 mo**	**±14 d**	**-7/+14 d**	**±2 mo[kk]**	**±14 d**	**-7/+14 d**
Visit Type	Screening and VACCINATION 1	ALL PARTICIPANTS	SAFETY SUBSET ONLY	IMMUNO SUBSET ONLY	IMMUNO SUBSET ONLY	ALL PARTICIPANTS	ALL PARTICIPANTS	IMMUNO SUBSET ONLY	ALL PARTICIPANTS	ALL PARTICIPANTS (except Revacc. Subcohorts A+B)	IMMUNO SUBSET ONLY	ALL PARTICIPANTS (except Revacc. Subcohorts A+B)
SAFETY SUBSET ONLY:												
- Ruler training and distribution	●											
- Solicited AE recording [ff]	●											
- Unsolicited AE recording [gg,hh]	--- *Continuous* ----											
- Concomitant medications[ii]	--- *Continuous* ----											
- Vital signs[ij]	●											
- eDiary review of solicited AEs by study staff		●										
	Blood Draw Volumes: IMMUNO SUBSET PARTICIPANTS (N=200)											
Approx. daily blood draw, mL	55	55		55	55		55	55		55	55	
Approx. cumulative blood draw, mL	55	110	110	165	220	220	275	330	330	385	440	440
	Blood Draw Volumes: NON-IMMUNO SUBSET PARTICIPANTS (N=5,600)											
Approx. daily blood draw, mL	15	15					15			15		
Approx. cumulative blood draw, mL	15	30	30	30	30	30	45	45	45	60	60	60

❶ pre-dose; ❷ any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after study vaccination; SARS-CoV-2 vaccination must occur as follows: Live-attenuated SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination; Non-live SARS-CoV-2 vaccine: at least 14 days before or at least 14 days after study vaccination; Viral-vectored SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination

The ☎ symbol may refer to a telephone call or a telemedicine interview/contact.

Footnotes:

a. For Immuno Subset participants, where the timing of the 24-week, 18 months, or 30 months post-vaccination visits and the end of RSV season visits overlap, procedures can be combined.
b. Visits 4 to 9 will only take place when the study progresses beyond the first year (see Figure 1 and Figure 2).
c. An optional visit could be scheduled during the second and third RSV season for additional eDiary re-training and midturbinate nasal swab kit re-training. In addition, an optional telephone call or contact by telemedicine may take place to discuss participation in a Revaccination Subcohort and/or extension of the study.
d. At the end of the first RSV season or 6 months after vaccination, whichever comes later, and at the end of the second and third RSV season. Of note, for the NH, the end of the first RSV season for the onset of an ARI is defined as 20 March 2020, the end of the second RSV season for the onset of an ARI will be defined as 17 May 2021, and the end of the third RSV season for the onset of an ARI will be defined as 15 April 2022. The defined end-of-season dates for the second and third NH RSV season may be updated in case there would be indications of a shift in season. The end of the RSV season for the SH countries is country/territory-specific and will be specified to the sites prior to the start of dosing in the SH.
e. When the window for the end of season visit at the end of the first NH RSV season (as defined in footnote d) is not coinciding with at least 6 months SAE follow-up, a separate SAE safety follow-up call should be conducted 6 months after vaccination and captured as an unscheduled visit.
f. The timings of the post-vaccination visits will be determined relative to the actual day of vaccination in the first RSV season.
g. Signing the ICF should be done before any study-related activity on Day 1 and resigned on Day 365 and no later than the end of the second RSV season. Participants in the Immuno Subset and/or Safety Subset will need to consent for the additional study procedures in these subsets.
h. Medical conditions of interest will be used in the calculation of the frailty index score. For collection of medical conditions of interest, refer to Section 9.2.1.3.
i. Therapies administered up to 30 days before vaccination on Day 1 will be recorded.
j. Medical conditions of interest will be re-assessed to capture any changes that may have developed between the start of the study and the Day 365 visit, and between the Day 365 and the Day 730 visit, and to understand if any participants have developed chronic heart and lung conditions.
k. A full physical examination, including height and body weight, will be carried out before the vaccination for the first RSV season and at the Day 365 and the Day 730 visit for the second and third RSV season, respectively. Note: height should only be measured on Day 1.
l. A cap will be installed to ensure that 50 participants (from selected sites) enrolled in the Immuno Subset and 350 participants (from all sites) enrolled in the Safety Subset are at increased risk for severe RSV disease, ie, chronic heart disease (congestive heart failure [CHF], coronary artery disease [eg, angina pectoris, ischemic cardiomyopathy, history of myocardial infarct (MI), history of coronary artery bypass graft or coronary artery stent]) and chronic lung disease (eg, asthma and chronic obstructive pulmonary disease [COPD]).
m. Includes measurement of vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation [after at least 5 minutes rest] and body temperature) by a qualified member of the study staff, and a targeted physical examination by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. It is recommended that vital signs are measured before collection of midturbinate nasal swabs and/or nasosorption samples and blood draws. The sponsor's preference is to enter the results of the clinical assessment directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.
n. The RiiQ and the PGI-H will be completed before vaccination for the first RSV season and at the Day 365 and the Day 730 visit for the second and third RSV season, respectively, by the participant on the site's eDevice.
o. The RiiQ and the PGI-H at the end of each RSV season will be completed by the participant in the eDiary or by telephone or telemedicine contact. If completed by telephone or telemedicine interview, the study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
p. The Lawton-Brody at the end of each RSV season will be completed by telephone or telemedicine contact. The study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
q. The Lawton-Brody IADL and MRU will be collected before vaccination for the first RSV season and at the Day 365 and Day 730 visits for the second and third RSV season, respectively, by interview with the participant and recorded on the site's eDevice.

r. Participants may use their own eDevice using a study-specific application instead if their device (smartphone or tablet) is compatible. eDevices provided to participants should be returned to the site at the end of the third RSV season. Participants using their own eDevice will be instructed to delete the app from their personal device. A paper safety diary may be used, if designated by the sponsor.
s. Participants will be re-trained on how to use the eDiary, if needed, and on how to collect a midturbinate nasal swab.
t. To include Inclusion Criteria 1, 7, 8, and 9 and Exclusion Criteria 7, 11, 14.2, 17, and 18.
u. All participants will be closely observed for a minimum of 30 minutes post-vaccination. For Safety Subset participants, any unsolicited, solicited local and systemic AEs will be documented by study-site personnel following this observation period and vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the adverse event page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.
v. All SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later). From the Day 365 visit until the end of the second RSV season, from the end of the second RSV season until the Day 730 (Month 24) visit, and from the Day 730 visit until the end of the third RSV season, SAEs associated with ARIs and complications related to ARIs that classify as SAEs will be collected. In addition, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the entire study.
w. Concomitant medications will be collected for all participants when associated with an SAE. Note: refer to footnote v for the SAEs collected during the RSV seasons.
x. On Day 365 and Day 730, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
y. During all 3 RSV seasons, and between the second and third RSV season, ARI surveillance will be via the eDiary which participants must complete at least twice weekly. Procedures in the event of an ARI are described in the Schedule of Activities – Assessments for Participants with an ARI Episode.
z. The cut-off date for the ARI surveillance of the first NH RSV season is 20 March 2020, 17 May 2021 for the second NH RSV season, and 15 April 2022 for the third NH RSV season. The defined end-of-season dates for the second and third NH RSV season may be updated in case there would be indications of a shift in season.
aa. Each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.
bb. Blood for humoral immune assessments before vaccination on Day 1 and 14, 365, and 730 days after vaccination on Day 1 will be drawn from all participants.
cc. Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request. Please refer to Table 13 for a non-exhaustive list of tests that may be requested to be performed on these samples in case of potential AESI reporting.
dd. Blood for humoral immune responses at the time points indicated will be drawn only from Immuno Subset participants.
ee. Blood for cellular immune responses at the time points indicated will be drawn only from Immuno Subset participants.
ff. Solicited local and systemic AEs will be collected via the eDiaries from vaccination until 7 days after the vaccination for Safety Subset participants. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.
gg. All AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards until the end of the study for all participants. All other AEs (unsolicited) and special reporting situations will be reported from the vaccination through the following 28 days for Safety Subset participants only.
hh. Safety Subset participants will be contacted by telephone or telemedicine contact at 28 days (+3 days) after the vaccination to collect information on unsolicited AEs and any special reporting situations.
ii. Concomitant medications will be collected from the time of the vaccination, through the following 28 days for Safety Subset participants only.

jj. Vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the adverse event page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.
kk. The Day 730 visit should take place no later than by the end of November 2021.
ll. Participants may be provided a new nasal swab kit in case of expiration of their current kit.

AE =adverse event, ARI =acute respiratory infection, d =day, eCRF=electronic Case Report Form, IADL =Instrumental Activities of Daily Living, ICF =informed consent form, IEC/IRB =Independent Ethics Committee/Institutional Review Board, mo =month, MRU =Medical Resource Utilization, NH =Northern Hemisphere, PGI-H =Patient Global Impression of Health, RiiQ =Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) v2 (2018), RSV =respiratory syncytial virus, SAE =serious adverse event, SAM =synthetic absorptive matrix, SARS-CoV-2 =Severe Acute Respiratory Syndrome Coronavirus-2, SH = Southern Hemisphere, vac =vaccination, we =week

SCHEDULE OF ACTIVITIES – COHORT 2 (N=2,000)*

Clinic Visit #	1	2	3 ☎
Visit Timing	Vac	Vac +14 d	End RSV Season[a]
Visit Week	0	2	
Visit Day	1	15[b]	
Visit Window		+3 d	-7/+14 d
Visit Type	Screening and VACCINATION	ALL PARTICIPANTS	ALL PARTICIPANTS
Written informed consent [c]	❶		
Inclusion/exclusion criteria	❶		
Demographics	❶		
Medical history	❶		
Medical conditions of interest [d]	❶		
Pre-vaccination medications [e]	❶		
Check for seasonal influenza and SARS-CoV-2 vaccination	❶ ❷	❷	
Physical examination [f]	❶		
Randomization	❶		
Clinical assessment [g] (collected by study staff)	❶		
Lawton-Brody IADL [k]	❶		●[j]
eDiary training and distribution [l]	●	●[m]	
RiiQ™ v2	❶[h]		●[i]
Patient Global Impression of Health (PGI-H)	❶[h]		●[i]
MRU questionnaire (baseline version) [k]	❶		
Midturbinate nasal swab kit training and distribution	●	●[m]	
Thermometer training and distribution	●		
Vaccination	●		
30-minute post-vaccination observation [n]	●		

* If proof of concept is not demonstrated at the interim analysis and there is evidence for efficacy (assessed via conditional power), 2,000 new participants will be added to the study who will be vaccinated in the next NH RSV season and followed up for one RSV season. For details refer to Section 11.12.

Clinic Visit #	**1**	**2**	**3 ☎**
Visit Timing	**Vac**	**Vac +14 d**	**End RSV Season[a]**
Visit Week	**0**	**2**	
Visit Day	**1**	**15[b]**	
Visit Window		**+3 d**	**-7/+14 d**
Visit Type	**Screening and VACCINATION**	**ALL PARTICIPANTS**	**ALL PARTICIPANTS**
SAEs [o]	*Continuous until the end of each RSV season (or 6 months after vaccination, whichever comes later)*		
AEs related to study procedures and non-investigational (concomitant) Janssen products	*Continuous until the end of the study*		
AEs leading to discontinuation (from study)	*Continuous until the end of the study*		
Concomitant medications [p]	*Continuous*		
ARI surveillance [q]	*Twice per week via the eDiary from vaccination until the end of the RSV season*		
Experience Survey			● [r]
Humoral immunity sample, mL [s] (all participants)	❶ 15	15	
Blood Draw Volumes: ALL PARTICIPANTS (N=2,000)			
Approx. daily blood draw, mL	15	15	
Approx. cumulative blood draw, mL	15	30	30

❶ pre-dose; ❷ any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after study vaccination; SARS-CoV-2 vaccination must occur as follows: Live-attenuated SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination; Non-live SARS-CoV-2 vaccine: at least 14 days before or at least 14 days after study vaccination; Viral-vectored SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination

The ☎ symbol may refer to a telephone call or a telemedicine interview/contact.

Footnotes:

a. At the end of the RSV season or 6 months after vaccination, whichever comes later.
b. The timings of the post-vaccination visits will be determined relative to the actual day of vaccination.
c. Signing the ICF should be done before any study-related activity.
d. Medical conditions of interest will be used in the calculation of the frailty index score. For collection of medical conditions of interest, refer to Section 9.2.1.3.
e. Therapies administered up to 30 days before vaccination will be recorded.
f. A full physical examination, including height and body weight, will be carried out before vaccination.
g. Includes measurement of vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation [after at least 5 minutes rest] and body temperature) by a qualified member of the study staff, and a targeted physical examination by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. It is recommended that vital signs are measured before collection of midturbinate nasal swabs and/or nasosorption samples and blood draws. The sponsor's preference is to enter the results of the clinical assessment directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.
h. The RiiQ and the PGI-H will be completed before vaccination by the participant on the site's eDevice.
i. The RiiQ and the PGI-H at the end of the RSV season will be completed by the participant in the eDiary or by telephone or telemedicine contact. If completed by telephone or telemedicine interview, the study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
j. The Lawton-Brody at the end of the RSV season will be completed by telephone or telemedicine contact. The study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
k. The Lawton-Brody IADL and MRU will be collected before vaccination by interview with the participant and recorded on the site's eDevice.
l. Participants may use their own eDevice using a study-specific application instead if their device (smartphone or tablet) is compatible. eDevices provided to participants should be returned to the site at the end of the RSV season. Participants using their own eDevice will be instructed to delete the app from their personal device. A paper safety diary may be used, if designated by the sponsor.
m. Participants will be re-trained on how to use the eDiary, if needed, and on how to collect a midturbinate nasal swab.
n. All participants will be closely observed for a minimum of 30 minutes post-vaccination.
o. All SAEs related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards until the end of the study for all participants. All other SAEs will be reported from administration of study vaccine until the end of the RSV season (or 6 months after vaccination, whichever comes later) for all participants.
p. Concomitant medications will be collected when associated with any SAE.
q. During the RSV season, ARI surveillance will be via the eDiary which participants must complete at least twice weekly. Procedures in the event of an ARI are described in the Schedule of Activities – Assessments for Participants with an ARI Episode.
r. Each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.
s. Blood for humoral immune assessments pre-dose on Day 1 and 14 days after vaccination will be drawn from all participants.

AE =adverse event, ARI =acute respiratory infection, d =day, IADL =Instrumental Activities of Daily Living, ICF =informed consent form, IEC/IRB=Independent Ethics Committee/Institutional Review Board, MRU =Medical Resource Utilization, PGI-H =Patient Global Impression of Health, RiiQ =Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) v2 (2018), RSV =respiratory syncytial virus, SAE =serious adverse event, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2, vac =vaccination

SCHEDULE OF ACTIVITIES – REVACCINATION SUBCOHORT 1A (N=120)

Participants in Revaccination Subcohort 1A received active vaccine on Day 1 (Group 1) and will receive a revaccination at 1 year (Day 365) after the first vaccination. In the table below, all visits that overlap with the Schedule of Activities Cohort 1 (N 5,800) are greyed out. *

Clinic Visit #	1	2	2a ☎	3 ☎	4	5	5a	5b	5c[a]	6[a]	7
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	End of 1st RSV Season	Vac 2	Vac 2 +14 d	Vac 2 +28 d	Vac 2 +84 d	Vac 2 +24 we	End of 2nd RSV Season	Vac 2 +52 we/
Visit Month	0		1		12		13	15	18		24
Visit Day	1	15[b]	29[b]		365[b]	379[b]	393[b]	449[b]	533[b]		730[b]
Visit Window		+3 d	+3 d	+35 d	±2 mo	+3 d relative to Vac 2	+3 d relative to Vac 2	±7 d relative to Vac 2	±14 d relative to Vac 2	7/+14 d	±1 mo relative to Vac 2[cc]
Revaccination Subcohort 1A (N=120)											
Written informed consent [c]	❶										
Written informed consent for participation in subcohort					❶[d]					●[e]	
Inclusion/exclusion criteria	❶										
Demographics	❶										
Medical history	❶										
Medical conditions of interest	❶[f]				❶[g]						
Pre vaccination medications	❶[h]				❶[i]						
Check for seasonal influenza and SARS CoV 2 vaccination	❶ ❷	❷		●	❶ ❷	❷	❷			●	
Physical examination [j]	❶				❶						
Randomization	❶										
Clinical assessment [k] (collected by study staff)	❶				❶						
RiiQ™ v2 [l]	❶			●[m]	❶					●	
Patient Global Impression of Health (PGI H) [l]	❶			●[m]	❶					●	
Lawton Brody IADL [n]	❶			●[o]	❶					●	
MRU questionnaire (baseline version) [n]	❶				❶						
eDiary training and distribution [p]	●	●[q]			●[q]						

* Participants in Revaccination Subcohort 1A cannot have participated in the Immuno Subset of Cohort 1. Therefore, visits from the Schedule of Activities – Cohort 1 (N=5,800) which pertain to the Immuno Subset only (Day 85 and Day 169) are not included here.

Clinic Visit #	1	2	2a ☎	3 ☎	**4**	**5**	**5a**	**5b**	**5c**[a]	**6**[a]	**7**
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	End of 1st RSV Season	**Vac 2**	**Vac 2 +14 d**	**Vac 2 +28 d**	**Vac 2 +84 d**	**Vac 2 +24 we**	**End of 2nd RSV Season**	**Vac 2 +52 we/**
Visit Month	0		1		**12**		**13**	**15**	**18**		**24**
Visit Day	1	15[b]	29[b]		**365**[b]	**379**[b]	**393**[b]	**449**[b]	**533**[b]		**730**[b]
Visit Window		+3 d	+3 d	+35 d	**±2 mo**	**+3 d relative to Vac 2**	**+3 d relative to Vac 2**	**±7 d relative to Vac 2**	**±14 d relative to Vac 2**	**7/+14 d**	**±1 mo relative to Vac 2**[cc]
Revaccination Subcohort 1A (N=120)											
Midturbinate nasal swab kit training and distribution	●	●[q]			●[q]						
Thermometer training and distribution	●				●						
Ruler training and distribution	●				●						
Verification of selected eligibility criteria					❶[r]						
Contraindications to vaccination					❶						
Vaccination	●				●						
30 minute post vaccination observation[s]	●				●						
Solicited AE recording[t]	●				●						
Unsolicited AE recording[u]	*Continuous*				*Continuous*						
SAEs[v]		*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from revaccination on Day 365 until the end of the second RSV season (or 6 months after vaccination, whichever comes later)*[dd]									
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products	*Continuous until the end of the participant's study participation*										
AEs leading to discontinuation (from study)		*Continuous until the end of the participant's study participation*									
Concomitant medications[w,x]		*Continuous until the end of the participant's study participation*[y]									
ARI surveillance[z]		*Twice per week via the eDiary from vaccination on Day 1 until the end of the first RSV season, and from revaccination on Day 365 until the end of the second RSV season*									
eDiary review of solicited AEs by study staff		●				●					
Experience Survey				●[bb]							
Humoral immunity sample, mL	❶ 15[aa]	15[aa]			❶ 15	15	15	15	15		15
	Blood Draw Volumes										
Approx. daily blood draw, mL	15	15			15	15	15	15	15		15
Approx. cumulative blood draw, mL	15	30	30	30	45	60	75	90	105	105	**120**

❶ pre-dose; ❷ any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after any study vaccination; SARS-CoV-2 vaccination must occur as follows: Live-attenuated SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination; Non-live SARS-CoV-2 vaccine: at least 14 days before or at least 14 days after study vaccination; Viral-vectored SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination

The ☎ symbol may refer to a telephone call or a telemedicine interview/contact.

Footnotes:

a. For participants where the timing of the 24-week post-vaccination visit and the end-of-season visit overlap, procedures can be combined.
b. The visit day is relative to the actual day of vaccination in the first RSV season. The timing of the visit day is determined by the visit window relative to the last vaccination.
c. Signing the ICF should be done before any study-related activity on Day 1.
d. Signing of the separate ICF for participation in the subcohort should be done before or at the start of the Day 365 visit.
e. Signing of a separate ICF for the Day 730 visit should be done at the end of second RSV season visit.
f. Medical conditions of interest will be used in the calculation of the frailty index score. For collection of medical conditions of interest, refer to Section 9.2.1.3.
g. Medical conditions of interest will be re-assessed to capture any changes that may have developed between the start of the study and revaccination and to understand if any participants have developed chronic heart and lung conditions. For collection of medical conditions of interest, refer to Section 9.2.1.3.
h. Therapies administered up to 30 days before vaccination on Day 1 will be recorded.
i. Before revaccination, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
j. A full physical examination, including height (Day 1 only) and body weight, will be carried out before vaccination.
k. Includes measurement of vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation [after at least 5 minutes rest] and body temperature) by a qualified member of the study staff, and a targeted physical examination by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. It is recommended that vital signs are measured before collection of midturbinate nasal swabs and blood draws. The sponsor's preference is to enter the results of the clinical assessment directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.
l. The RiiQ and the PGI-H will be completed before vaccination on Day 1/Day 365 by the participant on the site's eDevice.
m. The RiiQ and the PGI-H at the end-of-season visit will be completed by the participant in the eDiary or by telephone or telemedicine contact. If completed by telephone or telemedicine interview, the study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
n. The Lawton-Brody IADL and MRU will be collected before vaccination on Day 1/Day 365 by interview with the participant and recorded on the site's eDevice.
o. The Lawton-Brody at the end-of-season visit will be completed by telephone or telemedicine contact. The study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
p. Participants may use their own eDevice using a study-specific application instead if their device (smartphone or tablet) is compatible. eDevices provided to participants should be returned to the site at the end of their study participation. Participants using their own eDevice will be instructed to delete the app from their personal device. A paper diary may be used as indicated by the sponsor.
q. Participants will be re-trained on how to use the eDiary, if needed, and on how to collect a midturbinate nasal swab.
r. To include Inclusion Criteria 5.1, 6, and 7 and Exclusion Criteria 1, 2, 4, 12, 13, 14.2, 20.1, 21.1, and 22.
s. All participants will be closely observed for a minimum of 30 minutes post-revaccination. Any unsolicited, solicited local and systemic AEs will be documented by study-site personnel following this observation period. Vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the AE page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.
t. Solicited local and systemic AEs will be collected from vaccination until 7 days after vaccination. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.

u. All AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards until the end of the participant's study participation. All other AEs (unsolicited) and special reporting situations will be reported from revaccination through the following 28 days.
v. All SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and all SAEs will be reported from revaccination on Day 365 until the end of the second RSV season (or 6 months after vaccination, whichever comes later). In addition, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the participant's entire study participation. Note: refer to footnote z for SAEs related to ARIs.
w. Concomitant medications will be collected for all participants when associated with an SAE. Note: refer to footnote v for the SAEs collected during the RSV season.
x. On Day 365 and Day 730, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
y. Concomitant medications will be collected from the time of revaccination through the following 28 days. Other concomitant medications will be collected only when associated with any SAE.
z. ARI surveillance will be via the eDiary which participants must complete at least twice weekly. Procedures in the event of an ARI are described in the Schedule of Activities – Assessments for Participants with an ARI Episode. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season.
aa. Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request. Please refer to Table 13 for a non-exhaustive list of tests that may be requested to be performed on these samples in case of potential AESI reporting.
bb. Each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.
cc. The Day 730 visit should take place no later than by the end of November 2021.
dd. When the window for the end-of-season visit at the end of the NH RSV season is not coinciding with at least 6 months SAE follow-up, a separate SAE safety follow-up call should be conducted 6 months after revaccination and captured as an unscheduled visit.

AE=adverse event, ARI=acute respiratory infection, d=day, eCRF=electronic Case Report Form, IADL=Instrumental Activities of Daily Living, ICF=informed consent form, IEC/IRB=Independent Ethics Committee/Institutional Review Board, mo=month, MRU=Medical Resource Utilization, NH=Northern Hemisphere, PGI-H=Patient Global Impression of Health, RiiQ=Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) v2 (2018), RSV=respiratory syncytial virus, SAE=serious adverse event, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2, vac=vaccination, we=week

SCHEDULE OF ACTIVITIES – REVACCINATION SUBCOHORT 2A (N=120)

Participants in Revaccination Subcohort 2A received placebo on Day 1 (Group 2) and will receive a revaccination at 1 year (Day 365) and at 2 years (Day 730) after the first vaccination. In the table below, all visits that overlap with the Schedule of Activities Cohort 1 (N 5,800) are greyed out.[*]

Clinic Visit #	1	2	2a ☎	3 ☎	4	5	5a	5b	5c[a]	6[a]
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	End of 1st RSV Season	**Vac 2**	**Vac 2 +14 d**	**Vac 2 +28 d**	**Vac 2 +84 d**	**Vac 2 +24 we**	**End of 2nd RSV Season**
Visit Month	0		1		**12**		**13**	**15**	**18**	
Visit Day	1	15[b]	29[b]		**365[b]**	**379[b]**	**393[b]**	**449[b]**	**533[b]**	
Visit Window		+3 d	+3 d	+35 d	**±2 mo**	**+3 d relative to Vac 2**	**+3 d relative to Vac 2**	**±7 d relative to Vac 2**	**±14 d relative to Vac 2**	**-7/+14 d**
Revaccination Subcohort 2A (N=120)										
Written informed consent [c]	❶									
Written informed consent for participation in subcohort [d]					❶					●[e]
Inclusion/exclusion criteria	❶									
Demographics	❶									
Medical history	❶									
Medical conditions of interest	❶[f]				❶[g]					
Pre vaccination medications	❶[h]				❶[i]					
Check for seasonal influenza and SARS CoV 2 vaccination	❶ ❷	❷		●	❶ ❷	❷	❷			●
Physical examination [j]	❶				❶					
Randomization	❶									
Clinical assessment k (collected by study staff)	❶				❶					
RiiQ™ v2 [l]	❶			●[m]	❶					●
Patient Global Impression of Health (PGI H) [l]	❶			●[m]	❶					●
Lawton Brody IADL [n]	❶			●[o]	❶					●
MRU questionnaire (baseline version) [n]	❶				❶					
eDiary training and distribution [p]	●	●[q]			●[q]					
Midturbinate nasal swab kit training and distribution	●	●[q]			●[q]					

* Participants in Revaccination Subcohort 2A cannot have participated in the Immuno Subset of Cohort 1. Therefore, visits from the Schedule of Activities – Cohort 1 (N=5,800) which pertain to the Immuno Subset only (Day 85 and Day 169) are not included here.

Clinic Visit #	1	2	2a ☎	3 ☎	4	5	5a	5b	5c[a]	6[a]
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	End of 1st RSV Season	**Vac 2**	**Vac 2 +14 d**	**Vac 2 +28 d**	**Vac 2 +84 d**	**Vac 2 +24 we**	**End of 2nd RSV Season**
Visit Month	0		1		**12**		**13**	**15**	**18**	
Visit Day	1	15[b]	29[b]		**365[b]**	**379[b]**	**393[b]**	**449[b]**	**533[b]**	
Visit Window		+3 d	+3 d	+35 d	**±2 mo**	**+3 d relative to Vac 2**	**+3 d relative to Vac 2**	**±7 d relative to Vac 2**	**±14 d relative to Vac 2**	**-7/+14 d**
Revaccination Subcohort 2A (N=120)										
Thermometer training and distribution	●				●					
Ruler training and distribution	●				●					
Verification of selected eligibility criteria					❶[r]					
Contraindications to vaccination					❶					
Vaccination	●				●					
30 minute post vaccination observation [s]	●				●					
Solicited AE recording [u]	●				●					
Unsolicited AE recording [v]	*Continuous*				*Continuous*					
SAEs [w]	*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), from revaccination on Day 365 until the end of the second RSV season (or 6 months after vaccination, whichever comes later), and from revaccination on Day 730 until 6 months after revaccination[ff]*									
AESIs [w,x]										
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products	*Continuous until the end of the participant's study participation*									
AEs leading to discontinuation (from study)	*Continuous until the end of the participant's study participation*									
Concomitant medications [y,z]	*Continuous until the end of the participant's study participation [bb]*									
ARI surveillance [cc]	*Twice per week via the eDiary from vaccination on Day 1 until the end of the first RSV season, and from revaccination on Day 365 until the end of the second RSV season*									
eDiary review of solicited AEs by study staff		●				●				
Experience Survey				●[dd]						
Humoral immunity sample, mL	❶ 15[aa]	15[aa]			❶ 15	15	15	15	15	
	Blood Draw Volumes									
Approx. daily blood draw, mL	15	15			15	15	15	15	15	
Approx. cumulative blood draw, mL	15	30	30	30	45	60	75	90	105	105

The table continues on the next page with Visit 7 through Visit 8f.

Clinic Visit #	7	8a	8b	8c	8d	8e	8f
Visit Timing	**Vac 2 +52 we/ Vac 3**	**Vac 3 +7 d**	**Vac 3 +14 d**	**Vac 3 +28 d**	**Vac 3 +84 d**	**Vac 3 +24 we**	**Vac 3 +52 we**
Visit Month	**24**			**25**	**27**	**30**	**36**
Visit Day	**730[b]**	**737[b]**	**744[b]**	**758[b]**	**814[b]**	**898[b]**	**1,095[b]**
Visit Window	**±1 mo relative to Vac 2[ee]**	**±2 d**	**+3 d relative to Vac 3**	**+3 d relative to Vac 3**	**±7 d relative to Vac 3**	**±14 d relative to Vac 3**	**±1 mo relative to Vac 3**
Revaccination Subcohort 2A (N=120)							
Pre vaccination medications	❶[i]						
Check for seasonal influenza and SARS CoV 2 vaccination	❶ ❷	❷	❷	❷			
Physical examination[j]	❶						
eDiary training and distribution[p]	●[q]						
Thermometer training and distribution	●						
Ruler training and distribution	●						
Verification of selected eligibility criteria	❶[r]						
Contraindications to vaccination	❶						
Randomization[t]	❶						
Vaccination	●						
30 minute post vaccination observation[s]	●						
Solicited AE recording[u]	●	●					
Unsolicited AE recording[v]	*Continuous*						
SAEs[w]	*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), from revaccination on Day 365 until the end of the second RSV season (or 6 months after vaccination, whichever comes later), and from revaccination on Day 730 until 6 months after revaccination[ff]*						
AESIs[w, x]	*Continuous from revaccination on Day 730 until 6 months after revaccination[ff]*						
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products	*Continuous until the end of the participant's study participation*						
AEs leading to discontinuation (from study)	*Continuous until the end of the participant's study participation*						
Concomitant medications[y,z]	*Continuous until the end of the participant's study participation[bb]*						
eDiary review of solicited AEs by study staff		●					
Humoral immunity sample, mL	❶ 20	20	20	20	20	20	20
Cellular immunity sample, mL (at certified sites)	❶ 40		40	40	40	40	40
Paxgene sample, mL	❶ 2.5	2.5					
	Blood Draw Volumes						
Approx. daily blood draw, mL	62.5	22.5	60	60	60	60	60
Approx. cumulative blood draw, mL	167.5	190	250	310	370	430	**490**

❶ pre-dose; ❷ any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after any study vaccination; SARS-CoV-2 vaccination must occur as follows: Live-attenuated SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination; Non-live SARS-CoV-2 vaccine: at least 14 days before or at least 14 days after study vaccination; Viral-vectored SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination

The ☎ symbol may refer to a telephone call or a telemedicine interview/contact.

Footnotes:

a. For participants where the timing of the 24-week post-vaccination visit and the end-of-season visit overlap, procedures can be combined.
b. The visit day is relative to the actual day of vaccination in the first RSV season. The timing of the visit day is determined by the visit window relative to the last vaccination.
c. Signing the ICF should be done before any study-related activity on Day 1.
d. Signing of the separate ICF for participation in the subcohort should be done before or at the start of the Day 365 visit.
e. Signing of a separate ICF for the Day 730 visit and onwards should be done at the end of second RSV season visit.
f. Medical conditions of interest will be used in the calculation of the frailty index score. For collection of medical conditions of interest, refer to Section 9.2.1.3.
g. Medical conditions of interest will be re-assessed to capture any changes that may have developed between the start of the study and the Day 365 visit, and to understand if any participants have developed chronic heart and lung conditions. For collection of medical conditions of interest, refer to Section 9.2.1.3.
h. Therapies administered up to 30 days before vaccination on Day 1 will be recorded.
i. Before revaccination, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
j. A full physical examination, including height (Day 1 only) and body weight, will be carried out before vaccination.
k. Includes measurement of vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation [after at least 5 minutes rest] and body temperature) by a qualified member of the study staff, and a targeted physical examination by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. It is recommended that vital signs are measured before collection of midturbinate nasal swabs and blood draws. The sponsor's preference is to enter the results of the clinical assessment directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.
l. The RiiQ and the PGI-H will be completed before vaccination on Day 1/Day 365 by the participant on the site's eDevice.
m. The RiiQ and the PGI-H at the end-of-season visit will be completed by the participant in the eDiary or by telephone or telemedicine contact. If completed by telephone or telemedicine interview, the study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
n. The Lawton-Brody IADL and MRU will be collected before vaccination on Day 1/Day 365 by interview with the participant and recorded on the site's eDevice.
o. The Lawton-Brody at the end-of-season visit will be completed by telephone or telemedicine contact. The study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
p. Participants may use their own eDevice using a study-specific application instead if their device (smartphone or tablet) is compatible. eDevices provided to participants should be returned to the site at the end of their study participation. Participants using their own eDevice will be instructed to delete the app from their personal device. A paper diary may be used as indicated by the sponsor.
q. Participants will be re-trained on how to use the eDiary, if needed, and on how to collect a midturbinate nasal swab, if applicable.
r. To include Inclusion Criteria 5.1, 6, and 7 and Exclusion Criteria 1, 2, 4, 12, 13, 14.2, 20.1, 21.1 and 22.
s. All participants will be closely observed for a minimum of 30 minutes post-revaccination. Any unsolicited, solicited local and systemic AEs will be documented by study-site personnel following this observation period. Vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the AE page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.

t. Participants will be re-randomized in a 1:1:1 ratio to revaccination with Ad26.RSV.preF alone, RSV preF protein alone, or Ad26.RSV.preF/RSV preF protein. Refer to Table 2 and Figure 5/Figure 6.
u. Solicited local and systemic AEs will be collected from vaccination until 7 days after vaccination. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.
v. All AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards until the end of the participant's study participation. All other AEs (unsolicited) and special reporting situations will be reported from revaccination through the following 28 days.
w. All SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later) and from revaccination on Day 365 until the end of the second RSV season (or 6 months after revaccination, whichever comes later. All SAEs and AESIs (including potential AESIs) will be reported from revaccination on Day 730 until 6 months after revaccination. In addition, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the participant's entire study participation. Note: refer to footnote cc for SAEs related to ARIs.
x. Only applicable from the time of local approval of protocol amendment 6.
y. Concomitant medications will be collected for all participants when associated with an SAE or AESI. Note: refer to footnote w for the SAEs and AESIs collected during the RSV season.
z. On Day 365/Day 730, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
aa. Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request. Please refer to Table 13 for a non-exhaustive list of tests that may be requested to be performed on these samples in case of potential AESI reporting.
bb. Concomitant medications will be collected from the time of revaccination through the following 28 days. Other concomitant medications will be collected only when associated with any SAE or AESI.
cc. ARI surveillance will be via the eDiary which participants must complete at least twice weekly. Procedures in the event of an ARI are described in the Schedule of Activities – Assessments for Participants with an ARI Episode. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season.
dd. Each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.
ee. The Day 730 visit should take place no later than by the end of November 2021.
ff. When the window for the end of season visit at the end of the NH RSV season is not coinciding with at least 6 months SAE or AESI follow-up, a separate SAE or AESI safety follow-up call should be conducted 6 months after revaccination and captured as an unscheduled visit.

AE=adverse event, AESI=adverse event of special interest, ARI=acute respiratory infection, d=day, eCRF=electronic Case Report Form, IADL=Instrumental Activities of Daily Living, ICF=informed consent form, IEC/IRB=Independent Ethics Committee/Institutional Review Board, mo=month, MRU=Medical Resource Utilization, NH=Northern Hemisphere, PGI-H=Patient Global Impression of Health, RiiQ=Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) v2 (2018), RSV=respiratory syncytial virus, SAE=serious adverse event, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2, vac=vaccination, we=week

SCHEDULE OF ACTIVITIES – REVACCINATION SUBCOHORT 1B (N=135)

Participants in Revaccination Subcohort 1B received active vaccine on Day 1 (Group 1) and will receive a revaccination at 2 years (Day 730) after the first vaccination. In the table below, all visits that overlap with the Schedule of Activities Cohort 1 (N 5,800) are greyed out.[*]

Clinic Visit #	1	2	2a ☎	3 ☎	4	5
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	End of 1st RSV Season	Vac 1 + 365 d	End of 2nd RSV Season
Visit Month	0		1		12	
Visit Day	1	15[a]	29[a]		365[a]	
Visit Window		+3 d	+3 d	+35 d	±2 mo	-7/+14 d
Revaccination Subcohort 1B (N=135)						
Written informed consent [b]	❶				●	●
Inclusion/exclusion criteria	❶					
Demographics	❶					
Medical history	❶					
Medical conditions of interest	❶[d]				●[e]	
Pre vaccination medications	❶[f]					
Check for seasonal influenza and SARS CoV 2 vaccination	❶ ❷	❷		●	●	●
Physical examination [h]	❶				●	
Randomization	❶					
Clinical assessment [i] (collected by study staff)	❶				●	
RiiQ™ v2 [j]	❶			●[k]	●	●
Patient Global Impression of Health (PGI H) [j]	❶			●[k]	●	●
Lawton Brody IADL [l]	❶			●[m]	●	●
MRU questionnaire (baseline version) [l]	❶				●	
eDiary training and distribution [n]	●	●[o]				
Midturbinate nasal swab kit training and distribution	●	●[o]				●[r]
Thermometer training and distribution	●					
Ruler training and distribution	●					
Verification of selected eligibility criteria					●[p]	
Vaccination	●					
30 minute post vaccination observation [s]	●					

* Participants in Revaccination Subcohort 1B cannot have participated in the Immuno Subset of Cohort 1. Therefore, visits from the Schedule of Activities – Cohort 1 (N=5,800) which pertain to the Immuno Subset only (Day 85, Day 169, and Day 533) are not included here.

Clinic Visit #	1	2	2a ☎	3 ☎	4	5
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	End of 1st RSV Season	Vac 1 + 365 d	End of 2nd RSV Season
Visit Month	0		1		12	
Visit Day	1	15[a]	29[a]		365[a]	
Visit Window		+3 d	+3 d	+35 d	±2 mo	-7/+14 d
Revaccination Subcohort 1B (N=135)						
Solicited AE recording [t]	●					
Unsolicited AE recording [u]	*Continuous*					
SAEs [v]		*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from revaccination on Day 730 until 6 months after revaccination*[dd]				
AESIs [v]						
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products	*Continuous until the end of the participant's study participation*					
AEs leading to discontinuation (from study)		*Continuous until the end of the participant's study participation*				
Concomitant medications [w,x]		*Continuous until the end of the participant's study participation*[z]				
ARI surveillance [aa]		*Twice per week via the eDiary from vaccination on Day 1 until the end of the first RSV season, from Day 365 until the end of the second RSV season, and from the end of the second RSV season until revaccination on Day 730*				
eDiary review of solicited AEs by study staff		●				
Experience Survey				●[bb]		
Humoral immunity sample, mL	❶ 15[y]	15[y]			15	
	Blood Draw Volumes					
Approx. daily blood draw, mL	15	15			15	
Approx. cumulative blood draw, mL	15	30	30	30	45	45

The table continues on the next page with Visit 6 through Visit 7e.

Clinic Visit #	6	7	7a	7b	7c	7d	7e
Visit Timing	**Vac 2**	**Vac 2 +7 d**	**Vac 2 +14 d**	**Vac 2 +28 d**	**Vac 2 +84 d**	**Vac 2 +24 we**	**Vac 2 +52 we/**
Visit Month	**24**			**25**	**27**	**30**	**36**
Visit Day	**730[a]**	**737[a]**	**744[a]**	**758[a]**	**814[a]**	**898[a]**	**1,095[a]**
Visit Window	**±1 mo[cc]**	**±2 d relative to Vac 2**	**+3 d relative to Vac 2**	**+3 d relative to Vac 2**	**±7 d relative to Vac 2**	**±14 d relative to Vac 2**	**±1 mo relative to Vac 2**
Revaccination Subcohort 1B (N=135)							
Written informed consent for participation in subcohort [c]	❶						
Pre vaccination medications	❶[g]						
Check for seasonal influenza and SARS CoV 2 vaccination	❶ ❷	❷	❷	❷			
Physical examination [h]	❶						
eDiary training and distribution [n]	●[o]						
Thermometer training and distribution	●						
Ruler training and distribution	●						
Verification of selected eligibility criteria	❶[q]						
Contraindications to vaccination	❶						
Vaccination	●						
30 minute post vaccination observation [s]	●						
Solicited AE recording [t]	●	●					
Unsolicited AE recording [u]	*Continuous*						
SAEs [v]	*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from revaccination on Day 730 until 6 months after revaccination[dd]*						
AESIs [v]	*Continuous from revaccination on Day 730 until 6 months after revaccination[dd]*						
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products	*Continuous until the end of the participant's study participation*						
AEs leading to discontinuation (from study)	*Continuous until the end of the participant's study participation*						
Concomitant medications [w,x]	*Continuous until the end of the participant's study participation[z]*						
eDiary review of solicited AEs by study staff		●					
Humoral immunity sample, mL	❶ 20	20	20	20	20	20	20
Cellular immunity sample, mL (at certified sites)	❶ 40		40	40	40	40	40
Paxgene sample, mL	❶ 2.5	2.5					
	Blood Draw Volumes						
Approx. daily blood draw, mL	62.5	22.5	60	60	60	60	60
Approx. cumulative blood draw, mL	107.5	130	190	250	310	370	**430**

❶ pre-dose; ❷ any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after any study vaccination; SARS-CoV-2 vaccination must occur as follows: Live-attenuated SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination; Non-live SARS-CoV-2 vaccine: at least 14 days before or at least 14 days after study vaccination; Viral-vectored SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination

The ☎ symbol may refer to a telephone call or a telemedicine interview/contact.

Footnotes:

a. The visit day is relative to the actual day of vaccination in the first RSV season. The timing of the visit day is determined by the visit window relative to the last vaccination.
b. Signing the ICF should be done before any study-related activity on Day 1 and resigned on Day 365 and no later than at the end of the second RSV season.
c. Signing of the separate ICF for participation in the subcohort should be done before or at the start of the Day 730 visit.
d. Medical conditions of interest will be used in the calculation of the frailty index score. For collection of medical conditions of interest, refer to Section 9.2.1.3.
e. Medical conditions of interest will be re-assessed to capture any changes that may have developed between the start of the study and the Day 365 visit, and to understand if any participants have developed chronic heart and lung conditions. For collection of medical conditions of interest, refer to Section 9.2.1.3.
f. Therapies administered up to 30 days before vaccination on Day 1 will be recorded.
g. Before revaccination, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
h. A full physical examination, including height (Day 1 only) and body weight, will be carried out before vaccination.
i. Includes measurement of vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation [after at least 5 minutes rest] and body temperature) by a qualified member of the study staff, and a targeted physical examination by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. It is recommended that vital signs are measured before collection of midturbinate nasal swabs and blood draws. The sponsor's preference is to enter the results of the clinical assessment directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.
j. The RiiQ and the PGI-H will be completed on Day 1 (before vaccination) and Day 365 by the participant on the site's eDevice.
k. The RiiQ and the PGI-H at the end-of-season visit will be completed by the participant in the eDiary or by telephone or telemedicine contact. If completed by telephone or telemedicine interview, the study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
l. The Lawton-Brody IADL and MRU will be collected on Day 1 (before vaccination) and Day 365 by interview with the participant and recorded on the site's eDevice.
m. The Lawton-Brody at the end-of-season visit will be completed by telephone or telemedicine contact. The study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
n. Participants may use their own eDevice using a study-specific application instead if their device (smartphone or tablet) is compatible. eDevices provided to participants should be returned to the site at the end of their study participation. Participants using their own eDevice will be instructed to delete the app from their personal device. A paper diary may be used as indicated by the sponsor.
o. Participants will be re-trained on how to use the eDiary, if needed, and on how to collect a midturbinate nasal swab, if applicable.
p. To include Inclusion Criteria 1, 7, 8, and 9 and Exclusion Criteria 7, 11, 14.2, 17, and 18.
q. To include Inclusion Criteria 5.1, 6, and 7 and Exclusion Criteria 1, 2, 4, 12, 13, 14.2, 20.1, 21.1 and 22.
r. Participants may be provided a new nasal swab kit in case of expiration of their current kit.
s. All participants will be closely observed for a minimum of 30 minutes post-revaccination. Any unsolicited, solicited local and systemic AEs will be documented by study-site personnel following this observation period. Vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the AE page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.
t. Solicited local and systemic AEs will be collected from vaccination until 7 days after vaccination. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.

u. All AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards until the end of the participant's study participation. All other AEs (unsolicited) and special reporting situations will be reported from revaccination through the following 28 days.
v. All SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and all SAEs and AESIs (including potential AESIs) will be reported from revaccination on Day 730 until 6 months after revaccination. In addition, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the participant's entire study participation. Note: refer to footnote aa for SAEs related to ARIs.
w. Concomitant medications will be collected for all participants when associated with an SAE or AESI. Note: refer to footnote v for the SAEs and AESIs collected during the RSV season.
x. On Day 365/Day 730, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
y. Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request. Please refer to Table 13 for a non-exhaustive list of tests that may be requested to be performed on these samples in case of potential AESI reporting.
z. Concomitant medications will be collected from the time of revaccination through the following 28 days. Other concomitant medications will be collected only when associated with any SAE or AESI.
aa. ARI surveillance will be via the eDiary which participants must complete at least twice weekly. Procedures in the event of an ARI are described in the Schedule of Activities – Assessments for Participants with an ARI Episode. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop on Day 730.
bb. Each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.
cc. The Day 730 visit should take place no later than by the end of November 2021.
dd. When the window for the end of season visit at the end of the NH RSV season is not coinciding with at least 6 months SAE or AESI follow-up, a separate SAE or AESI safety follow-up call should be conducted 6 months after revaccination and captured as an unscheduled visit.

AE=adverse event, AESI=adverse event of special interest, ARI=acute respiratory infection, d=day, eCRF=electronic Case Report Form, IADL=Instrumental Activities of Daily Living, ICF=informed consent form, IEC/IRB=Independent Ethics Committee/Institutional Review Board, mo=month, MRU=Medical Resource Utilization, NH=Northern Hemisphere, PGI-H=Patient Global Impression of Health, RiiQ=Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) v2 (2018), RSV=respiratory syncytial virus, SAE=serious adverse event, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2, vac=vaccination, we=week

SCHEDULE OF ACTIVITIES – REVACCINATION SUBCOHORT 2B (N=135)

Participants in Revaccination Subcohort 2B received placebo on Day 1 (Group 2) and will receive a revaccination at 2 years (Day 730) and at 3 years (Day 1,095) after the first vaccination. In the table below, all visits that overlap with the Schedule of Activities Cohort 1 (N 5,800) are greyed out.[*]

Clinic Visit #	1	2	2a ☎	3 ☎	4	5
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	End of 1st RSV Season	Vac 1 + 365 d	End of 2nd RSV Season
Visit Month	0		1		12	
Visit Day	1	15[a]	29[a]		365[a]	
Visit Window		+3 d	+3 d	+35 d	±2 mo	-7/+14 d
Revaccination Subcohort 2B (N=135)						
Written informed consent [b]	❶				●	●
Inclusion/exclusion criteria	❶					
Demographics	❶					
Medical history	❶					
Medical conditions of interest	❶[d]				●[e]	
Pre vaccination medications	❶[f]					
Check for seasonal influenza and SARS CoV 2 vaccination	❶ ❷	❷		●	●	●
Physical examination [h]	❶				●	
Randomization	❶					
Clinical assessment [i] (collected by study staff)	❶				●	
RiiQ™ v2 [j]	❶			●[k]	●	●
Patient Global Impression of Health (PGI H) [j]	❶			●[k]	●	●
Lawton Brody IADL [l]	❶			●[m]	●	●
MRU questionnaire (baseline version) [l]	❶				●	
eDiary training and distribution [n]	●	●[o]				
Midturbinate nasal swab kit training and distribution	●	●[o]				●[r]
Thermometer training and distribution	●					
Ruler training and distribution	●					
Verification of selected eligibility criteria					●[p]	

* Participants in Revaccination Subcohort 2B cannot have participated in the Immuno Subset of Cohort 1. Therefore, visits from the Schedule of Activities – Cohort 1 (N=5,800) which pertain to the Immuno Subset only (Day 85, Day 169, and Day 533) are not included here.

Clinic Visit #	1	2	2a ☎	3 ☎	4	5
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	End of 1st RSV Season	Vac 1 + 365 d	End of 2nd RSV Season
Visit Month	0		1		12	
Visit Day	1	15[a]	29[a]		365[a]	
Visit Window		+3 d	+3 d	+35 d	±2 mo	-7/+14 d
Revaccination Subcohort 2B (N=135)						
Contraindications to vaccination						
Vaccination	●					
30 minute post vaccination observation[s]	●					
Solicited AE recording[u]	●					
Unsolicited AE recording[v]	*Continuous*					
SAEs[w]		*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from revaccination on Day 730/Day 1,095 until 6 months after revaccination*[ee]				
AESIs[w]						
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products	*Continuous until the end of the participant's study participation*					
AEs leading to discontinuation (from study)		*Continuous until the end of the participant's study participation*				
Concomitant medications[x,y]		*Continuous until the end of the participant's study participation*[aa]				
ARI surveillance[bb]		*Twice per week via the eDiary from vaccination on Day 1 until the end of the first RSV season, from Day 365 until the end of the second RSV season, and from the end of the second RSV season until revaccination on Day 730*				
eDiary review of solicited AEs by study staff		●				
Experience Survey				●[cc]		
Humoral immunity sample, mL	● 15[z]	15[z]			15	
	Blood Draw Volumes					
Approx. daily blood draw, mL	15	15			15	
Approx. cumulative blood draw, mL	15	30	30	30	45	45

The table continues on the next page with Visit 6 through Visit 7d.

Clinic Visit #	6	7	7a	7b	7c	7d
Visit Timing	Vac 2	Vac 2 +7 d	Vac 2 +14 d	Vac 2 +28 d	Vac 2 +84 d	Vac 2 +24 we
Visit Month	24			25	27	30
Visit Day	730[a]	737[a]	744[a]	758[a]	814[a]	898[a]
Visit Window	±1 mo[dd]	±2 d relative to Vac 2	+3 d relative to Vac 2	+3 d relative to Vac 2	±7 d relative to Vac 2	±14 d relative to Vac 2
Revaccination Subcohort 2B (N=135)						
Written informed consent for participation in subcohort [c]	❶					
Pre vaccination medications	❶[g]					
Check for seasonal influenza and SARS CoV 2 vaccination	❶ ❷	❷	❷	❷		
Physical examination [h]	❶					
eDiary training and distribution [n]	●[o]					
Thermometer training and distribution	●					
Ruler training and distribution	●					
Verification of selected eligibility criteria	❶[q]					
Contraindications to vaccination	❶					
Vaccination	●					
30 minute post vaccination observation [s]	●					
Solicited AE recording [u]	●	●				
Unsolicited AE recording [v]	*Continuous*					
SAEs [w]	*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from revaccination on Day 730/Day 1,095 until 6 months after revaccination*[ee]					
AESIs [w]	*Continuous from revaccination on Day 730/Day 1,095 until 6 months after revaccination*[ee]					
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products	*Continuous until the end of the participant's study participation*					
AEs leading to discontinuation (from study)	*Continuous until the end of the participant's study participation*					
Concomitant medications [x,y]	*Continuous until the end of the participant's study participation* [aa]					
eDiary review of solicited AEs by study staff		●				
Humoral immunity sample, mL	❶ 20	20	20	20	20	20
Cellular immunity sample, mL (at certified sites)	❶ 40		40	40	40	40
Paxgene sample, mL	❶ 2.5	2.5				
	Blood Draw Volumes					
Approx. daily blood draw, mL	62.5	22.5	60	60	60	60
Approx. cumulative blood draw, mL	107.5	130	190	250	310	370

The table continues on the next page with Visit 7e through Visit 7k.

Clinic Visit #	7e	7f	7g	7h	7i	7j	7k
Visit Timing	**Vac 2 +52 we/ Vac 3**	**Vac 3 +7 d**	**Vac 3 +14 d**	**Vac 3 +28 d**	**Vac 3 +84 d**	**Vac 3 +24 we**	**Vac 3 +52 we**
Visit Month	**36**			**37**	**39**	**42**	**48**
Visit Day	**1,095[a]**	**1,102[a]**	**1,109[a]**	**1,123[a]**	**1,179[a]**	**1,263[a]**	**1,460[a]**
Visit Window	**±1 mo relative to Vac 2**	**±2 d**	**+3 d relative to Vac 3**	**+3 d relative to Vac 3**	**±7 d relative to Vac 3**	**±14 d relative to Vac 3**	**±1 mo relative to Vac 3**
Revaccination Subcohort 2B (N=135)							
Pre vaccination medications	❶[g]						
Check for seasonal influenza and SARS CoV 2 vaccination	❶ ❷	❷	❷	❷			
Physical examination [h]	❶						
eDiary training and distribution [n]	●[o]						
Thermometer training and distribution	●						
Ruler training and distribution	●						
Verification of selected eligibility criteria	❶[q]						
Contraindications to vaccination	❶						
Randomization [t]	❶						
Vaccination	●						
30 minute post vaccination observation [s]	●						
Solicited AE recording [u]	●	●					
Unsolicited AE recording [v]	*Continuous*						
SAEs [w]	*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from revaccination on Day 730/Day 1,095 until 6 months after revaccination[ee]*						
AESIs [w]	*Continuous from revaccination on Day 730/Day 1,095 until 6 months after revaccination[ee]*						
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products	*Continuous until the end of the participant's study participation*						
AEs leading to discontinuation (from study)	*Continuous until the end of the participant's study participation*						
Concomitant medications [x,y]	*Continuous until the end of the participant's study participation[z]*						
eDiary review of solicited AEs by study staff		●					
Humoral immunity sample, mL	❶ 20	20	20	20	20	20	20
Cellular immunity sample, mL (at certified sites)	❶ 40		40	40	40	40	40
Paxgene sample, mL	❶ 2.5	2.5					
	Blood Draw Volumes						
Approx. daily blood draw, mL	62.5	22.5	60	60	60	60	60
Approx. cumulative blood draw, mL	432.5	455	515	575	635	695	**755**

❶ pre-dose; ❷ any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after any study vaccination; SARS-CoV-2 vaccination must occur as follows: Live-attenuated SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination; Non-live SARS-CoV-2 vaccine: at least 14 days before or at least 14 days after study vaccination; Viral-vectored SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination

The ☎ symbol may refer to a telephone call or a telemedicine interview/contact.

Footnotes:

a. The visit day is relative to the actual day of vaccination in the first RSV season. The timing of the visit day is determined by the visit window relative to the last vaccination.
b. Signing the ICF should be done before any study-related activity on Day 1 and resigned on Day 365 and no later than at the end of the second RSV season.
c. Signing of the separate ICF for participation in the subcohort should be done before or at the start of the Day 730 visit.
d. Medical conditions of interest will be used in the calculation of the frailty index score. For collection of medical conditions of interest, refer to Section 9.2.1.3.
e. Medical conditions of interest will be re-assessed to capture any changes that may have developed between the start of the study and the Day 365 visit, and to understand if any participants have developed chronic heart and lung conditions. For collection of medical conditions of interest, refer to Section 9.2.1.3.
f. Therapies administered up to 30 days before vaccination on Day 1 will be recorded.
g. Before revaccination, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
h. A full physical examination, including height (Day 1 only) and body weight, will be carried out before vaccination.
i. Includes measurement of vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation [after at least 5 minutes rest] and body temperature) by a qualified member of the study staff, and a targeted physical examination by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. It is recommended that vital signs are measured before collection of midturbinate nasal swabs and blood draws. The sponsor's preference is to enter the results of the clinical assessment directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.
j. The RiiQ and the PGI-H will be completed before vaccination on Day 1 (before vaccination) and Day 365 by the participant on the site's eDevice.
k. The RiiQ and the PGI-H at the end-of-season visit will be completed by the participant in the eDiary or by telephone or telemedicine contact. If completed by telephone or telemedicine interview, the study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
l. The Lawton-Brody IADL and MRU will be collected before vaccination on Day 1 (before vaccination) and Day 365 by interview with the participant and recorded on the site's eDevice.
m. The Lawton-Brody at the end-of-season visit will be completed by telephone or telemedicine contact. The study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
n. Participants may use their own eDevice using a study-specific application instead if their device (smartphone or tablet) is compatible. eDevices provided to participants should be returned to the site at the end of their study participation. Participants using their own eDevice will be instructed to delete the app from their personal device. A paper diary may be used as indicated by the sponsor.
o. Participants will be re-trained on how to use the eDiary, if needed, and on how to collect a midturbinate nasal swab, if applicable.
p. To include Inclusion Criteria 1, 7, 8, and 9 and Exclusion Criteria 7, 11, 14.2, 17, and 18.
q. To include Inclusion Criteria 5.1, 6, and 7 and Exclusion Criteria 1, 2, 4, 12, 13, 14.2, 20.1, 21.1 and 22.
r. Participants may be provided a new nasal swab kit in case of expiration of their current kit.
s. All participants will be closely observed for a minimum of 30 minutes post-revaccination. Any unsolicited, solicited local and systemic AEs will be documented by study-site personnel following this observation period. Vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be

obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the AE page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.

t. Participants will be re-randomized in a 1:1:1 ratio to revaccination with Ad26.RSV.preF alone, RSV preF protein alone, or Ad26.RSV.preF/RSV preF protein. Refer to Table 2 and Figure 5/Figure 6.
u. Solicited local and systemic AEs will be collected from vaccination until 7 days after vaccination. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.
v. All AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards until the end of the participant's study participation. All other AEs (unsolicited) and special reporting situations will be reported from revaccination through the following 28 days.
w. All SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and all SAEs and AESIs (including potential AESIs) will be reported from revaccination on Day 730/Day 1,095 until 6 months after revaccination. In addition, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the entire study. Note: refer to footnote bb for SAEs related to ARIs.
x. Concomitant medications will be collected for all participants when associated with an SAE or AESI. Note: refer to footnote w for the SAEs and AESI collected during the RSV season.
y. On Day 365/Day 730/Day 1,095, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
z. Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request. Please refer to Table 13 for a non-exhaustive list of tests that may be requested to be performed on these samples in case of potential AESI reporting.
aa. Concomitant medications will be collected from the time of revaccination through the following 28 days. Other concomitant medications will be collected only when associated with any SAE or AESI.
bb. ARI surveillance will be via the eDiary which participants must complete at least twice weekly. Procedures in the event of an ARI are described in the Schedule of Activities – Assessments for Participants with an ARI Episode. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop on Day 730.
cc. Each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.
dd. The Day 730 visit should take place no later than by the end of November 2021.
ee. When the window for the end of season visit at the end of the NH RSV season is not coinciding with at least 6 months SAE or AESI follow-up, a separate SAE or AESI safety follow-up call should be conducted 6 months after revaccination and captured as an unscheduled visit.

AE=adverse event, AESI=adverse event of special interest, ARI=acute respiratory infection, d=day, eCRF=electronic Case Report Form, IADL=Instrumental Activities of Daily Living, ICF=informed consent form, IEC/IRB=Independent Ethics Committee/Institutional Review Board, mo=month, MRU=Medical Resource Utilization, NH=Northern Hemisphere, PGI-H=Patient Global Impression of Health, RiiQ=Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) v2 (2018), RSV=respiratory syncytial virus, SAE=serious adverse event, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2, vac=vaccination, we=week

SCHEDULE OF ACTIVITIES – REVACCINATION SUBCOHORTS 1C AND 2C (N=240)*

Participants in Revaccination Subcohort C received active vaccine (Group 1) or placebo (Group 2) on Day 1 and will receive a revaccination at 3 years (Day 1,095) after the first vaccination. In the table below, all visits that overlap with the Schedule of Activities Cohort 1 (N 5,800) are greyed out.

Clinic Visit #	1	2	2a ☎	2b[a]	2c[a,b]	3[b] ☎	4	5[a,b]	6[b]
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	Vac 1 +84 d	Vac 1 +24 we	End of 1st RSV Season	Vac 1 + 365 d	Vac 1 +18 mo	End of 2nd RSV Season
Visit Month	0		1	3	6		12	18	
Visit Day	1	15[c]	29[c]	85[c]	169[c]		365[c]	533[c]	
Visit Window		+3 d	+3 d	±7 d	±14 d	+35 d	±2 mo	±14 d	-7/+14 d
Revaccination Subcohorts 1C and 2C (N=240)									
Written informed consent [d]	❶						●		●
Inclusion/exclusion criteria	❶								
Demographics	❶								
Medical history	❶								
Medical conditions of interest	❶[f]						●[g]		
Pre vaccination medications	❶[h]								
Check for seasonal influenza and SARS CoV 2 vaccination	❶ ❷	❷				●	●		●
Physical examination [j]	❶						●		
Randomization	❶								
Clinical assessment [k] (collected by study staff)	❶						●		
RiiQ™ v2 [l]	❶					●[m]	●		●
Patient Global Impression of Health (PGI H) [l]	❶					●[m]	●		●
Lawton Brody IADL [n]	❶					●[o]	●		●
MRU questionnaire (baseline version) [n]	❶						●		
eDiary training and distribution [p]	●	●[q]							
Midturbinate nasal swab kit training and distribution	●	●[q]							●[r]
Thermometer training and distribution	●								
Ruler training and distribution	●								
Verification of selected eligibility criteria							●[s]		
Contraindications to vaccination									

* The study will continue with Revaccination Subcohort C depending on the 28-days post second vaccination analysis results from Revaccination Subcohort B.

Clinic Visit #	1	2	2a ☎	2b[a]	2c[a,b]	3[b] ☎	4	5[a,b]	6[b]
Visit Timing	Vac 1	Vac 1 +14 d	Vac 1 +28 d	Vac 1 +84 d	Vac 1 +24 we	End of 1st RSV Season	Vac 1 + 365 d	Vac 1 +18 mo	End of 2nd RSV Season
Visit Month	0		1	3	6		12	18	
Visit Day	1	15[c]	29[c]	85[c]	169[c]		365[c]	533[c]	
Visit Window		+3 d	+3 d	±7 d	±14 d	+35 d	±2 mo	±14 d	-7/+14 d
Revaccination Subcohorts 1C and 2C (N=240)									
Vaccination	●								
30 minute post vaccination observation[u]	●								
Solicited AE recording[v]	●								
Unsolicited AE recording[w]	*Continuous*								
SAEs[x,y]		*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from revaccination on Day 1,095 until 6 months after revaccination*[gg]							
AESI[x]									
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products[y]	*Continuous until the end of the participant's study participation*								
AEs leading to discontinuation (from study)[y]		*Continuous until the end of the participant's study participation*							
Concomitant medications[z,aa]		*Continuous until the end of the participant's study participation*[cc]							
ARI surveillance[dd]		*Twice per week via the eDiary from vaccination on Day 1 until the end of the first RSV season, from Day 365 until the end of the second RSV season, and from the end of the second RSV season until Day 730, and from Day 730 until the end of the third season*							
eDiary review of solicited AEs by study staff		●							
Experience Survey						●[ee]			
Humoral immunity sample, mL	❶ 15[bb]	15[bb]					15		
	Blood Draw Volumes								
Approx. daily blood draw, mL	15	15					15		
Approx. cumulative blood draw, mL	15	30	30	30	30	30	45	45	45

The table continues on the next page with Visit 7 through Visit 15.

Clinic Visit #	7	8[b]	9[b] ☎	10	11	12 ☎	13	14	15
Visit Timing	Vac 1 +730 d	Vac 1 +30 mo	End of 3rd RSV Season	**Vac 2**	**Vac 2 +14 d**	**Vac 2 +28 d**	**Vac 2 +84 d**	**Vac 2 +24 we**	**Vac 2 +52 we/**
Visit Month	24	30		**36**		**37**	**39**	**42**	**48**
Visit Day	730[c]	912[c]		**1,095[c]**	**1,109[c]**	**1,123[c]**	**1,179[c]**	**1,263[c]**	**1,460[c]**
Visit Window	±2 mo[ff]	±14 d	-7/+14 d	**±1 mo**	**+3 d relative to Vac 2**	**+3 d relative to Vac 2**	**±7 d relative to Vac 2**	**±14 d relative to Vac 2**	**±1 mo relative to Vac 2**
Revaccination Subcohorts 1C and 2C (N=240)									
Written informed consent for participation in subcohort [e]				❶					
Medical conditions of interest	●[g]								
Pre vaccination medications				❶[i]					
Check for seasonal influenza and SARS CoV 2 vaccination	●		●	❶ ❷	❷		❷		
Physical examination [j]	●			❶					
Clinical assessment [k] (collected by study staff)	●								
RiiQ™ v2 [l]	●		●[m]						
Patient Global Impression of Health (PGI H) [l]	●		●[m]						
Lawton Brody IADL [n]	●		●[o]						
MRU questionnaire (baseline version) [n]	●								
eDiary training and distribution [p]				●[q]					
Midturbinate nasal swab kit training and distribution	●								
Thermometer training and distribution				●					
Ruler training and distribution				●					
Verification of selected eligibility criteria	●[s]			❶[t]					
Contraindications to vaccination				❶					
Vaccination				●					
30 minute post vaccination observation [u]				●					
Solicited AE recording [v]				●					
Unsolicited AE recording [w]				*Continuous*					
SAEs [x,y]	*Continuous until the end of the first RSV season (or 6 months after vaccination, whichever comes later), And from revaccination on Day 1,095 until 6 months after revaccination[gg]*								
AESI [x]				*Continuous from revaccination on Day 1,095 until 6 months after revaccination[gg]*					
AEs and special reporting situations related to study procedures and non investigational (concomitant) Janssen products [y]	*Continuous until the end of the participant's study participation*								
AEs leading to discontinuation (from study) [y]	*Continuous until the end of the participant's study participation*								
Concomitant medications [z,aa]	*Continuous until the end of the participant's study participation [cc]*								

Clinic Visit #	7	8[b]	9[b] ☎	10	11	12 ☎	13	14	15
Visit Timing	Vac 1 +730 d	Vac 1 +30 mo	End of 3rd RSV Season	Vac 2	Vac 2 +14 d	Vac 2 +28 d	Vac 2 +84 d	Vac 2 +24 we	Vac 2 +52 we/
Visit Month	24	30		36		37	39	42	48
Visit Day	730[c]	912[c]		1,095[c]	1,109[c]	1,123[c]	1,179[c]	1,263[c]	1,460[c]
Visit Window	±2 mo[ff]	±14 d	-7/+14 d	±1 mo	+3 d relative to Vac 2	+3 d relative to Vac 2	±7 d relative to Vac 2	±14 d relative to Vac 2	±1 mo relative to Vac 2
Revaccination Subcohorts 1C and 2C (N=240)									
ARI surveillance[dd]	*Twice per week via the eDiary from Day 730 until the end of the third season*								
eDiary review of solicited AEs by study staff					●				
Humoral immunity sample, mL	15			❶ 20	20		20	20	20
Cellular immunity sample, mL (in a subset of ~100 participants [~50 per group])				❶ 40	40		40	40	40
	Blood Draw Volumes								
Approx. daily blood draw, mL	15			60	60		60	60	60
Approx. cumulative blood draw, mL	60	60	60	120	180	180	240	300	360

❶ pre-dose; ❷ any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after any study vaccination; SARS-CoV-2 vaccination must occur as follows: Live-attenuated SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination; Non-live SARS-CoV-2 vaccine: at least 14 days before or at least 14 days after study vaccination; Viral-vectored SARS-CoV-2 vaccine: at least 28 days before or at least 28 days after study vaccination

The ☎ symbol may refer to a telephone call or a telemedicine interview/contact.

Footnotes:

a. Visits 2b, 2c, 5, and 8 are for Immuno Subset participants only; refer to the Schedule of Activities – Cohort 1 (N=5,800) for details.
b. For participants where the timing of the 24-week, 18-month, or 30-months post-vaccination visits and the end-of-season visits overlap, procedures can be combined.
c. The visit day is relative to the actual day of vaccination in the first RSV season. The timing of the visit day is determined by the visit window relative to the last vaccination .
d. Signing the ICF should be done before any study-related activity on Day 1 and resigned on Day 365 and no later than at the end of the second RSV season.
e. Signing of the separate ICF for participation in the subcohort should be done before the Day 1,095 visit (ie, before the end of the third RSV season).
f. Medical conditions of interest will be used in the calculation of the frailty index score. For collection of medical conditions of interest, refer to Section 9.2.1.3.
g. Medical conditions of interest will be re-assessed to capture any changes that may have developed between the start of the study and the Day 365 visit, and between the Day 365 and Day 730 visits, and to understand if any participants have developed chronic heart and lung conditions. For collection of medical conditions of interest, refer to Section 9.2.1.3.
h. Therapies administered up to 30 days before vaccination on Day 1 will be recorded.
i. Before revaccination, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).

j. A full physical examination, including height (Day 1 only) and body weight, will be carried out before vaccination.
k. Includes measurement of vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation [after at least 5 minutes rest] and body temperature) by a qualified member of the study staff, and a targeted physical examination by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. It is recommended that vital signs are measured before collection of midturbinate nasal swabs and blood draws. The sponsor's preference is to enter the results of the clinical assessment directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.
l. The RiiQ and the PGI-H will be completed on Day 1 (before vaccination) and Day 365 by the participant on the site's eDevice.
m. The RiiQ and the PGI-H at the end-of-season visit will be completed by the participant in the eDiary or by telephone or telemedicine contact. If completed by telephone or telemedicine interview, the study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
n. The Lawton-Brody IADL and MRU will be collected on Day 1 (before vaccination) and Day 365 by interview with the participant and recorded on the site's eDevice.
o. The Lawton-Brody at the end-of-season visit will be completed by telephone or telemedicine contact. The study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice.
p. Participants may use their own eDevice using a study-specific application instead if their device (smartphone or tablet) is compatible. eDevices provided to participants should be returned to the site at the end of their study participation. Participants using their own eDevice will be instructed to delete the app from their personal device. A paper diary may be used as indicated by the sponsor.
q. Participants will be re-trained on how to use the eDiary, if needed, and on how to collect a midturbinate nasal swab, if applicable.
r. Participants may be provided a new nasal swab kit in case of expiration of their current kit.
s. To include Inclusion Criteria 1, 7, 8, and 9 and Exclusion Criteria 7, 11, 14.2, 17, and 18.
t. To include Inclusion Criteria 5.1, 6, and 7 and Exclusion Criteria 1, 2, 4, 12, 13, 14.2, 20.1, 21.1 and 22.
u. All participants will be closely observed for a minimum of 30 minutes post-revaccination. Any unsolicited, solicited local and systemic AEs will be documented by study-site personnel following this observation period. Vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the AE page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.
v. Solicited local and systemic AEs will be collected from vaccination until 7 days after vaccination. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.
w. All AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from ICF signature onwards until the end of the participant's study participation. Note that for the time period between the last end of the RSV season visit and the revaccination, the aforementioned AEs and special reporting situations will be collected retrospectively upon the day of revaccination. All other AEs (unsolicited) and special reporting situations will be reported from revaccination through the following 28 days.
x. All SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and all SAEs and AESIs (including potential AESIs) will be reported from revaccination on Day 1,095 until 6 months after revaccination. Note: refer to footnote dd for SAEs related to ARIs.
y. SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the participant's entire study participation. Note that for the time period between the last end of the RSV season visit and the revaccination these (S)AEs will be collected retrospectively upon the day of revaccination.
z. Concomitant medications will be collected for all participants when associated with an SAE or AESI. Note: refer to footnote x for the SAEs and AESIs collected during the RSV season.

aa. On Day 365/Day 730/Day 1,095, changes in the use of any concomitant medication since the last visit should be recorded (refer to Section 8).
bb. Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request. Please refer to Table 13 for a non-exhaustive list of tests that may be requested to be performed on these samples in case of potential AESI reporting.
cc. Concomitant medications will be collected from the time of revaccination through the following 28 days. Other concomitant medications will be collected only when associated with any SAE or AESI.
dd. ARI surveillance will be via the eDiary which participants must complete at least twice weekly. Procedures in the event of an ARI are described in the Schedule of Activities – Assessments for Participants with an ARI Episode. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the latest at the end of the third RSV season.
ee. Each study participant will be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.
ff. The Day 730 visit should take place no later than by the end of November 2021.
gg. When the window for the end of season visit at the end of the NH RSV season is not coinciding with at least 6 months SAE follow-up, a separate SAE safety follow-up call should be conducted 6 months after revaccination and captured as an unscheduled visit.

AE=adverse event, AESI=adverse event of special interest, ARI=acute respiratory infection, d=day, eCRF=electronic Case Report Form, IADL=Instrumental Activities of Daily Living, ICF=informed consent form, IEC/IRB=Independent Ethics Committee/Institutional Review Board, mo=month, MRU=Medical Resource Utilization, NH=Northern Hemisphere, PGI-H=Patient Global Impression of Health, RiiQ=Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) v2 (2018), RSV=respiratory syncytial virus, SAE=serious adverse event, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2, vac=vaccination, we=week

SCHEDULE OF ACTIVITIES – ASSESSMENTS FOR PARTICIPANTS WITH AN ARI EPISODE

Timing relative to ARI onset	ARI onset (ARI Day 1)	ARI Days 1-2	ARI Days 3-5	Daily after ARI onset until resolution[a,g]	ARI Day 29 (±7 days)[g]
Location	**Home**	**Home**	**Site or Home**	**Home**	**Site or Home**
Participant should contact study site as soon as symptoms of possible ARI occur or site should contact participant if any ARI symptom is recorded in eDiary	●				
Midturbinate nasal swab (collected by the participant at home)		●[b]			
Midturbinate nasal swab (collected by qualified study staff)			●[c,d]		
Sputum sample, when possible (collected by qualified study staff)			●		
Midturbinate nasal swab kit training and distribution			●		
Serology blood sample for seroconfirmation of RSV infection and exploration of biomarkers that correlate with RSV infection and RSV disease severity, mL			20[e]		15
DNA and RNA preserved whole blood sample for exploration of biomarkers correlating with RSV infection and disease severity, mL			5[f]		
eDiary (completed by the participant) [i]					
RiiQ™v2 Symptom Scale and RiiQ Impact on Daily Activities Scale	*Daily*				
Patient Global Impression of Health (PGI-H)	*Daily*				
Patient Global Impression of Severity (PGI-S)	*Daily*				
Patient Global Impression of Change (PGI-C)		*Daily*			
Return to Usual Health question		*Daily*			
Temperature (measured by the participant)	*Daily*				
Completed by the participant on the site's eDevice:					
RiiQ™ v2			●		●
Patient Global Impression of Health (PGI-H)					●
Patient Global Impression of Severity (PGI-S)					●
Patient Global impression of Change (PGI-C)					●
Return to Usual Health question					●
Clinical assessment [h] (collected by study staff)			●		●
Lawton-Brody IADL (collected by interview with participant)			●		●
MRU questionnaire (collected by interview with participant)			●		●
Capture medical information from medical visits for ARIs (medically-attended ARI Information Form) and complications of ARIs [m]	*Continuous*				
ARIs and complications of ARI [j]	*Continuous*				
Concomitant medications associated with ARI [k]	*Continuous*				
Check for seasonal influenza and SARS-CoV-2 vaccination [l]			●		●

Footnotes:

a. Resolution is defined as 2 consecutive days with no symptoms listed on the RiiQ Symptom Scale or, for participants who have RiiQ symptoms present at baseline (assessed pre-vaccination for the first RSV season, at the Day 365 visit for the second RSV season [pre-vaccination if applicable], and from the Day 730 visit until the end of the third RSV season), 2 consecutive days where all symptoms on the RiiQ Symptom Scale have returned to the severity level reported at baseline).
b. The midturbinate nasal swab collected by the participant at home should preferably be taken between 12 to 24 hours after onset of symptoms.
c. The midturbinate nasal swab collected by the study staff at the site or at home should ideally be taken at least 24 hours after the midturbinate nasal swab collected by the participant at home.
d. For participants hospitalized with symptoms of an ARI, confirmation of RSV infection using an FDA-approved RT-PCR test from the local (hospital) laboratory will also be used for the analysis of case definitions if results from the central laboratory are not available.
e. Five mL of cryopreserved whole blood samples may be collected from participants during Day3-5 visit following an ARI episode and may be used for determination of exploratory biomarkers on the premise that the markers may play a role in RSV infection and RSV disease severity.
f. 2.5 mL of whole blood may be collected in a DNA Paxgene tube and 2.5 mL of whole blood may be collected in a RNA Paxgene tube during the Day 3-5 visit following an ARI episode and may be used for determination of exploratory biomarkers on the premise that the markers may play a role in RSV infection and RSV disease severity.
g. For the first NH RSV season due to the COVID-19 pandemic, if possible, participants with ongoing ARIs (with ARI onset up to 20 March 2020) who have already had ARI Day 3-5 visit including a nasal midturbinate swab should continue collecting daily questionnaires until symptom resolution and, if possible, sites should collect ARI Day 29 data, excluding procedures that require on-site visit (ie, serology and clinical assessment), over the telephone or by telemedicine contact.
h. Includes measurement of vital signs (supine systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation [after at least 5 minutes rest] and body temperature) by a qualified member of the study staff, and a targeted physical examination by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent. It is recommended that vital signs are measured before collection of midturbinate nasal swabs and/or nasosorption samples and blood draws. The sponsor's preference is to enter the results of the clinical assessment directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.
i. Participants complete the eDiary to respond to the ARI Surveillance question, Attachment 5 (RiiQ Symptom Scale) and Attachment 11 (RiiQ Impact on Daily Activity Scale, as part of the Combined Impact Assessment), Patient Global impression of Health (PGI-H), the Patient Global Impression of Severity (PGI-S), the Patient Global impression of Change (PGI-C), and the Return to Usual Health question on a daily basis, as part of the Combined Impact Assessment. (Note that the PGI-C and the Return to Usual Health question will not be completed on ARI Day 1). Participants should also record body temperature on a daily basis in the eDiary. Details are provided in Attachment 4, ARI Surveillance Assessment.
j. ARIs and complications related to ARIs that classify as SAEs will be captured in all participants and will be reported as SAEs in the eCRF for the duration of the first RSV season, or 6 months after vaccination, whichever is longer, and for the duration of the second and third RSV season. The cut-off date for a new ARI is defined as 20 March 2020 for the first NH RSV season, 17 May 2021 for the second NH RSV season, and 15 April 2022 for the third NH RSV season. The defined end-of-season dates for the second and third NH RSV season may be updated in case there would be indications of a shift in season. ARIs and complications related to ARIs that do not classify as SAEs will be reported as AEs in the eCRF from the time of vaccination through the following 28 days for Safety Subset and Revaccination Cohort participants only. In addition, all ARIs and all complications related to ARIs will be captured on the ARI form for all participants who experience an ARI episode.
k. Concomitant medications associated with ARI episodes and with complications of ARI will be recorded for all participants during all ARI episodes for the duration of the RSV season. Concomitant medications associated with ARIs will also be captured on the ARI form for all participants who experience an ARI episode
l. Information on seasonal influenza and SARS-CoV-2 vaccination must be recorded on the concomitant medication page of the eCRF.
m. For medically attended RT-PCR-confirmed RSV-mediated ARIs, including those resulting in hospitalization, a standard question list will be provided (Attachment 12, Medically Attended Acute Respiratory Infection (MA-ARI) Information Form) to collect additional information on any other diagnostic tests (eg, chest x-rays, spirometry, pulmonary function tests, etc.) or on any interventions during the clinical course of the ARI.

ARI =acute respiratory infection, COVID-19 =Coronavirus Disease 2019, DNA =deoxyribonucleic acid, FDA =Food and Drug Administration, IADL =Instrumental Activities of Daily Living, MRU =Medical Resource Utilization, NH =Northern Hemisphere, PGI-C =Patient Global impression of Change, PGI-H =Patient Global Impression of Health, PGI-S =Patient Global Impression of Severity, RiiQ =Respiratory Infection Intensity and Impact Questionnaire (RiiQ™) v2 (2018), RNA =ribonucleic acid, RT-PCR =reverse transcriptase polymerase chain reaction, SAE =serious adverse event, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus-2

ABBREVIATIONS

Ad26	adenovirus serotype 26
AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
ARI	acute respiratory infection
BMI	body mass index
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot (assay)
ePRO	electronic patient-reported outcome
ERD	enhanced respiratory disease
F protein	fusion protein
FAS	Full Analysis Set
FDA	(US) Food and Drug Administration
FI	formalin-inactivated
FIH	first-in-human
G	glycoprotein
GCP	Good Clinical Practice
GMT	geometric mean titer
HCP	health care professional
HITT	heparin-induced thrombocytopenia and thrombosis
HIV	human immunodeficiency virus
IA	interim analysis
IADL	Instrumental Activities of Daily Living
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	intracellular cytokine staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IF	information fraction
IFN-γ	interferon gamma
IM	intramuscularly
IPPI	Investigational Product Preparation Instruction
IRB	Institutional Review Board
IWRS	interactive web response system
LRTD	lower respiratory tract disease
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
NH	Northern Hemisphere
NHP	non-human primate
NSAIDs	non-steroidal anti-inflammatory drugs
PCC	protocol clarification communication
PGI-C	Patient Global Impression of Change
PGI-H	Patient Global Impression of Health

PGI-S	Patient Global Impression of Severity
PPE	Per-protocol Efficacy
PPI	Per-protocol Immunogenicity
PQC	Product Quality Complaint
RiiQ™	Respiratory Infection Intensity and Impact Questionnaire (Version 2, 2018)
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
RWE	real world evidence
SAE	serious adverse event
SAM	synthetic absorptive matrix
SD	standard deviation
SH	Southern Hemisphere
SUSAR	suspected unexpected serious adverse reaction
Th	T-helper
TNF-α	tumor necrosis factor alpha
TTS	thrombosis with thrombocytopenia syndrome
TTSAC	thrombosis with thrombocytopenia syndrome Adjudication Committee
URTI	upper respiratory tract infection
US	United States
VE	vaccine efficacy
VITT	vaccine-induced immune thrombotic thrombocytopenia
VNA	virus neutralizing antibody
VNT	virus neutralizing antibody titer
vp	viral particles

1. INTRODUCTION

A human adenovirus-vectored vaccine candidate and a pre-fusion conformation-stabilized respiratory syncytial virus (RSV) fusion (F) protein that have shown promise in preclinical animal models of RSV will be assessed in this study:

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

The active study vaccines used in the current study are Ad26.RSV.preF and RSV preF protein each administered alone as a single injection, and Ad26.RSV.preF/RSV preF protein mixture administered as a single injection.

1.1. Background

RSV is an important cause of serious respiratory infections in adults aged ≥60 years, immunocompromised, and those with underlying chronic cardiopulmonary conditions.[9] Although most adults mount a long-lasting fully protective immune response, waning immune responses in the elderly might contribute to increased susceptibility to severe disease after RSV infection causing significant morbidity and mortality. 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%).[10] In an epidemiology study of RSV burden, it was estimated that 11,000 elderly persons die annually of RSV in the United States.[28] These data support the importance of developing an effective vaccine for certain adult populations, such as the elderly.

RSV is also considered to be the most important cause of serious acute respiratory infection (ARI) in infants and children under 5 years of age: worldwide in 2005, RSV caused an estimated 33.8 million new episodes of acute lower respiratory tract infections (LRTIs) in this age range, with 3.4 million cases requiring hospitalization due to severe illness.[12,24,27]

Despite the high RSV disease burden, no licensed vaccine is available for RSV. The first vaccine candidate for use in young children, which consisted of formalin-inactivated RSV (FI-RSV), was associated with enhanced respiratory disease (ERD) upon infection with RSV.[16] Although the mechanisms for ERD are not fully understood, it is thought that FI-RSV failed to induce adequate neutralizing antibody titers and $CD8^+$ priming, and induced a T-helper (Th)2 skewed response in RSV-naïve individuals.[20] As all adults have been exposed to RSV, and therefore previously primed by a live virus infection, ERD is not expected to be a concern in adults aged ≥60 years.[8]

Adenoviral-vectored Vaccines

The immunogenicity profile of adenoviral vectors, with particular emphasis on Th1 responses, is illustrated by data obtained following the immunization of adults with Ad26-vectored human immunodeficiency virus (HIV) vaccines (Ad26.ENVA.01, Ad26.Mos.HIV and Ad26.Mos4.HIV), an Ad26-vectored Ebola vaccine (Ad26.ZEBOV) and an Ad26-vectored malaria vaccine

(Ad26.CS.01). These data demonstrate predominantly interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) production in $CD4^+$ and $CD8^+$ T cells.[1,3,7,15,19,21]

Clinical Safety Experience With Ad26-based Vaccines

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

Ad26.RSV.preF and RSV preF Protein Preclinical Data

Ad26.RSV.preF:

Studies to evaluate the immunogenicity of intramuscularly (IM) administered Ad26.RSV.preF in mice showed induction of T-helper type 1 (Th1)-skewed cellular immune responses, as measured by enzyme-linked immunospot (ELISpot) assay, intracellular cytokine staining (ICS) and multiplex cytokine enzyme-linked immunosorbent assay (ELISA). In addition, dose-dependent induction of RSV neutralizing and RSV F binding antibodies was observed using virus neutralization assays and ELISA, respectively. In neonatal mice, immunization with Ad26.RSV.preF at a dose of 1×10^{10} viral particles (vp) induced durable (ie, up to the last observation at 25 weeks) virus neutralizing antibodies (VNA) and RSV F-specific cellular immune responses that were boostable by a second administration of Ad26.RSV.preF. Similar to the observations in adult mice, immunization with Ad26.RSV.preF skewed the cytokine response towards a Th1-type immune response.

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RSV preF Protein:

Ad26.RSV.preF and RSV preF Protein Clinical Data

Ad26.RSV.preF:

At the time of protocol amendment 4 writing, 2 Phase 1 studies (VAC18193RSV1003 and VAC18193RSV1005) and 2 Phase 2a studies (VAC18193RSV2002 and VAC18193RSV2003) with Ad26.RSV.preF have been completed. Three Phase 1/2a studies (VAC18193RSV1004, VAC18194RSV2001, and VAC18194RSV2002) and 1 Phase 2a study (VAC18193RSV2005) are ongoing (Table 1).

Table 1: Completed and Ongoing Studies with Ad26.RSV.preF

Study Identifier	Clinical Phase	Study Vaccine	N Planned	Study Population
Senior Program				
VAC18193RSV1003 completed	1	Ad26.RSV.preF	72	Adult participants aged 60 years and older
VAC18193RSV1005 completed*	1	Ad26.RSV.preF	24	Adult participants aged 18 years and older in stable health (including 3 participants aged >65 years)
VAC18193RSV2002 completed	2a	Ad26.RSV.preF	63	Adult participants aged 18 to 50 years
VAC18193RSV2003 completed	2a	Ad26.RSV.preF	180	Adult participants aged 60 years and older
VAC18193RSV1004 ongoing	1/2a	Ad26.RSV.preF/ RSV preF protein	667	Adult participants aged 60 years and older
VAC18193RSV2005 ongoing	2a	Ad26.RSV.preF/ RSV preF protein	450	Adult participants aged 60 years and older in stable health
Junior Program				
VAC18194RSV2001 ongoing	1/2a	Ad26.RSV.preF	12 adults 48 toddlers	Adult participants aged 18 to 50 years and RSV-seropositive toddlers aged 12 to 24 months
VAC18194RSV2002 ongoing	1/2a	Ad26.RSV.preF	36 toddlers	Healthy RSV-seronegative toddlers aged 12 to 24 months

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

Study VAC18193RSV1003, a single-center, randomized, placebo-controlled, double-blind, first-in-human (FIH), Phase 1 study in male and female participants aged 60 years and older, evaluated the safety, reactogenicity and immunogenicity of 2 Ad26.RSV.preF vaccinations, administered 1 year apart. Safety data demonstrated that 2 single doses of 5×10^{10} vp or 1×10^{11} vp Ad26.RSV.preF vaccine (administered approximately 12 months apart) had acceptable safety and tolerability in participants aged over 60 years old in stable health. Immunogenicity data confirmed the immunogenicity of the vaccine and suggested a trend that the 1×10^{11} vp dose of Ad26.RSV.preF was more immunogenic than the 5×10^{10} vp dose.

Note: In Study VAC18193RSV1003, Ad26.RSV.preF was provided in Formulation Buffer 1[a]. Subsequent studies, including the current study, use Formulation Buffer 2[b].

Study VAC18193RSV1005, a single-center, open-label, single-arm Phase 1 study in participants aged 18 years and older in stable health (including 3 participants aged >65 years), is evaluating the shedding and kinetics of Ad26.RSV.preF after 1 IM injection of 1×10^{11} vp in 24 adults aged

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≥18 years and, assessing shedding in 3 adults aged 65 years and older. Partial study results showed that although Ad26.RSV.preF-specific DNA was observed in samples from this study, it remained primarily at the injection site, which disappeared by Day 8, and only infrequently and at very low levels, for other body locations/fluids.

Study VAC18193RSV2002, a single-center, randomized, placebo-controlled, double-blind Phase 2a exploratory human RSV challenge study in healthy 18- to 50-year-old adults, evaluated the prophylactic efficacy of a single immunization of Ad26.RSV.preF against RSV infection in a virus challenge model. In total, 63 participants have been enrolled and have received the study vaccine and 53 participants have been challenged with RSV. Results showed that the primary objective of the study was met. These results showed a significant reduction in the area under the curve (AUC) of viral load (measured by reverse transcriptase polymerase chain reaction [RT-PCR]) over time in Ad26.RSV.preF participants compared with placebo and indicated that the Ad26.RSV.preF vaccine shows protection against virologic RSV infection and symptomatic RSV infection. In addition, the results showed that vaccination with Ad26.RSV.preF reduced the percentage of infected participants following RSV challenge. And in those participants that were infected, vaccination with Ad26.RSV.preF led to a reduction in viral load (based on the quantitative culture assay) and symptoms compared to placebo. Vaccination with Ad26.RSV.preF induced favorable humoral responses compared to placebo as measured prior to RSV challenge. No safety concerns were identified.

Study VAC18193RSV2003, a single-center, randomized, placebo-controlled, double-blind Phase 2a study in 180 male and female participants aged 60 years and older, evaluated the safety and immunogenicity of Ad26.RSV.preF and seasonal influenza vaccine (Fluarix®), with and without co-administration. Co-administration of Ad26.RSV.preF with Fluarix did not impact the immune responses to both seasonal influenza vaccine and to Ad26.RSV.preF. A higher frequency of solicited systemic adverse events (AEs) was observed in the Ad26.RSV.preF group compared to placebo, but overall results demonstrated that the Ad26.RSV.preF vaccine at 1×10^{11} vp had an acceptable tolerability profile and no safety concerns were identified.

Study VAC18194RSV2001, a randomized, double-blind, Phase 1/2a study in adults 18 to 50 years of age and RSV-seropositive toddlers 12 to 24 months of age, is evaluating the safety, reactogenicity and immunogenicity of Ad26.RSV.preF. Participant enrollment is completed and the study is still blinded. Safety data from the adult cohort from the group-unblinded primary analysis at 28 days post-dose 2 revealed no safety concerns after Ad26.RSV.preF dosing at 1×10^{11} vp. The Independent Data Monitoring Committee (IDMC) reviewed group-unblinded data (safety and immunogenicity data gathered up to when 12 toddlers had reached Day 8 post-dose 1 [Ad26.RSV.preF at 5×10^{10} vp or placebo]) during a prescheduled interim group-unblinded analysis and recommended to continue the study unmodified.

Study VAC18193RSV1004, a multi-center, randomized, double-blind, placebo-controlled Phase 1/2a study in participants aged ≥60 years in stable health, is evaluating safety and immunogenicity for regimen selection of Ad26.RSV.preF and RSV preF protein combinations (Cohorts 1 and 2), followed by expanded safety evaluation of the selected regimen (Cohort 3). The study is fully enrolled, all dosing is completed for Cohort 1 and 2, and all participants from

Cohort 3 have received the first dose of study vaccine. The active study vaccine dose and regimen to be used in the current study was determined from the primary analysis of Cohort 2.

RSV preF Protein:

Study VAC18193RSV1004 is the FIH study for RSV preF protein, and for the Ad26.RSV.preF/RSV preF protein combination (administered as separate injections in opposite arms) and Ad26.RSV.preF/RSV preF protein mixture (administered as a single injection).

For the most comprehensive nonclinical and clinical information regarding Ad26.RSV.preF and nonclinical information regarding RSV preF protein, refer to the latest version of the Investigator's Brochure for Ad26.RSV.preF and RSV preF protein.[13,14]

Ad26.RSV.preF and RSV preF Protein Dose Selection

The dose levels for Ad26.RSV.preF and RSV preF protein used in the current study were determined from the primary analysis of Cohort 2 in Study VAC18193RSV1004. From the primary analysis, a significant increase in VNA A2 titers was observed in the groups combining Ad26.RSV.preF and RSV preF protein compared to Ad26.RSV.preF 1×10^{11} vp alone. No relevant differences between the mixture groups and Ad26.RSV.preF alone were noted for other immunogenicity assays available at the time of primary analysis. All regimens had acceptable safety and reactogenicity profiles, which were similar across groups. Based on these data, the mixture of Ad26.RSV.preF 1×10^{11} vp and 150 µg of the RSV preF protein was selected for the present study.

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

1.2. Overall Rationale for the Study

The current study will investigate the efficacy of an Ad26.RSV.preF/RSV preF protein mixture in participants aged ≥65 years. Three different case definitions, which all include clinical symptoms reported by participants and positive RSV RT-PCR as a criterion, will be tested (see Section 11.4.1) to allow selection of an appropriate case definition for the pivotal Phase 3 efficacy study. Study vaccine or placebo will be dosed on Day 1, with surveillance for ARI[a] from the time of vaccination through the ensuing RSV season.

The aim is to establish vaccine efficacy (VE) of the study vaccine during the RSV season after single vaccination. The goal is to recruit all participants from the Northern Hemisphere (NH). If enrollment is delayed or slower than expected so that the target sample size in the NH is not reached, enrollment might continue in the Southern Hemisphere (SH).

[a] An ARI is defined as the occurrence of at least one upper respiratory tract infection (URTI) or lower respiratory tract infection (LRTI) symptom that the participant reports that is different or worse than he or she usually experiences. See Attachment 1.

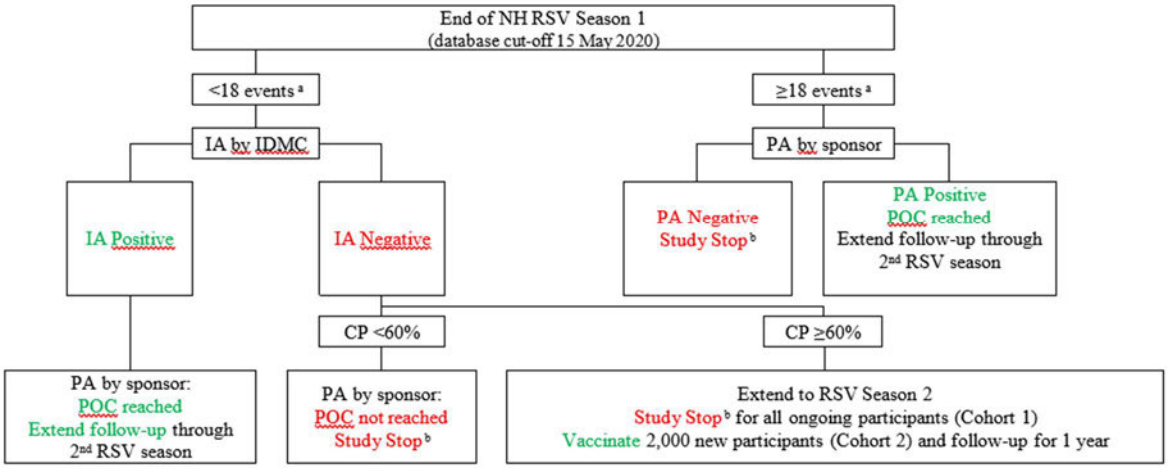
The Interim Analysis (IA) plan is outlined in detail in Section 11.12, Planned Analyses. A summary is provided below, and in Figure 3 (in case the study is performed in the NH only), and Figure 4 (in case the study is performed in both hemispheres). In brief:

- If participants are only enrolled from the NH, the primary analysis will be performed at the end of the first NH RSV season, except if the incidence is exceptionally low (less than 18 observed RT-PCR-confirmed RSV-mediated lower respiratory tract disease (LRTD) events per Case Definition #2). In that case, the IDMC will perform an IA. If successful, proof of concept is demonstrated. If proof of concept is not demonstrated at the IA and there is evidence for efficacy (assessed via conditional power), 2,000 new participants (Cohort 2) will be added to the study who will be vaccinated in the next NH RSV season and followed up for one RSV season. In that case, the ongoing participants (Cohort 1) will be stopped at the end of the first RSV season or 6 months after vaccination on Day 1, whatever comes later.
- If enrollment is spread over the NH and SH, a single IA may be performed during the NH or SH RSV season. The IA will be performed by the IDMC at the earliest of 2 predetermined time points (ie, database cut-off dates of 15 May 2020 and 15 August 2020) when at least 14 RT-PCR-confirmed RSV-mediated LRTD events per Case Definition #2 are observed. If the IA is successful, proof of concept is demonstrated. If proof of concept is not demonstrated at the IA or if less than 14 events are observed at the second time point, the primary analysis will be performed at the end of the SH RSV season in a similar way as in a NH study only.

If superiority is demonstrated at the end of the first NH RSV season, the study will continue and the ongoing participants from Cohort 1 will be followed up for a second RSV season. If this is the case, additional analyses will be performed at the end of the second RSV season to evaluate if there is a trend for durable efficacy. If analyses at the end of the second RSV season indicate a trend for durable efficacy or in case results on durability are inconclusive, the study will continue and the ongoing participants from Cohort 1 will be followed up for a third RSV season. If this is the case, additional analyses will be performed at the end of the third RSV season to further evaluate durability of efficacy.

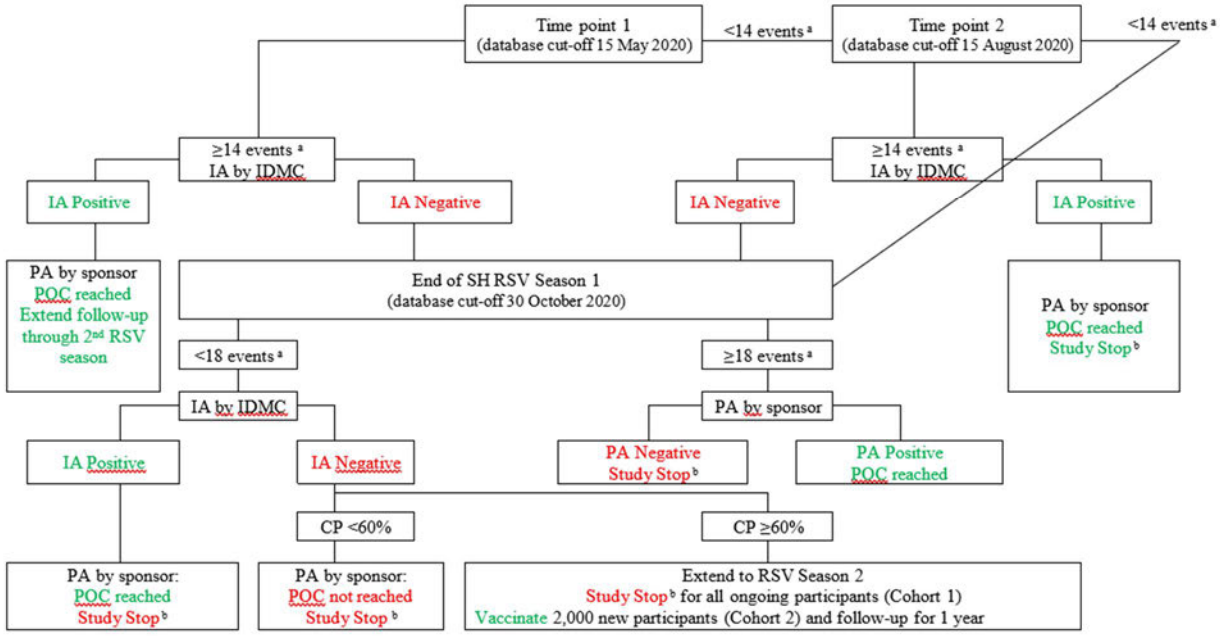
If VE is not demonstrated at the time of the primary analysis, the study will be stopped. The ongoing participants from Cohort 1 will no longer be followed up.

Figure 3: Flow Chart for the Primary Analysis in Case the Study is Performed at the Northern Hemisphere Only



[a] Number of RT-PCR-confirmed RSV-mediated LRTD cases (based on Case Definition #2)
[b] The study will stop at the end of the RSV season or 6 months after vaccination on Day 1, whichever comes later.
CP =conditional power, IA =interim analysis, IDMC =Independent Data Monitoring Committee, LRTD =lower respiratory tract disease, NH =Northern Hemisphere, PA =primary analysis, POC =proof of concept

Figure 4: Flow Chart for the Primary Analysis in Case the Study is Performed at the Northern and Southern Hemisphere



[a] Number of RT-PCR-confirmed RSV-mediated LRTD cases (based on Case Definition #2).
[b] The study will stop at the end of the RSV season or 6 months after vaccination, whichever comes later.
If the number of participants enrolled in the NH is less than 5,500 but 18 or more RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed in the NH before opening sites in the SH, no sites will be opened in the SH and the study will be performed as a NH study only (see Section 11.12, Planned Analyses).
CP =conditional power, IA =interim analysis, IDMC =Independent Data Monitoring Committee, LRTD =lower respiratory tract disease, NH =Northern Hemisphere, PA =primary analysis, POC =proof of concept, SH =Southern Hemisphere

In addition, this study will assess the safety and immunogenicity of revaccination with Ad26/protein preF RSV vaccine administered at different yearly time intervals after the first vaccination in subcohorts of participants (Revaccination Subcohorts A, B, and C) to determine the optimal time for revaccination, and to explore the relative contribution of each component of the vaccine (Ad26.RSV.preF and RSV preF protein) to the immune response after vaccination.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	*Endpoints*
PRIMARY	
• To demonstrate the efficacy of active study vaccine in the prevention of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #1[a], when compared to placebo	• First occurrence[b] of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #1
• To demonstrate the efficacy of active study vaccine in the prevention of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #2[a], when compared to placebo	• First occurrence of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #2
• To demonstrate the efficacy of active study vaccine in the prevention of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #3[a], when compared to placebo	• First occurrence of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #3
SECONDARY	
• To assess the efficacy of active study vaccine in the prevention of any RT-PCR-confirmed RSV disease when compared to placebo	• First occurrence of any RT-PCR-confirmed RSV disease
• In the Immuno Subset and in subgroups of this subset (eg, participants at increased risk of severe RSV disease), to evaluate the immunogenicity of active study vaccine	• Characterization of the humoral and cellular immune responses with emphasis on neutralizing and binding antibodies and antigen-specific cytokine production by T cells
• In the Safety Subset and in subgroups of this subset (eg, participants at increased risk of severe RSV disease), to evaluate the safety and reactogenicity in terms of solicited local and systemic AEs during 7 days after vaccination, and in terms of unsolicited AEs during 28 days after vaccination	• Occurrence, severity, duration and relationship to vaccination of solicited local and systemic AEs during 7 days after vaccination and of unsolicited AEs during 28 days after vaccination
• In the Revaccination Subcohorts, to evaluate the safety and reactogenicity in terms of solicited local and systemic AEs during 7 days after revaccination with active study vaccine administered at 1, 2, or 3 years after the first vaccination, and in terms of unsolicited AEs during 28 days after revaccination	• Occurrence, severity, duration and relationship to vaccination of solicited local and systemic AEs during 7 days after revaccination at 1, 2, or 3 years after the first vaccination and of unsolicited AEs during 28 days after revaccination at 1, 2, or 3 years after the first vaccination

[a] Clinical case definitions for RSV-mediated LRTD are presented in Section 11.4.1, Primary Efficacy Endpoints.

[b] First occurrence of the considered endpoint is defined as the first episode of the considered endpoint in a given RSV season (regardless of RSV A or B strain, unless otherwise specified).

• To evaluate safety in terms of serious adverse events (SAEs) during the RSV season[a]	• Occurrence and relationship to vaccination of SAEs during the RSV season
• To evaluate safety in terms of adverse events of special interest (AESIs) during 6 months after revaccination[a]	• Occurrence and relationship to vaccination of AESIs during 6 months after revaccination
• To evaluate safety in terms of serious adverse events (SAEs) during the ARI follow-up periods[b]	• Occurrence and relationship to vaccination of SAEs during the ARI follow-up periods

[a] For participants who will not receive a revaccination, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later). In addition, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation, and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the entire study for all participants.

For Revaccination Subcohort A, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from the time of revaccination at Month 12 until the end of the second RSV season, or until 6 months after revaccination, whichever comes later. For Revaccination Subcohort 2A, all SAEs and AESIs will also be collected from the time of revaccination on Day 730 until 6 months after revaccination. For the other Revaccination Subcohorts (B and C), SAEs and AESIs will be collected from the time of revaccination until 6 months thereafter. In addition, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs resulting in study discontinuation, and (S)AEs resulting from procedures and non-investigational (concomitant) Janssen products will be collected during the entire study for all participants. For the participants in the Revaccination Subcohort C, these (S)AEs will be collected retrospectively for the time period between the last end of the RSV season visit and the revaccination upon the day of revaccination.

[b] For participants who will not receive a revaccination, SAEs associated with ARIs and complications related to ARIs that classify as SAEs will be collected from the Day 365 (Month 12) visit until the end of the second RSV season, from the end of the second RSV season until the Day 730 (Month 24) visit, and from the Day 730 (Month 24) visit until the end of the third RSV season.

For all Revaccination subcohorts, collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season for Subcohort A, on Day 730 (Month 24) for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

EXPLORATORY	
• Explore the relationship between G-ELISA and RT-PCR-confirmed RSV infection. Provided a cut-off for G-ELISA fold-rise is found that is sufficiently sensitive and specific, the following objectives will be explored:	• Fold-rise in G-ELISA between ARI Day 3-5 and ARI Day 29.
To assess the efficacy of active study vaccine in the prevention of any serology and/or RT-PCR-confirmed RSV disease when compared to placebo	First occurrence of any serology and/or RT-PCR-confirmed RSV disease
To assess the efficacy of active study vaccine in the prevention of serology-confirmed RSV-mediated LRTD according to each case definition, when compared to placebo	First occurrence of serology-confirmed RSV-mediated LRTD according to each case definition
To assess the efficacy of active study vaccine in the prevention of any serology-confirmed RSV disease when compared to placebo	First occurrence of any serology-confirmed RSV disease
To assess the efficacy of active study vaccine in the prevention of any serology and/or RT-PCR-confirmed RSV-mediated LRTD according to each case definition, when compared to placebo	First occurrence of any serology and/or RT-PCR-confirmed RSV-mediated LRTD
• If VE is demonstrated: To explore the efficacy of active study vaccine during the second and third RSV season in the prevention of RT-PCR-confirmed RSV-mediated LRTD according to each of the 3 case definitions in each RSV season, respectively, when compared to placebo	• First occurrence of RT-PCR-confirmed RSV-mediated LRTD during the second and third RSV season according to each of the 3 case definitions
To explore the efficacy of active study vaccine over 2 and 3 RSV seasons in the prevention of RT-PCR-confirmed RSV-mediated LRTD according to each of the 3 case definitions, when compared to placebo	• First occurrence of RT-PCR-confirmed RSV-mediated LRTD over 2 and over 3 RSV seasons according to each of the 3 case definitions
The objectives assessed during the first year, might also be explored during the second and third year and over the 3-year period	• For objectives considering the VE during the second and third season, the first occurrence of the considered endpoint in the second and third season will be assessed • For objectives considering VE over 3 RSV seasons, the first occurrence of the considered endpoint over 3 seasons will be assessed
• To assess the effect of active study vaccine on the level of RSV infection when compared to placebo	• Assessment of the RSV viral load by quantitative RT-PCR

• To explore the efficacy of active study vaccine in the prevention of any RT-PCR-confirmed RSV disease caused by an RSV A strain and any RT-PCR-confirmed RSV disease caused by an RSV B strain when compared to placebo	• First occurrence of any RT-PCR-confirmed RSV disease caused by an RSV A strain or RSV B strain, respectively
• To explore the effect of active study vaccine on the potential complications of RSV disease and of any respiratory disease	• First occurrence of potential complications of respiratory disease (eg, pneumonia, new onset, worsening, or an exacerbation of congestive heart failure (CHF), asthma, and chronic obstructive pulmonary disease (COPD) linked to any respiratory disease and linked to any RT-PCR-confirmed RSV disease
• In the Revaccination Subcohorts, to evaluate humoral and cellular immunogenicity following a revaccination administered at 1 (humoral only), 2, or 3 years after the first vaccination	• Characterization of the humoral and cellular immune response following a revaccination at 1 (humoral only), 2, or 3 years after the first vaccination, with emphasis on neutralizing and binding antibodies
• To evaluate the immune response biomarkers in study participants as correlates of risk of RSV disease and as correlates of protection induced by the vaccine	• Assessment of the correlation of humoral immune responses with emphasis on neutralizing and binding antibodies with the risk of RSV disease and protection induced by the vaccine
• To explore biomarkers for the diagnosis of RSV infection and RSV disease severity	• Assessment of blood samples collected during ARI episodes for biomarkers that correlate with RSV infection and RSV disease severity
• To explore the efficacy of active study vaccine against other respiratory diseases	• Midturbinate nasal swabs may be tested for the presence of other respiratory pathogens
• To explore the effect of active study vaccine on hospitalization in the overall populations and in subgroups	• First occurrence of hospitalization linked to any respiratory disease and linked to any RT-PCR-confirmed RSV disease
• To explore the impact of active study vaccine on the course of respiratory disease and general health status	• Daily symptom severity reported by participants using the Respiratory Infection Intensity and Impact Questionnaire (RiiQ™)[a], patient global impression scales, temperature logs, medical resource utilization (MRU) and oxygen saturation in participants with an ARI (RSV-confirmed or any cause)
• To explore the impact of the baseline frailty and functioning in Instrumental Activities of Daily Living (IADL) on the incidence, severity, and duration of RT-PCR confirmed RSV-mediated LRTD	• Assessment of RSV incidence (by RT-PCR), RSV severity (per RiiQ questionnaire), and duration of ARI episode(s) in relation to the baseline frailty score and baseline Lawton-Brody IADL

[a] The Respiratory Infection Intensity and Impact Questionnaire used in this study is the RiiQ™ Version 2, 2018 (hereafter referred to as RiiQ).

• In Revaccination Subcohorts 2A and 2B, to explore the relative contribution of each component of the active vaccine on safety and reactogenicity in terms of solicited local and systemic AEs during 7 days after revaccination, and in terms of unsolicited AEs during 28 days after revaccination	• Occurrence, severity, duration, and relationship to vaccination of solicited local and systemic AEs during 7 days after revaccination and of unsolicited AEs during 28 days after revaccination
• In Revaccination Subcohorts 2A and 2B, to explore the relative contribution of each component of the active vaccine on humoral and cellular immunogenicity following revaccination	• Characterization of the humoral and cellular immune response following revaccination, with emphasis on neutralizing and binding antibodies

2.2. Hypothesis

The study is designed to test the primary hypothesis of VE in the Per-protocol Efficacy (PPE) population (see Section 11.1, for a definition of the PPE population).

- The null hypothesis is that the VE for each of the 3 primary endpoints is ≤0%
- The alternative hypothesis is that the VE for at least one of the primary endpoints is >0%

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multi-center, randomized, double-blind, placebo-controlled Phase 2b proof-of-concept study in male and female participants aged ≥65 years who are in stable health. A target of up to 5,800 participants (Cohort 1) will be enrolled and randomized in parallel in a 1:1 ratio to 1 of 2 groups to receive active study vaccine (Group 1) or placebo (Group 2) intramuscularly (Table 2).

Based on the primary analysis of safety and immunogenicity results from Cohort 2 in Study VAC18193RSV1004 (immunogenicity including, but not limited to RSV neutralizing antibodies), a sponsor committee has selected the study vaccine dose and regimen to be used in this study. In making the selection, additional factors such as data from other assays, cost of goods, and ease of administration were also taken into account.

The study comprises administration of an Ad26.RSV.preF/RSV preF protein mixture (or placebo) to be administered as a single injection on Day 1. After vaccination, participants will be followed for symptoms that could indicate an ARI until the end of the RSV season. The end of the first NH RSV season for the onset of an ARI is defined as 20 March 2020 (due to the coronavirus disease 2019 [COVID-19] pandemic, Amendment 2), the end of the second NH RSV season for the onset of an ARI will be defined as 17 May 2021, and the end of the third NH RSV season for the onset of an ARI will be defined as 15 April 2022[a]. The end of the SH RSV season is country/territory-specific and will be specified to the sites prior to the start of dosing in the SH. Study progression

[a] The defined end-of-season dates for the second and third NH RSV season may be updated in case there would be indications of a shift in season.

beyond the first and second RSV seasons is conditional on the results obtained at the end of each of these RSV seasons.

Due to the COVID-19 pandemic, the study was amended (Amendment 2, 20 March 2020): for the first NH RSV season, if possible, participants who had ongoing ARIs (with ARI onset up to 20 March 2020), where an ARI Day 3-5 visit including the collection of a nasal swab or sputum sample had occurred, had to continue collecting daily temperature monitoring, and RiiQ and PGI questionnaires on their eDevices until their symptoms resolved or returned to baseline for 2 days. If possible, sites had to collect ARI Day 29 visit data as described in the Schedule of Activities Assessments for Participants with an ARI Episode, but excluding procedures that required on-site visit (ie, serology and clinical assessment), over the telephone or by telemedicine contact.

Cohort 1 will contain the following subsets:

- Safety Subset (N 700): approximately 350 active study vaccine participants and 350 placebo participants who have given informed consent for the additional study procedures for assessment of safety.
- Immuno Subset (N 200 from selected study sites): approximately 100 active study vaccine participants and 100 placebo participants who have given informed consent for the additional study procedures for assessment of immunogenicity.

Under Amendment 4 (dated 25 August 2020), a subcohort of Cohort 1 participants will be implemented. This Revaccination Subcohort (N 240) will consist of approximately 120 participants from Group 1 who received active study vaccine on Day 1 and 120 participants from Group 2 who received placebo on Day 1, and who have given informed consent for the additional study procedures. Participants in this Revaccination Subcohort will receive a revaccination with active study vaccine on Day 365 (Month 12, 1 year after the first vaccination) to assess the safety and immunogenicity of a second vaccination.

Under Amendment 5 (dated 04 February 2021), additional Revaccination Subcohorts will be implemented. Participants in these additional Revaccination Subcohorts will receive a revaccination with active study vaccine at 2, 3, or 4 years after the first vaccination to assess the safety and immunogenicity of revaccination with Ad26.RSV.preF/RSV preF protein mixture or with the individual vaccine components as indicated in Table 2.

Under Amendment 8 (dated 16 February 2023), Revaccination Subcohort D (ie, participants who would have received a revaccination with the Ad26.RSV.preF/RSV preF protein mixture at 4 years after the first vaccination) will be removed as additional data with a Month 48 revaccination timepoint are not expected to provide novel insights on the kinetics of the immune response after revaccination with the Ad26.RSV.preF/RSV preF protein mixture.

A graphical display of all Revaccination Subcohorts is presented in Figure 5 for Group 1 (active study vaccine on Day 1) and in Figure 6 for Group 2 (placebo on Day 1).

Note: Participants can be enrolled in both the Safety and the Immuno Subset. Participants in Revaccination Subcohorts A and B cannot have participated in the Safety or the Immuno Subset.

Study duration will be approximately 2.6 years for participants in the first cohort. Study duration in the Revaccination Subcohorts will be 2 years for participants in Revaccination Subcohort 1A, 3 years for participants in Revaccination Subcohorts 2A and 1B, and 4 years for participants in Revaccination Subcohorts 2B and C.

If the study does not progress to a second RSV season, the study duration will be approximately 0.6 years. If the study does not progress to a third RSV season, the study duration will be approximately 1.6 years.

The study will continue with Revaccination Subcohort C depending on the 28-day post second vaccination analysis results from Revaccination Subcohort B.

Study duration will be approximately 0.6 years for the potential 2,000 extra participants in the second cohort.

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

Table 2: Study Design: VAC18193RSV2001

Cohort/Group/ Subcohort	Day 1 Vaccination	Day 365 (Month 12) Revaccination	Month 24 Revaccination	Month 36 Revaccination
		(Amendment 4)	(Amendment 5)	
Cohort 1[a,b] N=5,800				
Group 1 N=2,900	Active vaccine mixture *Safety Subset*[c] *(N 350)* *Immuno Subset*[c] *(N 100)*			
Revaccination Subcohort 1A[c] (N=120)	Active vaccine mixture	Active vaccine mixture		
Revaccination Subcohort 1B[c] (N=135)	Active vaccine mixture		Active vaccine mixture	
Revaccination Subcohort 1C[c,d] (N=120)	Active vaccine mixture			Active vaccine mixture
Group 2 N=2,900	Placebo *Safety Subset*[c] *(N 350)* *Immuno Subset*[c] *(N 100)*			
Revaccination Subcohort 2A[c] (N=120)	Placebo	Active vaccine mixture	Ad26.RSV.preF alone (N=40) RSV preF protein alone (N=40) Active vaccine mixture (N=40)	
Revaccination Subcohort 2B[c] (N=135)	Placebo		Active vaccine mixture	Ad26.RSV.preF alone (N=45) RSV preF protein alone (N=45) Active vaccine mixture (N=45)

Cohort/Group/ Subcohort	Day 1 Vaccination	Day 365 (Month 12) Revaccination (Amendment 4)	Month 24 Revaccination (Amendment 5)	Month 36 Revaccination (Amendment 5)
Revaccination Subcohort 2C[c,d] (N=120)	Placebo			Active vaccine mixture

Active vaccine mixture refers to Ad26.RSV.preF (1×10^{11} vp)/RSV preF protein (150 µg) administered as a single injection.
Ad26.RSV.preF alone refers to Ad26.RSV.preF at a dose of 1×10^{11} vp.
RSV preF protein alone refers to RSV preF protein at a dose of 150 µg.

[a] If 5,500 or more participants are enrolled from the NH, no additional participants from the SH will be enrolled (see Section 11.2, Sample Size Determination). In addition, if the number of participants enrolled in the NH is less than 5,500 but 18 or more RT PCR confirmed RSV mediated LRTD events (using Case Definition #2) are observed in the NH before opening sites in the SH, no sites will be opened in the SH and the study will be performed as a NH study only (see Section 11.12, Planned Analyses).

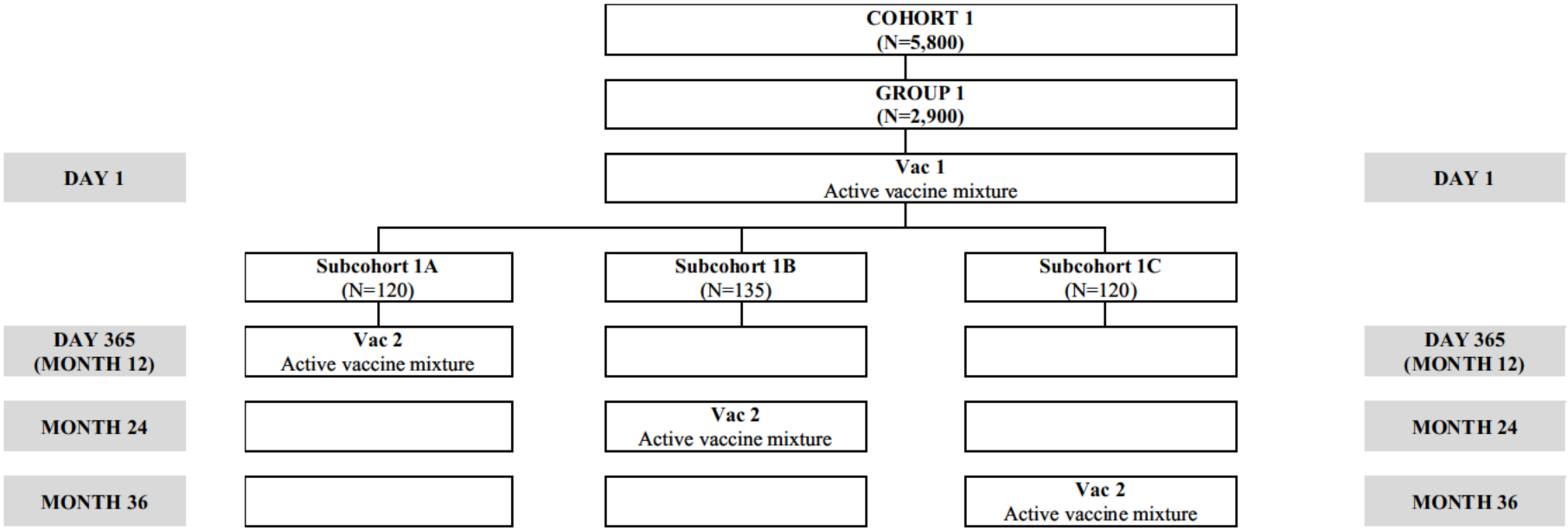
[b] The study progression beyond the first year is dependent on results obtained at the end of the first NH RSV season.

[c] Participants who provided separate informed consent.

[d] The study will continue with Revaccination Subcohort C depending on the 28 day post second vaccination analysis results from Revaccination Subcohort B.

LRTD=lower respiratory tract disease, NH=Northern Hemisphere, SH=Southern Hemisphere, vp=viral particles

Figure 5: Flow Chart for Group 1 (Active Study Vaccine on Day 1)

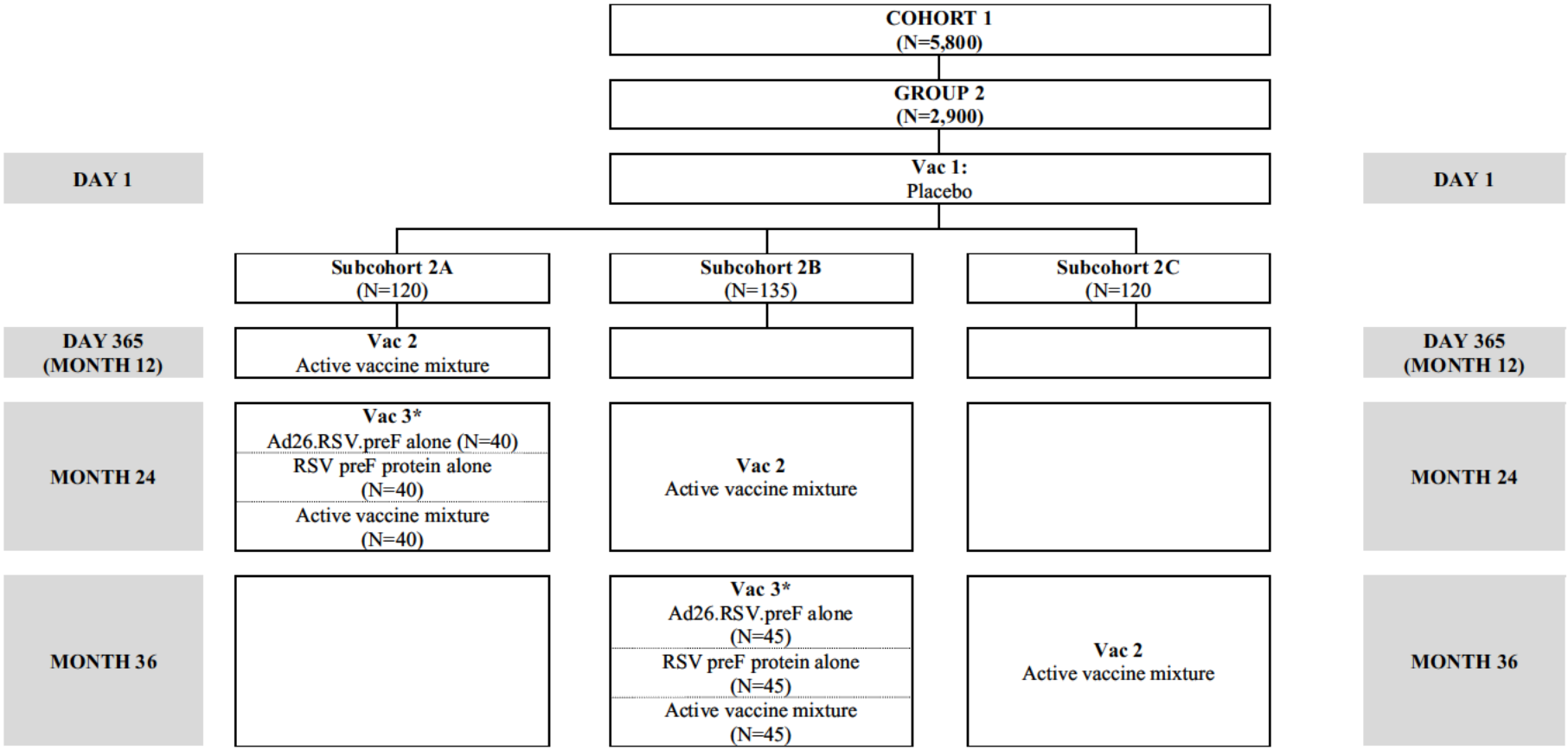


Active vaccine mixture refers to Ad26.RSV.preF (1×10^{11} vp)/RSV preF protein (150 µg) administered as a single injection.

Participants for Revaccination Subcohort B will be identified at the end of the second RSV season, and participants for Revaccination Subcohort C will be identified at the end of the third RSV season.

The blinding for study vaccination received on Day 1 will be maintained for site and participants until the database lock for the final analysis of the considered cohort, except for the participants in Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination prior to re randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

Figure 6: Flow Chart for Group 2 (Placebo on Day 1)



* Participants will be randomized 1:1:1 to either Ad26.RSV.preF alone, RSV preF protein alone, or active vaccine mixture.

Active vaccine mixture refers to Ad26.RSV.preF (1×10^{11} vp)/RSV preF protein (150 µg) administered as a single injection.
Ad26.RSV.preF alone refers to Ad26.RSV.preF at a dose of 1×10^{11} vp. RSV preF protein alone refers to RSV preF protein at a dose of 150 µg.

Participants for Revaccination Subcohort B will be identified at the end of the second RSV season, and participants for Revaccination Subcohort C will be identified at the end of the third RSV season.

The blinding for study vaccination received on Day 1 will be maintained for site and participants until the database lock for the final analysis of the considered cohort, except for the participants in Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination prior to re randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

Safety

All Participants

All participants will be closely observed for a minimum of 30 minutes after vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator.

For all participants, SAEs will be collected from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later).[a]

For all participants, some subsets of SAEs will be collected for additional study periods[a]:

- ARIs and complications related to ARIs that classify as SAEs will be captured and will be reported as SAEs in the electronic case report form (eCRF) for the duration of the second RSV season, between the second and the third RSV season, and for the duration of the third RSV season.
- From the time of vaccination (Day 1) until the end of the study period for each participant, SAEs classified as related to the study vaccine, SAEs resulting in death, and (S)AEs leading to discontinuation from the study will be collected.
- During the entire study, (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated informed consent form (ICF) is obtained onwards until the end of the study period for each participant.

The (S)AE listing in the eCRF will not be updated based on the RSV RT-PCR results and will remain listed on the eCRF as ARIs.

Safety Subset and Revaccination Subcohorts

For Revaccination Subcohort A, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from the time of revaccination at Month 12 until the end of the second RSV season, or until 6 months after revaccination, whichever comes later. For Revaccination Subcohort 2A, all SAEs and AESIs will also be collected from the time of revaccination on Day 730 until 6 months after revaccination. For Revaccination Subcohorts B and C, all SAEs and AESIs will be collected from the time of revaccination until 6 months thereafter. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season for Subcohort A, on Day 730 (Month 24) for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

For all Revaccination Subcohorts, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs leading to discontinuation from the study, and (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will

[a] The windows for SAE collection in the Revaccination Subcohorts are described below under "Safety Subset and Revaccination Subcohorts".

be collected during the entire study for all participants. For the participants in the Revaccination Subcohort C, these (S)AEs will be collected retrospectively for the time period between the last end of the RSV season visit and the revaccination upon the day of revaccination.

Additional procedures will be carried out in the Safety Subset following vaccination on Day 1, and in the Revaccination Subcohorts following revaccination on Day 365 (Month 12)/Day 730 (Month 24)/Day 1,095 (Month 36), as described below:

- Solicited local (at the injection site) AEs, solicited systemic AEs, and body temperatures will be recorded in the eDiary (or a paper diary, if designated by the sponsor), beginning on the evening of the vaccine dosing day and on a daily basis for the following 7 days. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.
- Any unsolicited, solicited local (at the injection site) and solicited systemic AEs will be documented in the eCRF by study-site personnel following the 30-minutes observation period. In addition, vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the adverse event page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.
- All other AEs (unsolicited) and special reporting situations will be reported from the time of vaccination through the following 28 days. Safety Subset participants will be contacted by telephone or telemedicine contact at 28 days (+3 days) after vaccination to collect information on unsolicited AEs; for participants in the Revaccination Subcohorts, this information will be collected at the 28-day (+3 days) post-revaccination visit.
- All ARIs and all complications related to ARIs will be reported as AEs in the eCRF from the time of vaccination through the following 28 days.

Immunogenicity

Blood will be collected for humoral immunogenicity assessments from all participants as specified in the Schedule of Activities. Additional procedures will be carried out in the Immuno Subset following vaccination on Day 1 and in the Revaccination Subcohorts following revaccination.

Other Procedures

From vaccination on Day 1 until the end of the first RSV season, from the Day 365 (Month 12) visit until the end of the second RSV season, from the end of the second RSV season until the Day 730 (Month 24) visit, and from the Day 730 visit until the end of the third RSV season, all participants will be followed-up twice per week to monitor for symptoms that could indicate an ARI, as described in Section 9.1.1, Overview. For participants in the Revaccination Subcohorts, follow-up of ARIs will stop at the end of the second RSV season for Subcohort A, at the Day 730 (Month 24) visit for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

Each participant will be asked twice each week if they have experienced any ARI-like symptoms since the previous eDiary completion, or for participants that have one or more of these symptoms at baseline, if they have experienced any additional ARI symptoms or a worsening of their baseline symptoms (Attachment 4).

Symptoms and impact of an ARI will be assessed on a daily basis in all participants with an ARI episode, using the RiiQ Symptom Scale (Attachment 5) and the RiiQ Impact on Daily Activities Scale (Attachment 11, as part of the Combined Impact Assessment), respectively, in the eDiary. The eDiary will also ask participants to complete the Patient Global Impression of Health (PGI-H), the Patient Global Impression of Severity (PGI-S), the Patient Global Impression of Change (PGI-C), and the Return to Usual Health question (Attachment 7, as part of the Combined Impact Assessment) after they complete the RiiQ Symptom Scale and RiiQ Impact on Daily Activities Scale. (Note that the PGI-C and the Return to Usual Health question will not be completed on ARI Day 1). The eDiary ARI assessment asks participants to record thermometer logs.

The participants will additionally complete all 4 scales of the RiiQ v2 (Attachment 6) on the site's eDevice during the study visits at ARI Days 3-5 and ARI Day 29 (±7 days), and each of the PGI scales and the Return to Usual Health question on the site's eDevice during the study visit at ARI Day 29 (±7 days). Refer to Section 9.2.1.1, Patient-Reported Outcomes for details.

Impact of an ARI on basic functioning will also be assessed by the study staff during study visits using the Lawton-Brody IADL assessment (Attachment 8).

Baseline MRU will be collected from all participants prior to vaccination (Attachment 9). MRU data will be collected from all participants with an ARI episode, using the MRU Questionnaire (Attachment 10) completed during study visits at ARI Days 3-5 and at ARI Day 29 (±7 days) of each ARI episode. Refer to Section 9.2.3, Medical Resource Utilization for details.

At the end of the first and third RSV season, the RiiQ questionnaire and the PGI-H in the eDiary will be completed by the participant in the eDiary or by telephone or telemedicine interview. The Lawton-Brody will be completed by telephone or telemedicine contact. The study-site personnel will read aloud the questions to the participant and record the participant's responses on the site's eDevice. At the end of the second RSV season, the Lawton-Brody IADL questionnaire will be collected on-site by interview with the participant and recorded on the site's eDevice; the RiiQ and the PGI-H will be completed by the participant on the site's eDevice.

In addition, at the end of the first RSV season, each study participant will be invited to complete an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved Experience Survey, to share his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor. An IDMC will be commissioned for this study. Refer to Section 11.13, Independent Data Monitoring Committee, for details.

3.2. Study Design Rationale

Vector Selection

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

Dose Selection

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

Rationale for Vaccine Regimen Selection

The active vaccine for this study was determined from the primary analysis of Cohort 2 in Study VAC18193RSV1004.

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to vaccine groups (ie, active vaccine [Group 1] or placebo [Group 2] for all participants in Cohort 1, and assignment to Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components for Revaccination Subcohorts 2A and 2B), to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across groups, and to enhance the validity of statistical comparisons across groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

For the Revaccination Subcohorts, all participants will receive active study vaccine at the time of revaccination. The blinding for the study vaccine received on Day 1 will be maintained for the site and participants until the database lock for the final analysis of the considered cohort, except for Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination prior to re-randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re-randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

Medical Resource Utilization Data Collection

Prophylaxis of RSV infection may reduce the need for and duration of supportive care (eg, hospitalization, oxygen supplementation, etc.). The study will evaluate the impact of active study vaccine versus placebo on the development and clinical course of RSV disease.

4. PARTICIPANT POPULATION

Screening for eligible participants will be performed pre-vaccination on Day 1. Only participants aged 65 years or older will be enrolled in the study.

Participants aged ≥65 years are generally considered at high risk for severe disease. Participants in this age range with chronic heart disease (CHF, coronary artery disease [eg, angina pectoris, ischemic cardiomyopathy, history of myocardial infarct (MI), history of coronary artery bypass

graft or coronary artery stent]) and chronic lung disease (eg, asthma and COPD) are generally at even higher risk for severe RSV disease[23]; hereafter, this population will be referred to as "increased risk". Participants at increased risk for severe RSV disease due to these underlying medical conditions will be enrolled in the study. Randomization will be set up to ensure enrollment of 350 participants at increased risk for severe RSV disease in the Safety Subset and 50 participants at increased risk for severe RSV disease in the Immuno Subset. Participants with severe chronic cardiac and lung diseases will be excluded from the study per Exclusion Criterion 2.

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

For a discussion of the statistical considerations of participant selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. Each participant must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study, is willing to participate in the study and attend all scheduled visits, and is willing and able to comply with all study procedures and adhere to the prohibitions and restrictions specified in this document.
2. Participant must be a man or woman, ≥65 years old on the day of signing the ICF and expected to be available for the duration of the study.
3. Participant must have a body mass index (BMI) <40 kg/m^2.
4. Before randomization, a woman 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: Hysterectomized women are also eligible for the study.
5. Criterion modified per Amendment 4:

5.1 In the investigator's clinical judgment, participant must be either in good or stable health. Participants may have mild to moderate (according to the Toxicity Table in Attachment 2) underlying illnesses such as chronic cardiac diseases and chronic lung disease (asthma and COPD), CHF, hypertension, type 2 diabetes mellitus, hyperlipoproteinemia, or hypothyroidism, as long as their symptoms and signs are stable and medically controlled in the judgment of the investigator. Participants will be

included on the basis of physical examination, medical history, and vital signs[a] performed between ICF signature and vaccination on Day 1.

Note: For participants in the Revaccination Subcohorts: In the investigator's clinical judgment, participant must be either in good or stable health. Participants may have mild to moderate (according to the Toxicity Table in Attachment 2) underlying illnesses as long as their symptoms and signs are stable and medically controlled in the judgment of the investigator at the time of revaccination.

6. From the time of vaccination through 3 months after vaccination, participant agrees not to donate blood.
7. Participant must be able to read, understand, and complete questionnaires in the eDiary (or a paper safety diary, if designated by the sponsor).
8. Participant must be able to work with smartphones/tablets/computers.
9. Participant must be willing to provide verifiable identification, have means to be contacted and to contact the investigator during the study.

4.2. Exclusion Criteria

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

1. Participant has an acute illness (including acute respiratory illnesses) or body temperature ≥38.0 ºC within 24 hours prior to administration of study vaccine. In such a situation, enrollment at a later date is permitted.
2. Participant has a severe or potentially life-threatening chronic disorder according to the Toxicity Table in Attachment 2, such as severe chronic cardiac diseases and severe chronic lung disease (asthma and COPD), advanced CHF, 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 well-being) or that could prevent, limit, or confound the protocol-specified assessments.
3. Participant has a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).
4. Participant has had major surgery (per the investigator's judgment), within 4 weeks before dosing, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study or within 6 months after (the last dose of) study vaccine.

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

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

5. Per medical history, participant has chronic active hepatitis B or hepatitis C infection.

6. Per medical history, participant has HIV type 1 or type 2 infection.

7. Participant has 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.

8. Participant has a known allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine components (including any of the constituents of the study vaccine).

9. Participant has a history of chronic urticaria (recurrent hives) or a history of chronic or recurrent eczema and/or atopic dermatitis that requires oral/parenteral immunomodulators/immunosuppressors.

10. Participant has a history of acute polyneuropathy (eg, Guillain-Barré syndrome).

11. Participant has abnormal function of the immune system resulting from:

- Clinical conditions (eg, autoimmune disease or immunodeficiency)
- Chronic (longer than 10 days) or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine (Note: *Ocular, topical, intra-articular, or inhaled steroids are allowed*)
- Administration of antineoplastic and immunomodulating agents or radiotherapy during the study and within 6 months before administration of study vaccine.

12. Participant has received treatment with immunoglobulins in the last 2 months, immunoglobulins specific to RSV, human metapneumovirus or parainfluenza viruses in the last 12 months, or blood products in the 4 months before the planned administration of study vaccine or has any plans to receive such treatment during the study.

13. Participant is in receipt of, or planning to receive, licensed live attenuated vaccine within 28 days of study vaccination (ie, before and after); other licensed vaccines (ie, not live: eg, influenza, tetanus, hepatitis A or B, rabies) should be given at least 14 days before or at least 14 days after study vaccination.

14. Criterion modified per Amendment 7:

14.1 Criterion modified per Amendment 8:

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

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

Note: Potential participants for revaccination subcohort C who are currently not participating in RSV ARI follow-up may be allowed to concurrently enroll in another clinical study upon approval of the sponsor. In general, concurrent participation in an

observational study is encouraged over an interventional study. The concurrent interventional studies must fulfill these criteria:

- *The concurrent interventional study must be finished before the planned administration of study vaccine in the revaccination subcohort.*
- *The concurrent interventional study must not administer another investigational RSV vaccine, other preventive RSV measures, or RSV treatments.*
- *The last administration of investigational vaccines in the concurrent interventional study must be at least 6 months before the planned administration of study vaccine in the revaccination subcohort.*
- *The last administration of investigational drugs or use of invasive medical devices in the concurrent interventional study must be at least 30 days before the planned administration of study vaccine in the revaccination subcohort.*
- *Any investigational products administered in the concurrent interventional study must not have a long-term impact in a participant's immune response (the last dose of radiotherapy, antineoplastic and immunomodulating agents, or systemic corticosteroids must be administered at least 6 months before the planned administration of study vaccine in the revaccination subcohort).*
- *The last dose of immunoglobulin-based therapies administered in the concurrent interventional study should follow Exclusion Criterion 12, relative to the planned administration of study vaccine in the revaccination subcohort.*

15. Participant has a contraindication to intramuscular injections and blood draws, eg, bleeding disorders.

16. Participant has received active RSV vaccine in a previous RSV vaccine study at any time prior to randomization.

17. Participant 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.

18. Participant cannot communicate reliably with the investigator.

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

20. Criterion modified per Amendment 4:

20.1 For participants in the Safety Subset and Revaccination Subcohorts only: participants 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.

21. Criterion modified per Amendment 5:

21.1 Participant is in receipt of, or planning to receive, a SARS-CoV-2 vaccine (licensed or used under Emergency Use Authorization):

- Live-attenuated SARS-CoV-2 vaccine: within 28 days before or within 28 days after study vaccination.
- Non-live SARS-CoV-2 vaccine: within 14 days before or within 14 days after study vaccination.
- A viral-vectored SARS-CoV-2 vaccine: within 28 days before or within 28 days after study vaccination.

22. Criterion added per Amendment 6:

22. Participant has a history of TTS or heparin-induced thrombocytopenia and thrombosis (HITT).

NOTE: Investigators must ensure that all study enrollment criteria have been met before randomization and administration of the study vaccine on Day 1. Section 17.5, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

1. Refer to Section 8 Prestudy and Concomitant Therapy, for details regarding prohibited and restricted therapies and vaccines during the study.
2. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (Section 4.1 and Section 4.2, respectively).

5. INTERVENTION ALLOCATION AND BLINDING

Study Vaccine Allocation

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 groups (active vaccine [Group 1] or placebo [Group 2]) on Day 1 based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. Participants who have given additional informed consent will be enrolled in the Safety Subset and/or in the Immuno Subset on Day 1. On Day 365 (Month12)/Day 730 (Month 24)/ Day 1,095 (Month 36), participants who have given their additional informed consent for revaccination will be enrolled in the Revaccination Subcohorts.

The interactive web response system (IWRS) will assign a unique code, which will dictate the group assignment for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

In elderly participants, the incidence of RSV-mediated LRTD is expected to increase with age. The incidence might also be higher in participants with chronic heart or lung disease (ie, participants at increased risk for severe RSV). Therefore, the randomization will be stratified by age categories (65-74 years, 75-84 years, ≥85 years) and by being at increased risk for severe RSV disease (yes/no), and done in blocks to ensure balance across arms.

The randomization will also be stratified to ensure balance across arms of participants in the Safety Subset and in the Immuno Subset (or a combination of both). The Safety Subset will consist of approximately 700 participants, and 350 of them should be at increased high risk for severe RSV disease. The Immuno Subset will consist of 200 participants, and 50 of them should be at increased high risk for severe RSV disease. The non-increased risk Safety Subset must be fully enrolled before further enrollment of non-increased risk participants in Cohort 1. The increased risk Safety Subset must be fully enrolled before further enrollment of increased risk participants in Cohort 1. Immuno Subset participants will be enrolled only at a selection of sites.

There are no restrictions on the size of the other strata.

Revaccination Subcohorts A, and C will each consist of approximately 120 participants from Group 1 who received active study vaccine on Day 1 and approximately 120 participants from Group 2 who received placebo on Day 1, and who have given informed consent for the additional study procedures. Revaccination Subcohort B will consist of at least 135 participants from Group 1 who received active study vaccine on Day 1 and at least 135 participants from Group 2 who received placebo on Day 1, and who have given informed consent for the additional study procedures. Participants in the Revaccination Subcohorts will receive a revaccination with active study vaccine at 1, 2, or 3 years after the first vaccination, as shown in Table 2. The enrollment of Revaccination Subcohorts A and C will stop when both groups have reached at least 120 participants. The enrollment of Revaccination Subcohorts B will stop when both groups have reached at least 135 participants.

Participants in Revaccination Subcohorts 2A and 2B will be re-randomized to Ad26.RSV.preF/ RSV preF protein mixture or the individual vaccine components in a 1:1:1 ratio in a blinded manner.

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.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. The study participants, study-site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and investigator will be blinded to study vaccine allocation throughout the study. The sponsor will be blinded to study vaccine allocation until the database lock for the primary analysis. Site staff and participants will remain blinded until the end of the study.

In the Revaccination Subcohorts, all participants will receive active study vaccine at the time of revaccination (Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components as shown in Table 2). The blinding for the study vaccine received on Day 1 will be maintained for site and participants until the database lock for the final analysis of the considered cohort, except for Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination prior to re-randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re-randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

From the primary analysis onwards, group level results may be shared externally as needed, however, efforts will be made to preserve the blinding to the individual participant allocation.

The investigator may in an emergency determine the identity of the intervention 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. Documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner. The investigator is advised not to reveal the study vaccine assignment to the study-site personnel or sponsor personnel/sponsor representative.

If the randomization code is broken by the investigator or the study-site personnel, the participant must discontinue further study vaccine administration (if applicable) and must be followed as appropriate until the end of the RSV season (refer to Section 10.2 for details). If the randomization code is broken by the sponsor for safety reporting purposes, the participant should not discontinue further study vaccine administration (if applicable) and may remain in the study (if the randomization code is still blinded to the study-site personnel and the participant).

6. DOSAGE AND ADMINISTRATION

The active study vaccines used in this study are Ad26.RSV.preF and RSV preF protein each administered alone as a single injection in the deltoid muscle, and an Ad26.RSV.preF/RSV preF protein mixture administered as a single injection in the deltoid muscle, according to the schedule shown in Table 2:

- Ad26.RSV.preF (JNJ-64400141) will be supplied at a concentration of 2×10^{11} vp/1 mL in single-use vials. Dose levels of 1×10^{11} vp will be used.
- RSV preF protein (JNJ-64213175) will be supplied at a concentration of 0.3 mg/1 mL in single-use vials. Dose levels of 150 µg will be used.
- Placebo for Ad26.RSV.preF and for RSV preF protein.

All injections will be 1 mL in volume.

On Day 1, an unblinded site pharmacist, or other qualified individual, who will have no other study function will prepare the syringe, labeled with the participant's identification number, and provide the syringes for Ad26.RSV.preF/RSV preF protein and placebo in a blinded manner to the blinded study vaccine administrator who will perform the injection. The unblinded pharmacist, or other qualified individual, may also perform vaccine administration, but will have no other study function following dosing.

Revaccination Subcohorts 2A and 2B will receive a revaccination with Ad26.RSV.preF/RSV preF protein mixture or with the individual vaccine components. The other Revaccination Subcohorts will receive a revaccination with Ad26.RSV.preF/RSV preF protein mixture.

Full details of study vaccine preparation will be provided in the Site Investigational Product Procedures Manual and in the Investigational Product Preparation Instruction (IPPI).

7. STUDY VACCINE COMPLIANCE

Study vaccine on Day 1 (active or placebo) will be administered IM by a blinded vaccine administrator a trained and qualified study nurse, medical doctor, or otherwise qualified healthcare professional. The unblinded pharmacist, or other qualified individual, may also perform vaccine administration, but will have no other study function following dosing.

The blinding for study vaccination received on Day 1 will be maintained for site and participants until the database lock for the final analysis of the considered cohort, except for Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination prior to re-randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re-randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

The date and time of study vaccine administration will be recorded in the eCRF.

8. PRESTUDY AND CONCOMITANT THERAPY

For All Participants

Prestudy therapies administered up to 30 days before first administration of study vaccine must be recorded in the eCRF.

Live attenuated vaccines should be given at least 28 days before (or at least 28 days after) any administration of study vaccine. Other licensed 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.

SARS-CoV-2 vaccines should be given as follows: Live-attenuated SARS-CoV-2 vaccine at least 28 days before or at least 28 days after any administration of study vaccine; Non-live SARS-CoV-2 vaccine at least 14 days before or at least 14 days after any administration of study vaccine; viral-vectored SARS-CoV-2 vaccine at least 28 days before or at least 28 days after any administration of study vaccine.

Seasonal influenza vaccination is recommended, but must occur at least 14 days before or at least 14 days after study vaccination.

Chronic use (longer than 10 days) or recurrent use of systemic corticosteroids must be documented during the study. Antineoplastic and immunomodulating agents or radiotherapy are prohibited during the study. If chronic use of systemic corticosteroids, antineoplastic or immunomodulating agents becomes medically indicated during the study for any participant, the sponsor should be contacted.

On Day 365 (Month 12), changes in the use of any concomitant medication since the last visit should be recorded.

Concomitant therapies associated with an SAE meeting the criteria outlined in Section 12.3.2, Serious Adverse Events will be collected and recorded in the eCRF from ICF signature through the end of the study.

Concomitant medications associated with ARI episodes and with complications of ARI will be recorded for all reported ARIs as defined in the protocol.

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

For Participants in the Safety Subset and the Revaccination Subcohorts

Concomitant therapies associated with unsolicited AEs will be collected and recorded in the eCRF from the time of each vaccine administration through 28 days after vaccination. Concomitant therapies associated with solicited AEs will be collected by the participants in the eCRF from the time of vaccine administration through 7 days after vaccination.

For the Revaccination Subcohorts, concomitant therapies associated with an AESI meeting the criteria outlined Section 12.3.4, Adverse Events of Special Interest will be collected and recorded in the eCRF from ICF signature through the end of the study.

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

Analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs (NSAIDs) may be used post-vaccination only in cases of medical need (eg, fever or pain) and their use must be documented in the eCRF through 28 days after vaccination.

On Day 730 (Month 24)/Day 1,095 (Month 36) (as applicable), changes in the use of any concomitant medication since the last visit should be recorded.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

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

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: electronic patient-reported outcome (ePRO), clinical assessments, midturbinate nasal swab and/or nasosorption sample, blood draws. Actual dates and times of assessments will be recorded in the source documentation and/or eCRF and/or eDevice.

eDevices will be provided for participants who require them. Instructions for completing eDiaries (on provided eDevice or the participant's own eDevice), thermometers, and a midturbinate nasal swab sample kit will be given to all participants[a] on Day 1. Participants will receive eDiary training on the day of study vaccination (Day 1), and they will be re-trained at Visit 2 (ie, 14 days post-vaccination site visit), if needed and at Visit 4 (see Schedule of Activities Cohort 1 (N 5,800)).

Participants will use an eDiary (or paper safety diary, if designated by the sponsor).[b] Participants who were provided an eDevice to complete assessments at home will be instructed to return the eDevice to the site at the end of their study participation. Participants using their own eDevice will be instructed to delete the app from their personal device.

Participants in the Revaccination Subcohorts will also receive eDiary training on the day of revaccination, and they will be retrained at the post-revaccination site visit(s), if needed (see Schedules of Activities for Revaccination Subcohorts).

Participants will also be trained when and how to collect a midturbinate nasal swab, and how to use a thermometer if they experience any symptoms that could indicate an ARI. Participants in the Safety Subset and in the Revaccination Subcohorts will additionally be provided with a ruler to measure local injection site reactions.

ARI Surveillance

From vaccination on Day 1 until the end of the first RSV season, from the Day 365 (Month 12) visit until the end of the second RSV season, from the end of the second RSV season until the Day 730 (Month 24) visit, and from the Day 730 visit until the end of the third RSV season, Cohort 1 participants will be followed-up to identify potential cases of RSV infection (see Attachment 1). For the participants in the Revaccination Subcohorts, follow-up of ARIs will stop

[a] Participants may also access the eDiary via their own eDevice if their device (smartphone or tablet) is compatible.

[b] Note that in view of safety data collection, all references to "eDiary" from this point in the protocol onwards may therefore mean eDiary or paper diary.

at the end of the second RSV season for Subcohort A, at the Day 730 (Month 24) visit for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

After administration of study vaccine, participants who experience any symptoms suggesting an ARI should contact the study site and start completing the eDiary ARI assessment on a daily basis (preferably in the evening) and/or the study site should contact the participant if any ARI symptoms are recorded in the eDiary. To help participants remember to report symptoms of a possible ARI, written instructions will be provided, and an eDiary reminder will be sent to the participant's eDevice twice per week during periods of ARI data collection. The reminder will ask participants if they have experienced any ARI symptoms, or for participants that have one or more of these symptoms at baseline (assessed pre-vaccination for the first RSV season, at the Day 365 [Month 12] visit for the second RSV season [pre-vaccination if applicable], and at the Day 730 [Month 24] visit for the third RSV season), if they have experienced any additional ARI symptoms or a worsening of their baseline symptoms. Participants continue to receive daily reminders during an ARI episode until they report 2 consecutive days without any symptoms of an ARI beyond those present at baseline. The daily eDiary ARI assessment will then end and twice weekly reminders to complete the eDiary ARI surveillance assessment will resume.

All ARIs, all complications related to ARIs, and concomitant medications associated with ARIs will be captured on the ARI form for all participants.

Procedures for Participants who Experience an ARI Episode

When any participant experiences any symptom of ARI, the following will take place:

- Participants should contact the site as soon as possible to notify the site of any symptoms suggesting an ARI (such as rhinitis, nasal congestion, sore throat, cough, etc.), or the site should contact the participants if ARI symptoms are recorded in the eDiary. During this telephone or telemedicine contact, the site may confirm if the reported symptoms qualify as an ARI episode, in order to determine whether to proceed with the ARI procedures. The participant will then be reminded to:
  - Complete the eDiary including the RiiQ (Attachment 5) and Impact on Daily Activities Scale (Attachment 11, as part of the Combined Impact Assessment), and thermometer readings every evening (preferably), beginning on the evening of the day of symptom onset (ARI Day 1) until the ARI episode resolves. The eDiary will also ask participants to complete the PGI-H, the PGI-S, the PGI-C, and the Return to Usual Health question (Attachment 7, as part of the Combined Impact Assessment). (Note that the PGI-C and the Return to Usual Health question will not be completed on ARI Day 1). A resolved ARI episode is defined as 2 consecutive days with no symptoms listed on the RiiQ Symptom Scale or, for participants who have RiiQ symptoms present at baseline (assessed pre-vaccination for the first RSV season, at the Day 365 [Month 12] visit for the second RSV season [pre-vaccination if applicable], and at the Day 730 [Month 24] visit for the third RSV season), 2 consecutive days where all symptoms on the RiiQ Symptom Scale have returned to the severity level reported at baseline.

    If a participant is unable to complete the eDiary, study staff can collect information on the participant's symptoms and temperature, by contacting the participant by telephone or telemedicine contact (or visit the participant at home), reading the questions aloud to the

participant and entering the participant's responses on the site's eDevice on the participant's behalf.

  - Collect a midturbinate nasal swab at home on the day of symptom onset or the day thereafter (ARI Days 1-2). If the participant requires it, the participant's caregiver can assist the participant to collect the midturbinate nasal swabs.
  - Ensure the midturbinate nasal swabs collected at home are provided to the study staff within 4 days (preferably) after collection.
  - Come to the site between 2 and 4 days after symptom onset (ARI Days 3-5), or, if a site visit is not feasible, a member of the study staff can visit the participant at home (or at the hospital, if needed) during this time frame.

- Between 2 and 4 days after symptom onset (ARI Days 3-5), a midturbinate nasal swab, a sputum sample (in participants with a productive cough, when possible) and a blood sample for seroconfirmation and exploration of biomarkers that correlate with RSV infection and RSV disease severity will be taken by a qualified member of the study staff, and vital signs, including body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation, will be measured. A clinical assessment, including a targeted physical examination, will be completed by qualified study staff, preferably by a physician, physician assistant, nurse practitioner, or equivalent. The participant's functional status will also be evaluated by the Lawton-Brody IADL questionnaire. The MRU questionnaire will be completed based on clinical interview. The participant will complete all 4 scales of the RiiQ v2 questionnaire on the site's eDevice and provide the study staff member the midturbinate nasal swab collected by the participant at home.
- At ARI Day 29 (±7 days), participants will be asked to return to the site where a blood sample will be drawn for seroconfirmation and exploration of biomarkers that correlate with RSV infection and RSV disease severity. A qualified member of the study staff will measure vital signs, including body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation. A clinical assessment (including a targeted physical examination) will be performed by qualified study staff, preferably by a physician, physician assistant, nurse practitioner or equivalent, and the Lawton-Brody IADL assessment and MRU questionnaire will be completed based on interview with the participant. Participants will complete all 4 scales of the RiiQ questionnaire, and each of the PGI scales and the Return to Usual Health question on the site's eDevice.

For all medically attended ARIs, including those resulting in hospitalization, a standard question list will be provided, with the aim to collect additional information (Attachment 12) on any other diagnostics (eg, chest x-rays, spirometry, pulmonary function tests, etc.) or interventions during the clinical course of the ARI. Every effort should be made to collect data on the clinical course of ARIs, including information on hospitalization, oxygenation status, supplemental oxygen requirements and specific drug treatments, as well as other concurrent respiratory illness present at the time of symptom onset and up to symptom resolution. If an expected eDiary recording has been missed by a participant, a member of the staff should contact the participant the next morning to confirm that eDiaries are being completed as required. Telephone calls to or telemedicine contacts with the participants to facilitate compliance with the study procedures between study visits are encouraged.

For participants who experience symptoms suggesting an ARI episode, RT-PCR assay of the midturbinate nasal swabs and sputum sample (when available) taken after symptom onset will be used to determine whether the infection was caused by RSV[a]. If at least one of these samples is positive for RSV, the collected information will be applied against the clinical case definitions for RSV-mediated LRTD. For participants hospitalized with symptoms of an ARI, confirmation of RSV infection using a Food and Drug Administration (FDA)-approved RT-PCR test at the local (hospital) laboratory will also be obtained.

Site staff and participants will remain blinded as to the outcome of the RT-PCR test results until study unblinding, but participants and their routine health care professional (HCP) can obtain external diagnostics, including RSV RT-PCR, as medically needed.

Collection of ARI data by the study site will be ceased for that particular episode if a participant has tested positive for SARS-CoV-2 (by a local test that is FDA-approved or by central laboratory PCR).

Immunogenicity

Blood will be collected from all participants for humoral immunogenicity assessments before vaccination on Day 1, and 14 days and 1 year after vaccination on Day 1. These samples will be used for humoral immunogenicity assessments for participants experiencing an ARI episode during the RSV season.

For participants in the Immuno Subset, blood will be collected for analysis of humoral and cellular immune responses before vaccination on Day 1, and at 14 days, 84 days, 24 weeks, 1 year, 18 months, 24 months, and 30 months after vaccination on Day 1.

For participants in the Revaccination Subcohorts, blood will be collected for analysis of humoral and cellular immune responses before and at different time points after revaccination as indicated in the Schedules of Activities for the Revaccination Subcohorts.

Nasosorption samples using synthetic absorptive matrix (SAM) will be taken from Immuno Subset participants prior to vaccination on Day 1 and at the 14-day post-vaccination visit.

Blood samples collected between 2 and 4 days after symptom onset (ARI Days 3-5) and at 28 days after symptom onset (ARI Day 29) from participants who experience ARI episodes will be assayed by serology for RSV exposure confirmation. These samples will also be used for exploration of biomarkers that correlate with RSV infection and RSV disease severity (including but not limited to RT-PCR for RSV, RNA transcriptomics to assess regulation of genes [clusters] and expression patterns, cytokine/chemokine analysis as available and applicable). Additionally, these samples might be used for other pathogen exposure seroconfirmation.

[a] For some secondary and exploratory endpoints, the determination will be made by serology.

Over the entire study, the total blood volume to be collected from each participant in the Immuno Subset will be approximately 220 mL when the study does not progress beyond the first year, 330 mL when the study is continued beyond the first year, and 440 mL when the study is continued beyond the second year. For all other participants in Cohort 1 who are not included in a Revaccination Subcohort, the total blood volume to be collected will be 30 mL when the study does not progress beyond the first year, 45 mL when the study is continued beyond the first year, and 60 mL when the study is continued beyond the second year.

For participants in the Revaccination Subcohorts, the total blood volume to be collected from each participant will be: Revaccination Subcohort 1A and 2A: 120 mL and 490 mL, respectively; Revaccination Subcohort 1B and 2B: 430 mL and 755 mL, respectively; and Revaccination Subcohort 1C and 2C: 160 mL (360 mL in a subset of approximately 100 participants).

For participants in Cohort 2, the total blood volume to be collected will be 30 mL.

The maximum volume of blood to be drawn at any given visit would be 55 mL for participants in the Immuno Subset, 15 mL for all other participants in Cohort 1 who are not included in a Revaccination Subcohort, and 62.5 mL for participants in the Revaccination Subcohorts.

During each ARI episode, 40 mL additional blood will be sampled.

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

Safety

All participants

All participants will be closely observed for a minimum of 30 minutes after vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator.

A full physical examination, including body weight, will be carried out before each vaccination. Height will be measured on Day 1 only.

For all participants, SAEs will be collected from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later).[a]

For all participants, some subsets of SAEs will be collected for additional study periods[a]:

- ARIs and complications related to ARIs that classify as SAEs will be captured and will be reported as SAEs in the eCRF for the duration of the second RSV season, between the second and the third RSV season, and for the duration of the third RSV season.

[a] The windows for SAE collection in the Revaccination Subcohorts are described below under "Safety Subset and Revaccination Subcohorts".

- From the time of vaccination (Day 1) until the end of the study period for each participant, SAEs classified as related to the study vaccine, SAEs resulting in death, and (S)AEs leading to discontinuation from the study will be collected.
- During the entire study, (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated informed consent form (ICF) is obtained onwards until the end of the study period for each participant.

The (S)AE listing in the eCRF will not be updated based on the RSV RT-PCR results and will remain listed on the eCRF as ARIs.

Safety Subset and Revaccination Subcohorts

The following additional procedures will be carried out in participants in the Safety Subset following vaccination on Day 1, and in the Revaccination Subcohorts following revaccination on Day 365 (Month 12)/Day 730 (Month 24)/Day 1,095 (Month 36), as described below:

- Any unsolicited, solicited local or solicited systemic AEs will be documented in the eCRF by study-site personnel following the 30-minutes observation period. In addition, vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the AE page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature
- Participants will be instructed how to properly record solicited AEs in their eDiary. Each participant will record solicited local (at the injection site) AEs, solicited systemic AEs, and body temperatures in the eDiary, beginning on the evening of the vaccine dosing day and on a daily basis for the following 7 days. Body temperatures (oral route preferred) should be taken at approximately the same time each day. Study-site personnel will review the participant's eDiary and complete the eCRF where appropriate. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.
- All other (unsolicited) AEs and special reporting situations will be collected from the time of vaccine administration through the following 28 days. AEs, including any that are ongoing at 28 days after vaccine administration will be followed until clinical resolution or stabilization. Concomitant therapies associated with unsolicited AEs will be collected and recorded in the eCRF from the time of vaccine administration through 28 days after vaccination. Safety Subset participants will be contacted by telephone or telemedicine contact at 28 days after vaccination to collect information on unsolicited AEs and associated concomitant medications. For participants in the Revaccination Subcohorts, this information will be collected at the 28-day post-revaccination visit.
- All ARIs and all complications related to ARIs will be reported in the eCRF as AEs from the time of vaccination through the following 28 days.

For Revaccination Subcohort A, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from the time of revaccination at Month 12 until the end of the second RSV season, or until 6 months after revaccination, whichever comes later. For Revaccination Subcohort 2A, all

SAEs and AESIs will also be collected from the time of revaccination on Day 730 until 6 months after revaccination. For Revaccination Subcohorts B and C, all SAEs and AESIs will be collected from the time of revaccination until 6 months thereafter. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season for Subcohort A, on Day 730 (Month 24) for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

For all Revaccination Subcohorts, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs leading to discontinuation from the study, and (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be collected during the entire study for all participants. For the participants in the Revaccination Subcohort C, these (S)AEs will be collected retrospectively for the time period between the last end of the RSV season visit and the revaccination upon the day of revaccination.

Medical Resource Utilization

Medical resource utilization data will be collected. Refer to Section 9.2.3, Medical Resource Utilization for details.

9.1.2. Visit Windows

For the following visits, windows will be allowed as indicated in Table 3.

Note that Table 3 applies to the Cohort 1 participants who are not included in a Revaccination Subcohort. The windows for participants in a Revaccination Subcohort are provided in the Schedules of Activities for the Revaccination Subcohorts.

Table 3: Visit Windows for Cohort 1 Participants Not Included in a Revaccination Subcohort

Clinic Visit #	Visit Day/ Visit Week	Visit Window	Primary Purpose
2	15/ 2	+ 3 days	14 days after vaccination, Safety and Immuno visit
2a	29/ 4	+ 3 days	28 days after vaccination, Safety visit, by telephone or telemedicine contact
2b	85/ 12	± 7 days	84 days after vaccination, Immuno visit
2c	169/ 24	± 14 days	24 weeks after vaccination, Immuno visit
3		+ 35 days	End of the first RSV season visit, by telephone or telemedicine contact (For Immuno Subset participants, where the timing of Visit 2c and Visit 3 overlap, procedures can be combined)
4	365/ 52	± 2 months	12 months after vaccination, Safety and Immuno visit
5	533/ 76	± 14 days	18 months after vaccination, Immuno visit

Clinic Visit #	Visit Day/ Visit Week	Visit Window	Primary Purpose
6		-7/+14 days	End of the second RSV season visit, by telephone or telemedicine contact (For Immuno Subset participants, where the timing of Visit 5 and Visit 6 overlap, procedures can be combined)
7	730/ 104	± 2 months	24 months after vaccination, Safety and Immuno visit
8	912/ 130	± 14 days	30 months after vaccination, Immuno visit
9		-7/+14 days	End of the third RSV season visit, by telephone or telemedicine contact (For Immuno Subset participants, where the timing of Visit 8 and Visit 9 overlap, procedures can be combined)

Visits 4 to 6 will only take place when the study progresses beyond the first year. Visits 7 to 9 will only take place when the study progresses beyond the second year.

Visit 2a is for Safety Subset participants only. Visits 2b, 2c, 5, and 8 are for Immuno Subset participants only.

9.1.3. Screening/Randomization and Vaccination (Day 1)

Only participants in good or stable health without acute illness or fever and complying with the inclusion and exclusion criteria specified in Section 4 will be included into the study. Screening may be split into 2 visits after consultation with the sponsor. Every effort should be made for split visits to occur within 3 to 5 days.

The investigator will provide detailed information on the study to the participants and will obtain written informed consent prior to each participant's participation in the study. All procedures described in the Schedule of Activities will only take place after written informed consent has been obtained.

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

- Physical examination including height and weight.
- Demographic information.
- Medical history, including social history (eg, smoking history).
- Medical conditions of interest, including medical conditions that place participants at increased risk for severe RSV disease and information needed to calculate the frailty index score.
- Review of pre-study medications administered up to 30 days before vaccination; any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after study vaccination.
- Review of inclusion/exclusion criteria.

- Clinical assessment (Attachment 3), including vital signs measurement (respiratory rate, heart rate, supine systolic and diastolic blood pressure, oxygen saturation and body temperature).
- After medical history, vital signs, and physical examination findings have been reviewed for completeness and adherence to inclusion and exclusion criteria, the participant can be deemed eligible for the study and randomized as described in Section 5.
- The RiiQ questionnaire (Attachment 6), the PGI-H (Attachment 7), and the Lawton-Brody IADL questionnaire (Attachment 8) will be completed and baseline MRU data (Attachment 9) will be collected prior to vaccination.
- Pre-dose blood samples for baseline immunogenicity will be collected.
- A nasosorption sample will be collected for participants in the Immuno Subset.
- Administration of study vaccine according to Table 2.

If a participant is a screen failure but at some point in the future is expected to meet the eligibility criteria, the participant may be rescreened on one occasion only. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.

Participants will be closely observed for a minimum of 30 minutes post vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. For Safety Subset participants, any unsolicited, solicited local or solicited systemic AEs will be documented in the eCRF by study-site personnel following this observation period and vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the adverse event page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.

Participants will receive eDiary training. Participants will be provided with a thermometer and a midturbinate nasal swab kit, and will be trained when and how to collect a swab at home, and how to use a thermometer if they experience any symptoms that could indicate an ARI. Participants in the Safety Subset will additionally be provided with a ruler.

9.1.4. Post-Vaccination Follow-up After Vaccination on Day 1

Visit 2 (14 Days After Vaccination)

- Check for seasonal influenza vaccination; any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after study vaccination.
- Blood samples for immunogenicity will be collected.
- The study staff will review the solicited local and systemic AEs collected via the eDiaries from participants in the Safety Subset.
- For participants in the Immuno Subset, a nasosorption sample will be collected at Visit 2.

Participants will also receive repeat eDiary training, if needed. Participants will also be re-trained when and how to collect a midturbinate nasal swab.

Visits 2a at 28 days post-vaccination will be a telephone call to collect information on unsolicited AEs (for Safety Subset participants only).

The additional visits (**Visit 2b** at 84 days after vaccination and **Visit 2c** at 24 weeks after vaccination) are for Immuno Subset participants only to collect blood samples for immunogenicity assessments to further characterize the vaccine-elicited humoral and cellular immune responses.

End of First RSV Season

At the end of the first RSV season, the study-site personnel will contact the participants by telephone, and read aloud the questions of the Lawton-Brody IADL (Attachment 8) questionnaire to the participant and record the participant's responses on the site's eDevice. The participant will complete the RiiQ questionnaire (Attachment 6) and the PGI-H (Attachment 7) in the eDiary or by telephone interview with the study site. Participants who were provided an eDevice to complete assessments at home during the first RSV season will be instructed to store their eDevice at a safe place at home in preparation of the second season. At the end of the first RSV season, each study participant will also be invited to complete an IEC/IRB approved Experience Survey, to share to his/her experience as a volunteer in this study. The responses will be collected by an external party and anonymously provided to the sponsor.

Day 365 (Month 12)

The study progression beyond the first year is conditional on results obtained at the end of the first NH RSV season (see Section 11.12). In the event that the study continues beyond the first NH RSV season, all ongoing participants will be followed up during a second RSV season. The study progression beyond the second year is conditional on results obtained at the end of the second NH RSV season (see Section 11.12). In the event that the study continues beyond the second NH RSV season, all ongoing participants will be followed up during a third RSV season. For the participants who do not receive a revaccination on Day 365, the following evaluations will be performed:

- Verification of selected eligibility criteria (see Schedule of Activities Cohort 1 (N 5,800), footnote t).
- A full physical examination, except height measurement, will be performed.
- Medical conditions of interest, including medical conditions that place participants at increased risk for severe RSV disease and information needed to calculate the frailty index score will be re-assessed.
- Changes in the use of any concomitant medication since the last visit should be recorded and any seasonal influenza vaccination and SARS-CoV-2 vaccination.
- Clinical assessment (Attachment 3), including vital signs measurement (respiratory rate, heart rate, supine systolic and diastolic blood pressure, oxygen saturation and body temperature).

- The RiiQ questionnaire (Attachment 6), the PGI-H (Attachment 7), and the Lawton-Brody IADL questionnaire (Attachment 8) will be completed and baseline MRU data (Attachment 9) will be collected.
- Blood samples for immunogenicity will be collected.

Participants will receive repeat eDiary training. Participants will also be provided with a midturbinate nasal swab kit (and a thermometer, if needed), will be re-trained when and how to collect a swab at home, and how to use a thermometer if they experience any symptoms that could indicate an ARI.

Note: Per Amendment 4 and Amendment 5, Schedule of Activities Cohort 1 (N 5,800) is for all participants who do not receive a revaccination. Procedures and assessments for the Revaccination Subcohorts are described in separate Schedules of Activities for the Revaccination Subcohorts.

End of Second RSV Season

At the end of the second RSV season, the RiiQ questionnaire (Attachment 6), the PGI-H (Attachment 7), and the Lawton-Brody IADL questionnaire (Attachment 8) will be completed on site.

End of Third RSV Season

At the end of the third RSV season, study-site personnel will contact the participants by telephone or telemedicine contact, and read aloud the questions of the Lawton-Brody IADL (Attachment 8) questionnaire to the participant and record the participant's responses on the site's eDevice. The participant will complete the RiiQ questionnaire (Attachment 6) and the PGI-H (Attachment 7) in the eDiary or by telephone or telemedicine interview with the study site. Participants who were provided an eDevice to complete assessments at home during the first RSV season will be instructed to return the eDevice to the site. Participants using their own eDevice will be instructed to delete the app from their personal device.

All SAEs will be reported continuously from vaccination on Day 1 until the end of the first RSV season, from the Day 365 (Month 12) visit until the end of the second RSV season, and from the Day 730 (Month 24) visit until the end of the third RSV season. SAEs associated with ARIs and complications related to ARIs that classify as SAEs will also be collected from the end of the second RSV season until the Day 730 visit.

9.1.5. Revaccination Subcohorts

Participants who provide separate informed consent for participation in a Revaccination Subcohort will follow the procedures and assessments as indicated in the Schedules of Activities for Revaccination Subcohorts.

The following evaluations will be performed:

Revaccination (Visits at Day 365 [Month 12]/Day 730 [Month 24]/Day 1,095 [Month 36], as applicable per Revaccination Subcohort)

- Verification of selected eligibility criteria.
- Medical conditions of interest, including medical conditions that place participants at increased risk for severe RSV disease and information needed to calculate the frailty index score will be re-assessed.
- Review of concomitant medications used since the last visit; any seasonal influenza vaccination must occur at least 14 days before or at least 14 days after study vaccination; live-attenuated SARS-CoV-2 vaccination must occur at least 28 days before or at least 28 days after study vaccination; non-live SARS-CoV-2 vaccination must occur at least 14 days before or at least 14 days after study vaccination; and viral-vectored SARS-CoV-2 vaccination must occur at least 28 days before or at least 28 days after study vaccination.
- A full physical examination, except height measurement, will be performed.
- Clinical assessment (Attachment 3), including vital signs measurement (respiratory rate, heart rate, supine systolic and diastolic blood pressure, oxygen saturation and body temperature).
- Check for any contraindications to revaccination, including symptoms of an acute illness or body temperature ≥38.0°C.
- The RiiQ questionnaire (Attachment 6), the PGI-H (Attachment 7), and the Lawton-Brody IADL questionnaire (Attachment 8) will be completed and baseline MRU data (Attachment 9) will be collected prior to revaccination (Day 365 only for Revaccination Subcohorts A and B; Day 365 and Day 730 only for Revaccination Subcohort C).
- Blood samples for immunogenicity will be collected prior to revaccination.
- Administration of active study vaccine according to Table 2.

Revaccination Subcohort participants will be closely observed for a minimum of 30 minutes post revaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or solicited systemic AEs will be documented in the eCRF by study-site personnel following this observation period and vital signs (body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation) will be obtained at the end of the observation period. Any clinically relevant abnormalities must be recorded on the AE page of the eCRF. Actual values (normal and abnormal) will only be documented in the eCRF for body temperature.

Revaccination Subcohort participants will receive repeat eDiary training, including how to record solicited local and systemic AEs and unsolicited AEs in the eDiary. Revaccination Subcohort participants will also be provided with a ruler, a thermometer, and a midturbinate nasal swab kit (as applicable per Revaccination Subcohort), and will be trained when and how to collect a swab at home, and how to use a thermometer if they experience any symptoms that could indicate an ARI.

Post-revaccination Visits

Post-revaccination visits are scheduled at the following time points:

- 7 days after revaccination at Month 24: for Revaccination Subcohort 2A
- 7 days after revaccination at Months 24 and 36: for Revaccination Subcohort B
- 14, 28 and 84 days after (each) revaccination: for Revaccination Subcohorts A, B, and C
- 24 weeks after (each) revaccination: for Revaccination Subcohorts A, B, and C
- 1 year after (each) revaccination: for Revaccination Subcohorts A, B, and C

At each post-revaccination visit, blood samples will be drawn for immunogenicity and information on unsolicited AEs will be collected until 28 days post dose. The solicited local and systemic AEs collected in the diaries will be reviewed by the study staff at the post-revaccination visits at 7 or 14 days after revaccination.

For Revaccination Subcohort A, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from the time of revaccination at Month 12 until the end of the second RSV season, or until 6 months after revaccination, whichever comes later. For Revaccination Subcohort 2A, all SAEs and AESIs will also be collected from the time of revaccination on Day 730 until 6 months after revaccination. For Revaccination Subcohorts B and C, all SAEs and AESIs will be collected from the time of revaccination until 6 months thereafter. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season for Subcohort A, on Day 730 (Month 24) for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

For all Revaccination Subcohorts, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs leading to discontinuation from the study, and (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be collected during the entire study for all participants. For the participants in the Revaccination Subcohort C, these (S)AEs will be collected retrospectively for the time period between the last end of the RSV season visit and the revaccination upon the day of revaccination.

9.1.6. Early Withdrawal – Early Exit Visit

For those participants who are unable to continue participation in the study until the final visit, but who do not withdraw consent, an early exit visit will be conducted. In the event of early withdrawal from the study, all procedures as required at the end of the RSV season (see Section 9.1.4 and Section 9.1.5) will be performed.

The early exit visit will be conducted by telephone or telemedicine contact.

9.2. Study Evaluations

9.2.1. Efficacy Evaluations

This is a proof-of-concept study to test VE. The vaccine is not expected to be 100% efficacious.

VE will be evaluated based on the first occurrence of RT-PCR-confirmed RSV-mediated LRTD (cases defined according to the 3 primary endpoint definitions) in the active vaccine group compared to the placebo group in the PPE population. Time at risk will also be taken into account.

To meet the primary endpoint according to the respective case definitions the following criteria will be taken into account:

- symptoms reported by participants on the RiiQ Symptom Scale and body temperature during the full ARI episode OR
- clinical assessment terms reported by a qualified study staff member during the ARI Days 3-5 clinical visit

  in combination with

- confirmation of RSV by RT-PCR in one or more of the midturbinate nasal swabs, or in the sputum sample (when available)

Of note, on the day of the ARI Days 3-5 clinical visit, the case definitions can be met by symptoms reported by participants on the RiiQ or by signs and symptoms reported by the qualified study staff member. Case definitions cannot be met by a combination of symptoms reported by the participant with signs and symptoms reported by the qualified study staff member.

Confirmation of RSV infection by RT-PCR (midturbinate swabs and sputum sample, when available) will be performed at the central laboratory. For participants hospitalized with symptoms of an ARI, confirmation of RSV infection using an FDA-approved RT-PCR test at the local (hospital) laboratory will also be used for the analysis of case definitions if results from the central laboratory are not available. One positive sample (defined as any sample with a value above the limit of detection) is sufficient.

9.2.1.1. Patient-Reported Outcomes

Participants in this study will complete self-assessments of their health, symptoms, and functional status in questionnaires on an eDevice (smartphone or tablet). During study visits, participants complete questionnaires on the site's eDevice. For ARI surveillance, participants complete questionnaires at home in an eDiary on their own eDevice or one provided for this study. In each case of portal/eDevice down time, data can only be collected upon sponsor approval via interview using paper versions of the questionnaires.

Timing for these ePRO assessments are described in the Schedule of Activities. Use of ePRO has been linked to many improvements in the quality, completeness, and adherence to assessment times required for PRO assessments in clinical studies.[25]

Requirements for investigators and study monitors will be detailed in separate documents.

9.2.1.1.1. ARI Surveillance Assessment

During the vaccination visits and Day 365 (Month 12)/Day 730 (Month 24) visits, as applicable, sites will instruct participants to report any new or worsening of usual cold-like symptoms in the eDiary on their eDevice at home. A reminder to complete the ARI Surveillance Assessment (Attachment 4) will be sent to the participants' eDevice twice a week during the periods of ARI data collection, to maintain awareness among participants that they should report any symptoms that could indicate an ARI episode in the eDiary within 24 hours of onset.

For participants in the Revaccination Subcohorts, follow-up of ARIs will stop at the end of the second RSV season for Subcohort A, at the Day 730 (Month 24) visit for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

If the participant indicates no new symptoms or no worsening of symptoms present at baseline in response to the ARI surveillance question, the eDiary reminds the participant to contact the site in case of any possible (S)AE and the ARI Surveillance assessment ends.

If the participant indicates a new symptom or worsening of existing symptoms possibly indicating an ARI episode, the eDiary will present the following for the participant to complete before ending the eDiary assessment and reminding the participant to contact the site in case of any possible (S)AE: RiiQ (Attachment 5), RiiQ Impact on Daily Activities Scale (Attachment 11, as part of the Combined Impact Assessment), PGI-H, PGI-S, PGI-C, Return to Usual Health question (Attachment 7, as part of the Combined Impact Assessment), and temperature log. Note that the PGI-C and the Return to Usual Health question will not be completed on ARI Day 1.

9.2.1.1.2. Respiratory Infection Intensity and Impact Questionnaire (RiiQ™v2)

The RiiQ will be used to identify possible ARI episodes, to define cases of RSV-mediated LRTD (for participants with RT-PCR confirmed RSV infection), to evaluate severity of RSV disease episodes, and to assess the impact of an ARI episode on the participant's daily life (Attachment 6). The RiiQ was adapted for RSV based on the Flu-iiQ™ originally developed and validated for monitoring influenza symptoms and their impact in vaccine studies.[22,29] The RiiQ includes 3 additional lower respiratory tract symptoms common in patients with RSV-related illness and one additional daily activity item to address limitations in opportunity for activity for patients hospitalized for treatment of RSV disease.

The RiiQ asks participants to rate level of severity or impairment on a 4-point scale with higher scores indicating greater severity or negative impact of an ARI episode. Questions ask participants to report symptoms at their worst during the past 24 hours to monitor the severity of RVS-related illness, but also identify pre-existing symptoms and functional limitations at baseline associated with comorbidities common in adults at risk for more severe illness due to RSV infection.

The RiiQ consists of 4 scales that are scored separately:

- RiiQ Symptom Scale captures presence and severity of 13 symptoms commonly reported by adults with RSV infection. The symptoms reported on the RiiQ symptom scale will be used to define cases of RSV-mediated LRTD for participants whose ARI episode has been confirmed as due to RSV infection via RT-PCR.
- RiiQ Impact Scales (Questions 2 to 4). The RiiQ also assesses health-related quality of life (HRQL) associated with RSV-related disease in 3 impact scales:

  RiiQ Impact on Daily Activity scale (Question 2) asks participants to rate degree of impairment they have in 7 common daily activities such as trouble concentrating or ability to do usual activities.

  RiiQ Impact on Emotions scale (Question 3) asks participants to rate the degree to which they felt 4 negative emotions - Irritable, Helpless, Worried, and Frustrated.

  RiiQ Impact on Relationships scale (Question 4) asks participants to rate the degree to which they were concerned about 5 problems that a respiratory infection may cause in relationships with others, such as being a burden, causing worry or annoyance, and dependence on others.

9.2.1.1.3. Patient Global Impression Scores

Patient Global Impression Scores (Attachment 7) developed for this study will be collected. These questions will be used to evaluate overall health and to help identify how much change in RiiQ scale scores can be considered clinically important.

- PGI-H asks participants to report their overall impression of their health status today.
- PGI-S asks participants experiencing symptoms associated with ARI episodes to rate the severity of their respiratory illness.
- PGI-C asks participants to rate the amount of change in their health each day during an ARI episode.*
- Return to Usual Health asks participants whether they have returned to their usual health after developing symptoms suggesting an ARI.*

* The PGI-C and the Return to Usual Health question will not be completed on ARI Day 1.

9.2.1.1.4. Thermometer Logs

Participants who experience symptoms suggestive of an ARI also will record readings from thermometers provided for this study as part of the ARI Surveillance eDiary assessment (Attachment 4) each evening (preferably) throughout each ARI episode.

9.2.1.2. Lawton-Brody Instrumental Activities of Daily Living (IADL) Scale

The Lawton-Brody IADL Scale (Attachment 8) will be used in this study to evaluate the participant's functional status.[18] The questionnaire will be completed (based on interview with the participant) at baseline (assessed pre-vaccination for the first RSV season, at the Day 365 [Month 12] visit for the second RSV season [pre-vaccination if applicable], and at the Day 730

[Month 24] visit for the third RSV season), during ARI episodes on ARI Days 3-5 and ARI Day 29, and at the end of the RSV seasons.

The questionnaire covers 8 domains (ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and ability to handle finances). Within each domain, participants are scored according to their highest level of functioning in that domain (either 0 or 1).

9.2.1.3. Frailty Index Score

The frailty index score will be calculated from medical conditions of interest, the RiiQ, and the Lawton-Brody IADL.

The medical conditions of interest used for the calculation of the frailty index score will include, but not be limited to, endocrine (diabetes mellitus), cardiac (angina, arrhythmia, valvular, previous myocardial infarction [MI], congestive heart failure), vascular (peripheral vascular, hyperlipidemia, hypertension, cerebrovascular (stroke, transient ischemic attack [TIA]), pulmonary (eg, asthma, COPD), renal (chronic renal failure, nephrotic syndrome), neuro-muscular (seizure disorder, spinal cord injury, Parkinson's), liver (hepatic cirrhosis), gastrointestinal (inflammatory bowel disease [Crohn's, ulcerative colitis], peptic ulcer, gastroesophageal reflux disease [GERD]), cancer (non-metastatic solid tumor), mental health (depression, anxiety, bipolar mood disorder).

9.2.1.4. Clinical Assessment

At baseline, and between 2 and 4 days after symptom onset (ARI Days 3-5) and at ARI Day 29, a study staff member will perform a clinical assessment (Attachment 3):

- Vital signs: body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation measurement.
- Symptom collection and targeted physical examination: cough, sputum production, shortness of breath, and malaise (tiredness)
- Upper respiratory: nasal discharge, pharyngitis, and sinus tenderness
- Lower respiratory: dyspnea, rales, rhonchi or other, wheezing, and respiratory effort

9.2.1.5. Diagnosis of RSV and Other Respiratory Infections

The midturbinate nasal swabs and a sputum sample (when available), taken after symptom onset will be analyzed at the central laboratory using a rapid RT-PCR based diagnostic assay to determine whether the infection was caused by RSV. For RSV positive cases, the RSV subtype, viral load and presence of other respiratory pathogens will also be determined from the midturbinate nasal swabs using a broad respiratory pathogen panels. Samples from RSV negative ARI episodes may also be assessed for the presence of other respiratory pathogens. Midturbinate nasal swabs from other ARI episodes may also be assessed for the presence of other respiratory pathogens.

Site staff and participants will remain blinded as to the outcome of RT-PCR test results until study unblinding.

For participants hospitalized with symptoms of an ARI, confirmation of RSV infection using an FDA-approved RT-PCR test at the local (hospital) laboratory will also be obtained.

9.2.2. Immunogenicity Evaluations

Venous blood samples of approximately 15 mL and 40 mL will be collected for the determination of humoral and cellular immune responses, respectively. Timings of blood draws are specified in the Schedule of Activities. Sample collection and processing will be performed according to current versions of approved standard operating procedures.

Immunogenicity assessments may include, but are not limited to, the humoral and cellular immunogenicity assays (as available and applicable) summarized in Table 4 and Table 5 below.

Humoral immune responses will be assessed in participants experiencing an ARI episode, participants in the Immuno Subset (ie, 200 randomized participants, 100 per group), and participants in the Revaccination Subcohorts (ie, approximately 240 participants, 120 per group [Revaccination Subcohorts A and C]; or approximately 270 participants, 135 per group [Revaccination Subcohort B]).

Cellular immune responses will be assessed in the Immuno Subset and in all participants (at certified sites) in Revaccination Subcohort 2A after the third vaccination and in Revaccination Subcohort B after the second and third vaccination. Cellular immune responses will be assessed in a subset of approximately 100 participants (approximately 50 per group) in Revaccination Subcohort C.

Table 4: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Secondary endpoints	
RSV neutralization A	Analysis of neutralizing antibodies to an A strain
F protein antibodies (ELISA; pre-F and/or post-F)	Analysis of antibodies binding to RSV F protein in pre-fusion and/or post-fusion form
Exploratory endpoints	
RSV strain cross-neutralization	Analysis of cross-neutralizing antibodies to B and/or a different A strain(s)
F protein antibody specificity characterization	Pre- and post-F specificity by binding or functional assays such as ELISA, and/or competition ELISA. Adsorption of serum with pre-F and post-F protein before any antibody assay, epitope mapping, functional VNAs
G protein antibodies (ELISA)	Analysis of antibodies binding to RSV G protein
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including, but not limited to, ADCC, ADCP, avidity, other respiratory viral neutralizing or binding assays, Ig isotype, functional VNAs to other respiratory viruses, and antibody assessments for antibody repertoire
Transcriptomic analysis	RNA transcriptomic analysis maybe conducted in the revaccination subcohorts to assess regulation of genes (clusters) and expression patterns

ADCC =antibody dependent cell mediated cytotoxicity, ADCP =antibody dependent cellular phagocytosis, ELISA =enzyme linked immunosorbent assay, F =fusion, G =glycoprotein, Ig =immunoglobulin, RNA =ribonucleic acid; VNA =virus neutralizing antibody
Note: Antibody analyses might be performed in nasosorption samples and serum.
The abovementioned assays may be performed on samples of the Revaccination Subcohorts to assess exploratory endpoints.

Table 5: Summary of Immunogenicity Assays (Cellular)

Assay	Purpose
Secondary endpoints	
IFN-γ ELISpot	T-cell IFN-γ responses to RSV F protein peptides
Exploratory endpoints	
ICS	Analysis of T-cell responses to RSV F protein peptide-stimulated PBMC (including, but not limited to, $CD4^+/CD8^+$, IL-2, IFN-γ, TNF-α, activation markers and memory)
Chemokine/cytokine analysis	Levels of chemokines and cytokines in nasosorption samples or produced by antigen-stimulated PBMC
Sequencing of B-cells	Including but not limited to sequencing of BCR (B-cell receptor) or VH/VL (heavy/light chain characterization) for specificity

ELISpot =enzyme linked immunospot, F =fusion; ICS =intracellular cytokine staining, IFN γ =interferon gamma, IL 2 =interleukin 2, PBMC =peripheral blood mononuclear cells, TNF α =tumor necrosis factor alpha

Nasosorption samples using SAM taken from Immuno Subset participants prior to vaccination on Day 1 and at the 14 days post-vaccination visit will be used for immunogenicity assessments including, but not limited to immunogenicity assessments of antigen specific immunoglobulins (IgG and IgA), microbiome and pathogen analysis.

Blood samples collected between 2 and 4 days after symptom onset (ARI Days 3-5) and at 28 days after symptom onset (ARI Day 29) from participants who experience ARI episodes will be assayed by serology (including but not limited to RSV VNAs or ELISA specific to RSV protein G [glycoprotein] as available and applicable) for RSV exposure confirmation. In addition, blood samples collected at ARI Day 3-5 including DNA and RNA preserved blood samples will be used for exploration of biomarkers that correlate with RSV infection and RSV disease severity

(including but not limited to immunoprofiling, RT-PCR for RSV, RNA transcriptomics and host genotyping array to assess regulation of genes [clusters] and expression patterns, associated cytokine/chemokine analysis as available and applicable). Additionally, these samples might be used for other pathogen exposure seroconfirmation.

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

9.2.3. Medical Resource Utilization

Medical resource utilization associated with medical encounters, related to RSV and/or respiratory illness will be collected in the site's eDevice by the investigator and study-site personnel between 2 and 4 days (ARI Days 3-5) and at 28 days after onset of each ARI episode (ARI Day 29 ±7 days) for all participants with an ARI episode. Protocol-mandated procedures, tests, and encounters are excluded. For comparison, baseline data MRU will be collected prior to vaccination for each participant in the study. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and type of medical consultations (including primary care and specialist visits)
- Number and duration of hospital and/or institutional care admissions (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and type of professional home care visits

9.2.4. Safety Evaluations

Details regarding the IDMC are provided in Section 11.13, Independent Data Monitoring Committee.

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

- Adverse Events
- Vital Signs
- Physical Examination
- Patient-reported Outcomes

9.2.4.1. Adverse Events

AEs will be reported as specified in Section 12, Adverse Event Reporting. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

All Participants

For all participants, SAEs will be collected from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later).[a]

For all participants, some subsets of SAEs will be collected for additional study periods[a]:

- ARIs and complications related to ARIs that classify as SAEs will be captured and will be reported as SAEs in the eCRF for the duration of the second RSV season, between the second and the third RSV season, and for the duration of the third RSV season.
- From the time of vaccination until the end of the study period for each participant, SAEs classified as related to the study vaccine, SAEs resulting in death, and (S)AEs leading to discontinuation from the study will be collected.
- During the entire study, (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated informed consent form (ICF) is obtained onwards until the end of the study period for each participant.

The (S)AE listing in the eCRF will not be updated based on the RSV RT-PCR results and will remain listed on the eCRF as ARIs.

Safety Subset and Revaccination Subcohorts

These participants will be asked to note in the eDiary occurrences of injection site pain/tenderness, erythema, and swelling at the study vaccine injection site daily for 7 days post-vaccination (Day 1 for the Safety Subset; Day 365 (Month 12)/Day 730 (Month 24)/Day 1,095 (Month 36) for the Revaccination Subcohorts). 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 Gidudu et al.[11] and in Kohl et al.[17]

Solicited systemic AEs: fatigue, headache, nausea, myalgia, and fever (defined as an endogenous elevation of body temperature ≥38.0°C, as recorded in at least one measurement). Body temperature (oral route preferred) should be measured at approximately the same time each day, preferably in the evening, using the thermometer supplied. If more than one measurement is made on any given day, the highest temperature of that day will be used in the eDiary.

Unsolicited AEs will be collected from the time of vaccine administration through the following 28 days.[b] All AEs, including any that are ongoing at 28 days after vaccine administration will be followed until clinical resolution or stabilization. Concomitant therapies associated with

[a] The windows for SAE collection in the Revaccination Subcohorts are described below under "Safety Subset and Revaccination Subcohorts".

[b] AEs that start more than 28 days after a vaccination, but that are still present at the time of the next vaccination will also be recorded.

unsolicited AEs will be collected and recorded in the eCRF from time of vaccine administration through 28 days after vaccination.

Relatedness and severity of these events will be graded by the investigator according to the criteria presented in Section 12.1.2 and Section 12.1.3, respectively.

All ARIs and all complications related to ARIs will be reported as AEs in the eCRF from the time of vaccination through the following 28 days for Safety Subset and Revaccination Subcohort participants only.

For Revaccination Subcohort A, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from the time of revaccination at Month 12 until the end of the second RSV season, or until 6 months after revaccination, whichever comes later. For Revaccination Subcohort 2A, all SAEs and AESIs will also be collected from the time of revaccination on Day 730 until 6 months after revaccination. For Revaccination Subcohorts B and C, all SAEs and AESIs will be collected from the time of revaccination until 6 months thereafter. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season for Subcohort A, on Day 730 (Month 24) for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

For all Revaccination Subcohorts, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs leading to discontinuation from the study, and (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be collected during the entire study for all participants. For the participants in the Revaccination Subcohort C, these (S)AEs will be collected retrospectively for the time period between the last end of the RSV season visit and the revaccination upon the day of revaccination.

From the time of local approval of protocol amendment 6 onwards, TTS is considered to be an AESI. Thrombotic events and/or thrombocytopenia (defined as platelet count below 150,000 cells/mm³) are considered to be potential AESIs. All AESIs, including potential AESIs, will be reported to the sponsor from the moment of revaccination until 6 months after revaccination.

9.2.4.2. Vital Signs

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

Vital signs measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

The following measurements will be performed:

- Heart rate (beats per minutes), respiratory rate (breaths per minute), supine systolic blood pressure (mmHg) and supine diastolic blood pressure (mmHg)

- Body temperature (oral route preferred, or in accordance with the local standard of care)
- Oxygen saturation (SpO_2)

9.2.4.3. Physical Examination

A full physical examination, including body weight, will be carried out before each vaccination. Height will be measured on Day 1 only.

9.2.4.4. Patient-reported Outcomes

Details for PRO assessments in this study are described in Section 9.2.1.1.

10. PARTICIPANT COMPLETION/DISCONTINUATION OF STUDY INTERVENTION/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A participant will be considered to have completed study vaccination if he or she has received the vaccination on Day 1, or if he or she has received the vaccination on Day 1 and Day 365 (Month 12)/Day 730 (Month 24)/Day 1,095 (Month 36), as applicable, in case of Revaccination Subcohort participants.

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

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

10.2. Discontinuation of Study Vaccine/Withdrawal from the Study

Discontinuation of Study Vaccine

A participant's study vaccination must be discontinued if:

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

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

Withdrawal from the Study

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

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Repeated failure to comply with protocol requirements
- Decision by the sponsor or the investigator to stop or cancel the study
- Decision by local regulatory authorities and IRB/IEC to stop or cancel the study
- If the randomization code is broken by the investigator or the study-site personnel.
  If the randomization code is broken by the sponsor for safety reporting purposes, the participant should not discontinue further study vaccine administration (if applicable) and may remain in the study (if the randomization code is still blinded to the study-site personnel and the participant).

Any unnecessary study discontinuation should be avoided. Should a participant be withdrawn, all efforts should be made to complete and report the observations as thoroughly as possible. Whenever a participant is withdrawn from the study, independent of the reason, all procedures required at the final visit will be performed (see Section 9.1.6) and the major reason for which the participant was withdrawn must be stated. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

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

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study vaccine assigned to the withdrawn participant may not be assigned to another participant. Additional participants will not be entered.

Participants who wish to withdraw consent from participation in the study will be offered a single exit visit for safety follow-up (prior to formal withdrawal of consent). They have the right to refuse.

Withdrawal from the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). 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 ICF.

10.3. Contraindications to Vaccination

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

- Severe acute illness at the time of vaccination.
- Fever (body temperature ≥38.0°C) at the time of vaccination.

If any of these events occur at the scheduled time for administration of study vaccine on Day 1, enrollment at a later date is permitted at the discretion of the investigator and after discussion with the sponsor. In case of occurrence at the time of revaccination, revaccination at a later date is permitted under the same conditions.

11. STATISTICAL METHODS

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

In the following sections, the following terminology is used to describe the different analyses of the primary efficacy endpoints of the study:

An interim analysis (IA) is any analysis performed by the IDMC before the primary analysis. The outcome of an IA can be any of the following:

- "superiority": proof of concept is reached, there is statistically significant proof that the active study vaccine prevents more RT-PCR-confirmed RSV-mediated LRTD compared to placebo (for at least one case definition),
- "futility": it is unlikely that continuing the study will result in statistically significant proof that the active study vaccine prevents more RT-PCR-confirmed RSV-mediated LRTD compared to placebo (for all case definitions),
- "continue": neither superiority nor futility is shown and the study should continue as planned.

The sponsor will remain blinded to the actual results of any IA and will only receive the outcome as described above from the IDMC. Interim analysis can occur at the end of the RSV season (if the required number of RT-PCR-confirmed RSV-mediated LRTD events is not reached[a]). In addition, if participants are also enrolled in the SH, an IA ("early IA") can also occur during the NH or SH RSV season.

The primary analysis is the analysis performed by the sponsor that addresses the primary efficacy objectives of the study. The primary analysis can be triggered in 1 of 3 ways:

- by an IA performed by the IDMC with "superiority" or "futility" as outcome;
- by a predefined number of RT-PCR-confirmed RSV-mediated LRTD events at the end of the first RSV season. The end of the first RSV season is defined as the end of the NH RSV season in case the study is performed in the NH only, and as the end of the SH RSV season in case the study is performed in both hemispheres;
- when the end of the second RSV season is reached (if applicable).

[a] The cut-off of 14 RT-PCR-confirmed RSV-mediated LRTD events at the early IA analysis and the cut-off of 18 RT-PCR-confirmed RSV-mediated LRTD events at the end of the RSV season are based on modelling and simulations described in a separate modeling and simulations report.

In case the primary analysis is triggered by an IA performed by the IDMC, the primary analysis will be performed on the same database as the IDMC to guarantee consistent results.

More information on the planned analyses can be found in Section 11.12.

11.1. Analysis Sets

Vaccination assignment will follow the as-treated principle.

- The Full Analysis Set (FAS) will include all randomized participants with a documented vaccine administration, regardless of the occurrence of protocol deviations. The FAS is the primary safety population. The analysis of solicited and unsolicited AEs after the Day 1 vaccination will be restricted to a subset of the FAS (ie, the Safety Subset).[a] The analysis of solicited and unsolicited AEs after revaccination on Day 365 (Month 12)/Day 730 (Month 24)/Day 1,095 (Month 36) will be restricted to participants of the Revaccination Subcohorts that are part of the FAS.
- The Per-protocol Immunogenicity (PPI) population will include all randomized and vaccinated participants, for whom immunogenicity data are available. Samples taken after a participant experienced a major protocol deviation expecting to impact the immunogenicity outcomes will be excluded from the PPI. The list of major protocol deviations to be excluded from the immunogenicity analysis will be specified in the Statistical Analysis Plan (SAP) or major protocol deviation criteria document which will be finalized before database lock and unblinding. The analysis of immunogenicity will focus on 2 subsets of the PPI, ie, the Immuno Subset and the Revaccination Subcohorts.

  In addition, for participants who experience a natural RSV infection (based on RT-PCR, or other sources), samples taken after the natural infection will not be taken into account in the assessment of the immunogenicity.

  The PPI population is the primary immunogenicity population. For key tables, sensitivity immunogenicity analyses will also be performed on the FAS, including participants for whom immunogenicity measures are available. Excluded samples might be taken into account as well in the sensitivity analysis.
- The Per-protocol Efficacy (PPE) population will include all randomized and vaccinated participants excluding participants with major protocol deviations expecting to impact the efficacy outcomes. The list of major protocol deviations to be excluded from the efficacy analysis will be specified in the SAP or major protocol deviation criteria document which will be finalized before database lock and unblinding. Any participant with an RT-PCR-confirmed RSV-mediated ARI with onset within 14 days after vaccination will be excluded from the PPE population. Participants who discontinue within 14 days after vaccination will be excluded from the PPE population as well.

  The PPE population is the primary efficacy population. Sensitivity efficacy analyses will also be performed on the FAS. For exploratory efficacy analyses focusing on data from the second

[a] The specification of this subset for analysis of solicited and unsolicited AEs does not preclude the investigator from reporting an AE in any participant if he/she considers the event to be of clinical relevance and/or related to the study vaccine.

RSV season only, the participants of Revaccination Subcohort A will be additionally excluded. For analyses focusing on data from the third RSV season, participants of Revaccination Subcohorts A and B will be excluded. For exploratory efficacy analyses focusing on data over 2 RSV seasons, the second RSV season data will be excluded for the participants of Revaccination Subcohort A. For analyses focusing on data over 3 RSV seasons, second and third RSV season data will be excluded for the participants of Revaccination Subcohort A, and third RSV season data will be excluded for participants of Revaccination Subcohort B. Participants who develop major protocol deviations expecting to impact the efficacy outcomes and occurring up to the considered RSV season will be **additionally** excluded from the PPE when focusing on data including the second or third RSV season.

11.2. Sample Size Determination

11.2.1. Efficacy

Under the following assumptions:

- a VE for Case Definition #2 of 70%
- and an incidence of Case Definition #2 of 0.75% in placebo recipients during the RSV season, assuming vaccination occurs before the RSV season
- 3 primary endpoints which are nested (see Section 11.4.1)
- a 1-sided α of 5% (total: as described in Section 11.4.1.1, corrections are performed for multiple endpoints and for IAs outlined in Section 11.12)
- 10% of exclusions (due to drop-out, major protocol deviations, etc.)

Simulations performed in R show that for a NH only study, 2,750 participants per vaccination group result in 80% total power to demonstrate VE >0 for Case Definition #2 at the end of the RSV season, resulting in a total sample size of 5,500 participants. The end of the first RSV season is then defined as the end of the NH RSV season.

In case recruitment is not completed in the NH (and less than 18 RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed in the NH before opening sites in the SH), enrollment will continue in the SH. As there is the possibility to have an early IA during the NH or SH RSV season (see Section 11.12), an additional 150 participants per vaccination group is needed to have 80% total power to demonstrate VE >0 for Case Definition #2 at the end of the RSV season. The end of the first RSV season is defined as the end of the SH RSV season in case the study is performed at both hemispheres. So, if recruitment is spread over 2 hemispheres, the total sample size will be 5,800 participants.

With respect to Case Definitions #1 and #3, further simulations showed that the power to obtain a significant result for any case definition, after multiplicity correction that control the type I error at 5%, tended to be similar or better than for Case Definition #2 alone, without multiplicity correction. This result was valid over a broad range of incidence and vaccine efficacies, unless the VE for the most common case definition (Case Definition #3), was >20% lower than the VE for Case Definition #2. Case Definition #2, which incidence lies between that of Case Definition #1

and #3, was chosen as basis for the power calculations and decision rule, as more prior information was available for this case definition in the literature. Under the assumptions described above, it is expected to observe 26 cases.

Under conditions described in Section 11.12 (less than 18 RT-PCR-confirmed RSV-mediated LRTD events by the end of the first RSV season for Case Definition #2, with a negative IA performed by the IDMC but a conditional power of 60% or more), 2,000 new participants may be vaccinated at the beginning of the second RSV season who will be followed up for one RSV season. This will increase the total power of the study to approximately 82%.

The operating characteristics of the methods used with the sample size are described in a separate modeling and simulations report.

11.2.2. Immuno Subset

Immunogenicity will be assessed in the Immuno Subset, ie, approximately 200 participants, of whom ~100 are active study vaccine participants. Approximately 25% of participants in the Immuno Subset in each region will be at increased risk of severe RSV disease.

Table 6 shows the actual distance from the mean to the limits of 95% CI around the actual value at Day 15 for different assays, accounting for 10% of exclusions with the current sample size for the Immuno Subset.

Table 6: Distance from the Mean to the Limits of 95% CI for Pre-F ELISA, VNA, and ELISpot

		Pre-F ELISA (SD=1.3)		VNA (SD=1.5)		ELISpot (SD=1.2)	
	N (Active Group)	Distance[a] from Mean to Limits 95%CI	95%CI if Observed Mean is eg, 6,000	Distance[a] from Mean to Limits 95%CI	95%CI if Observed Mean is eg, 6,500	Distance[a] from Mean to Limits 95%CI	95%CI if Observed Mean is eg, 400
All	100	0.272	(4,969;7,245)	0.314	(5,229;8,080)	0.251	(336;476)
Increased Risk	25	0.576	(4,025;8,944)	0.665	(4,099;10,306)	0.532	(277;578)

CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, ELISpot = enzyme-linked immunospot, SD = standard deviation, VNA = virus neutralization assay
[a] Calculated on the $\log_2$-scale.

11.2.3. Safety Subset

While mild to moderate vaccine reactions (local injection site, systemic responses) are expected, AEs that preclude further vaccine administration (if applicable) are not anticipated.

With ~350 active study vaccine participants in the Safety Subset, the observation of 0 events in the database would be associated with 95% confidence that the true rate is less than 1%. For SAEs, which will be captured in all participants, the observation of 0 events in the database would be associated with 95% confidence that the true rate is less than 0.1%.

In addition, a cap will be installed to ensure that 350 participants in the Safety Subset (~175 in each group) are at increased risk for severe RSV disease. With 175 active study vaccine

participants at increased risk of severe RSV disease in the Safety Subset, the observation of 0 events (solicited or unsolicited) in the database would be associated with 95% confidence that the true rate in participants at increased risk of severe RSV disease is less than 1.7%.

SAEs will be captured in all participants. Outside the Safety Subset and Immuno Subset, no cap is installed on the number of participants at increased risk of severe RSV disease. It is expected that participants at increased risk for severe RSV disease will represent approximately 30% of the overall population. Assuming that 30% of the participants in the overall population are at increased risk of severe RSV disease (~870 participants), the observation of 0 events in participants at increased risk of severe RSV disease would be associated with 95% confidence that the true rate is less than 0.4%.

Table 7 shows the probabilities of observing at least one AE in one of the arms at given true AE rates in the Safety Subset (overall population and participants at increased risk of severe RSV disease).

Table 7: Probability of Observing at Least One Adverse Event or Serious Adverse Event at a Given True Adverse Event Rate in the Safety Subset

True Adverse Event Rate	Probability of Observing at Least One Adverse Event in N Participants			
	Overall		Increased Risk	
	N=350	N=2,900	N=175	N=870[a]
0.1%	30%	95%	16%	58%
0.5%	83%	100%	58%	99%
1%	97%	100%	83%	100%
2.5%	>99.9%	100%	99%	100%

[a] Approximate number

11.2.4. Revaccination Subcohorts

Immunogenicity

Immunogenicity will also be assessed in participants of the Revaccination Subcohorts, which consist of ~120 participants (Revaccination Subcohorts A and C) or ~135 participants (Revaccination Subcohort B) who received active study vaccine on Day 1 and ~120 participants (Revaccination Subcohorts A and C) or ~135 participants (Revaccination Subcohort B) who received placebo on Day 1 for a total of ~750 participants. All participants in the Revaccination Subcohorts will receive a second vaccination with active study vaccine: on Day 365 (Month 12) (Revaccination Subcohort A), on Day 730 (Month 24) (Revaccination Subcohort B), or on Day 1,095 (Month 36) (Revaccination Subcohort C).

The geometric mean of the titer ratios (GMRs) between Day 15 post first vaccination and Day 15 post second vaccination within a group, as well as the ratio of Day 15 post second vaccination between the 2 groups (active study vaccine versus placebo on Day 1), for the different assays will be calculated.

Table 8 shows the actual distance from the mean to the limits of 95% CI around the ratio between Day 15 post first vaccination and Day 15 post second vaccination within a group for the different assays. The calculations consider an exclusion rate of ~10% from the sample size of revaccinated

participants (~108 participants per group for Revaccination Subcohorts A and C, and ~120 participants per group for Revaccination Subcohort B).

Table 8: Distance From the Mean to the Limits of 95% CI Around the Ratio Between Day 15 Post First Vaccination and Day 15 Post Second Vaccination Within a Group for Pre-F ELISA, VNA A2, and ELISpot

Revaccination Subcohort	Assay	N (per group)	Distance[a] from Mean to Limits 95%CI	95% CI if Observed Ratio is 1
A and C	Pre-F ELISA (SD=1.3)	120	0.248	(0.84;1.19)
	VNA A2 (SD=1.5)	120	0.286	(0.82;1.22)
	ELISpot (SD=1.2)*	50	0.341	(0.79; 1.27)
B	Pre-F ELISA (SD=1.3)	135	0.235	(0.85; 1.18)
	VNA A2 (SD=1.5)	135	0.271	(0.83; 1.21)
	ELISpot (SD=1.2)	135	0.217	(0.86;1.16)

CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, ELISpot = enzyme-linked immunospot (assay), SD = standard deviation, VNA = virus neutralization assay
[a] Calculated on the $\log_2$-scale assuming a correlation of 0.5 between the 2 timepoints.
*: No PBMC samples are taken for Revaccination Subcohort A.

Table 9 shows the actual distance from the mean to the limits of 95% CI around the Day 15 post second vaccination ratio between the 2 groups, for the different assays. The calculations consider an exclusion rate of 10% from the sample size of revaccinated participants (~108 participants per group for Revaccination Subcohorts A and C, and ~120 participants per group for Revaccination Subcohort B).

Table 9: Distance From the Mean to the Limits of 95% CI Around the Ratio on Day 15 Post Second Vaccination Between the 2 Groups for Pre-F ELISA, VNA A2, and ELISpot

Revaccination Subcohort	Assay	N (per group)	Distance[a] from Mean to Limits 95% CI	95% CI if Observed Ratio is 1
A and C	Pre-F ELISA (SD=1.3)	120	0.349	(0.79;1.27)
	VNA (SD=1.5)	120	0.402	(0.76;1.32)
	ELISpot (SD=1.2)*	50	0.476	(0.72; 1.39)
B	Pre-F ELISA (SD=1.3)	135	0.331	(0.79;1.26)
	VNA A2 (SD=1.5)	135	0.381	(0.77; 1.30)
	ELISpot (SD=1.2)	135	0.305	(0.81; 1.24)

CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, ELISpot = enzyme-linked immunospot (assay), SD = standard deviation, VNA = virus neutralization assay
[a] Calculated on the $\log_2$-scale.
*: No PBMC samples are taken for Revaccination Subcohort A.

Safety

With ~240 active study vaccine participants in Revaccination Subcohorts A and C, and ~270 active study vaccine participants in Revaccination Subcohort B, the observation of 0 events in the database would be associated with 95% confidence that the true rate is <1.5%.

Table 10 shows the probabilities of observing at least 1 AE in one of the arms at given true AE rates in the Revaccination Subcohorts.

Table 10: Probability of Observing at Least 1 Adverse Event or Serious Adverse Event at a Given True Adverse Event Rate in the Revaccination Subcohorts

True Adverse Event Rate	Revaccination Subcohorts A and C		Revaccination Subcohort B	
	Overall	Per Group	Overall	Per Group
	N=240[a]	N=120[a]	N=270 [a]	N=135[a]
0.1%	21%	11%	24%	13%
0.5%	70%	45%	74%	49%
1%	91%	70%	93%	74%
2.5%	>99.9%	95%	100%	97%

[a] Approximate number

11.3. Participant Information

For all participants in the FAS, demographic characteristics (eg, age, height, weight, BMI, race, and gender), and other baseline characteristics (eg, physical examination findings, medical history, and concomitant diseases) will be tabulated and summarized with descriptive statistics. Important tables might be repeated for other analysis sets.

11.4. Efficacy Analyses

11.4.1. Primary Efficacy Endpoints

Three primary efficacy endpoints are defined as follows:

- First occurrence of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #1
- First occurrence of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition #2
- First occurrence of RT-PCR-confirmed RSV-mediated LRTD according to Case Definition#3

The case definitions are defined as follows:

Case Definition #1	Case Definition #2	Case Definition #3
≥3 symptoms of LRTI (new onset or worsening)	≥2 symptoms of LRTI (new onset or worsening)	≥2 symptoms of LRTI, *OR* ≥1 symptom of LRTI *combined with* ≥1 systemic symptom (new onset or worsening)

LRTI = lower respiratory tract infection

To meet the primary endpoint according to the respective case definitions the following criteria will be taken into account:

- symptoms reported by participants on the RiiQ Symptom Scale and body temperature during the full ARI episode OR
- clinical assessment terms reported by a qualified study staff member during the ARI Days 3-5 clinical visit

in combination with

- confirmation of RSV by RT-PCR in one or more of the midturbinate nasal swabs, or in the sputum sample (when available)

Of note, on the day of the ARI Days 3-5 clinical visit, the case definitions can be met by symptoms reported by participants on the RiiQ or by signs and symptoms reported by the qualified study staff member. Case definitions cannot be met by a combination of symptoms reported by the participant with signs and symptoms reported by the qualified study staff member.

Confirmation of RSV infection by RT-PCR (midturbinate swabs and sputum sample, when available) will be performed at the central laboratory. For participants hospitalized with symptoms of an ARI, confirmation of RSV infection using an FDA-approved RT-PCR test at the local (hospital) laboratory will also be used for the analysis of case definitions if results from the central laboratory are not available. One positive sample (defined as any sample with a value above the limit of detection) is sufficient.

As a sensitivity analysis, the analysis of the primary endpoint will be repeated, but participants with RSV infection and a co-infection with at least one other respiratory virus (ie, confirmed using an FDA approved RT-PCR test in one or more of the midturbinate nasal swabs, or in the sputum sample, when available) will not be considered as a case for that episode, as the etiology of the symptoms will be indeterminate.

As an additional sensitivity analysis, the analysis of the primary endpoint will be repeated, taking into account only the RT-PCR test results from the central laboratory (ie, excluding the local test results for hospitalized participants).

Presence and severity of symptoms will be collected using participant responses to the RiiQ Symptom Scale and temperature readings participants report in the eDiary each day throughout each ARI episode. On the day of the ARI Days 3-5 clinical visit, signs and symptoms will also be collected by qualified study staff in a clinical assessment.

Table 11: Symptoms of Lower Respiratory Tract Infection and Systemic Symptoms as per RiiQ or Clinical Assessment

	Symptoms from Case Definition	RiiQ Term	Clinical Assessment Term (ARI Days 3-5 Clinical Visit)
Symptoms of LRTI	Cough	Cough	Cough
	Shortness of breath	Short of breath	Dyspnea or decreased oxygen saturation*
	Sputum production	Coughing up phlegm (sputum)	Sputum production
	Wheezing	Wheezing	Wheezing; rhonchi, rales or other sign of consolidation
	Tachypnea**		Tachypnea
Systemic Symptoms	Fatigue	Fatigue (tiredness)	Malaise (tiredness)
	Fever***,****		Fever
	Feverishness****	Feeling feverish	

* Decreased oxygen saturation is defined as oxygen saturation of <90% for participants with a baseline oxygen saturation of ≥90% at randomization; for participants with baseline oxygen saturation <90%, decreased oxygen saturation is defined as a ≥3% decrease in their oxygen saturation from baseline.

** Tachypnea is defined as respiratory rate >20 breaths per minute.
*** Fever (ie, temperature >37.8ºC) will be reported via daily temperature measurement and during ARI Days 3-5 clinical visit.
**** Feeling feverish and fever are considered as 1 symptom.
LRTI =lower respiratory tract infection, RiiQ = Respiratory Infection Intensity and Impact Questionnaire

Symptoms (new onset or worsening) occurring at the same day will be counted. When during ARI Days 3-5, symptoms are reported more than once per day by the participant (eg, on the site's eDevice and in the participant eDiary), the worst severity from the RiiQ will be taken into account. On the day of the ARI Days 3-5 clinical visit, signs and symptoms collected during the clinical assessment by a qualified study staff member will be considered separately from the symptoms reported by the participant on the site's eDevice or in the participant eDiary. A new onset of a symptom is a symptom that is reported during the ARI episode and that was not reported at baseline (defined by pre-dose assessment on the day of vaccination for the first RSV season, the Day 365 [Month 12] visit for the second RSV season [pre-vaccination if applicable], and at the Day 730 [Month 24] visit for the third RSV season). Worsening of a symptom is defined as a symptom that is reported at baseline (defined by pre-dose assessment on the day of vaccination for the first RSV season, at the Day 365 visit for the second RSV season [pre-vaccination if applicable], and at the Day 730 visit for the third RSV season) that worsens in severity during the ARI episode compared to baseline.

First occurrence of a considered endpoint is defined as the first episode of the considered endpoint in a given RSV season (regardless A or B strain, unless otherwise specified).

11.4.1.1. Analysis

Any analysis of the primary endpoints for VE will evaluate the number of participants with (at least one episode of) RT-PCR-confirmed RSV-mediated LRTD (cases defined according to the 3 primary endpoint definitions) in the active vaccine group compared to the placebo group in the PPE population. Time at risk will also be taken into account. The null hypothesis of VE ≤0% for all 3 primary endpoints will be tested versus the alternative hypothesis VE >0% for at least one primary endpoint.

The α-levels for all efficacy analyses will be adjusted:

- To account for the multiple endpoint approach. The multiplicity correction method for the 3 primary endpoints is based on the approach by Spiessens and Debois.[26] The exact value will be calculated based on the number of events observed for each definition at the time of analysis, targeting the same α-level for each of the 3 primary endpoints.
- To account for multiple analyses (see Section 11.12 for details on the planned analyses):

  use estimated proportion of events already observed (P_{IA}) and Pocock rule to set α' for the IA

  - P_{IA} obtained from epidemiological/disease transmission model and real world evidence (RWE)
  - *This α' will be equally divided across the 3 primary endpoints based on the observed incidence*

at the end of the study, based on Case Definition #2, calculate the actual information fraction (IF) at the IA based on the total number of events

- From this information and α', calculate the α'' level for the final analysis.
- *This α'' will again be equally divided across the 3 primary endpoints based on the incidence of the 3 case definitions.*

Both methods will be combined to come to one cut-off that will be used to define significance. The exact values cannot yet be provided as they depend on the number of cases already observed at the time of (interim) analysis.

For example: assume in a NH and SH study an IA was performed with 18 RT-PCR-confirmed RSV-mediated LRTD events observed of the expected 26: the IFs for the interim and primary analyses are 0.7 and 1, respectively. With a total α of 0.05, the α at each analysis (IA and primary analysis) will be 0.0335 using Pocock's rule. If then at the IA the total number of events are as follows: 14 events with Case Definition #1, 18 events with Case Definition #2, and 25 events with Case Definition #3, the IFs at the IA are: 0.56, 0.72, and 1. Again, using Pocock's rule, the α for each individual case definition will be 0.0175. So, proof of concept will be declared at the IA if, for any endpoint, the comparison of the number of events on vaccine compared to placebo if the p-value is <0.0175.

For each of the 3 primary endpoints the following will be performed: an exact Poisson regression will be fitted with the event rate, defined as the number of cases over the follow-up time (offset) as dependent variable and the vaccination group and age and being at increased risk for severe RSV disease (both as stratified) as independent variables. For cases, the follow-up time is defined as the time between vaccination and the occurrence of the first event (according to the considered endpoint), for non-cases, it is the time between vaccination and the end of season visit. However, for participants that discontinued before the end of the season and had an event (according to the considered endpoint), the follow-up time is defined as the time between vaccination and the occurrence of the first event and for participants that discontinued before having an event, follow-up time is the time between vaccination and the date of last contact. Thus, all participants are included in the analysis according to their follow-up time. The exact p-value corresponding to vaccination group will be compared with the cut-off as described above.

If the p-value is below the cut-off for at least 1 of the 3 primary endpoints, proof of concept is demonstrated. The individual 2-sided CIs (1-2 × cut-off) for the VE (1-relative risk rate), measured by each of the 3 endpoints, will be calculated from the regression model described above.

The primary analysis will be performed on the PPE population, which will take cases into account with an onset at least 14 days after vaccination.

As a sensitivity analysis, the above model will be repeated based on the FAS (which also does not take into account the restriction on the onset [at least 14 days] and will count cases from vaccination on Day 1 onwards). Additional sensitivity analyses will include an exact binomial test, not taking into account the strata, based on the PPE population and the FAS. The VE (1-relative

risk) and the corresponding corrected 2-sided CI based on the exact binomial will be calculated as well.

11.4.2. Secondary Efficacy Endpoints

Secondary objectives are defined as follows:

- First occurrence of any RT-PCR-confirmed RSV disease
  This is defined as new onset or worsening of any of the clinical symptoms (LRTI or upper respiratory tract infection [URTI]) indicated in Attachment 1 in combination with RSV confirmation by RT-PCR in at least one of the samples taken at the visits after symptom onset (one positive sample is sufficient)
- First occurrence of a considered endpoint is defined as the first episode of the considered endpoint in a given RSV season (regardless A or B strain, unless otherwise specified).

11.4.2.1. Analysis

For each of the above secondary endpoints an exact Poisson regression will be fitted in a similar way as for the primary endpoint. The 95% 2-sided CI for the VE (1-relative risk rate) will be calculated from the regression model described above.

In addition, for each of the above secondary endpoints, the proportion of participants with an event will be tabulated. The corresponding VE (1- relative risk) and the 95% 2-sided CI will be calculated without taking the strata into account based on an exact binomial test.

11.4.3. Exploratory Efficacy Endpoints

- Explore the relationship between G-ELISA and RT-PCR confirmed RSV infection.

  Provided a cut-off for G-ELISA fold-rise between ARI Day 3-5 and ARI Day 29 is found that is sufficiently sensitive and specific for serology confirmation of RSV infection, the following objectives will be explored:

  First occurrence of any serology and/or RT-PCR-confirmed RSV disease
  This is defined as new onset or worsening of any of the clinical symptoms (LRTI or URTI) indicated in Attachment 1 in combination with RSV confirmation by RT-PCR in at least one of the samples taken at the visits after symptom onset (one positive sample is sufficient) or serology confirmation of RSV

  First occurrence of serology-confirmed RSV-mediated LRTD according to each case definition
  This is determined in a similar way as the primary endpoints but instead of RT-PCR confirmation of RSV, serology confirmation of RSV is needed. Serology confirmation is determined based on the serology sample obtained approximately 28 days after ARI onset.

  First occurrence of any serology-confirmed RSV disease
  This is defined as new onset or worsening of any of the clinical symptoms (LRTI or URTI) indicated in Attachment 1 in combination with serology confirmation of RSV

- If the primary objective is demonstrated after one RSV season:

  First occurrence of RT-PCR-confirmed RSV-mediated LRTD during the second RSV season and during the third RSV season according to each of the 3 case definitions

  This is defined similarly as the primary endpoint, but only counted in the respective season. The baseline assessment for the second RSV season is the Day 365 (Month 12) visit and for the third RSV season it is the Day 730 (Month 24) visit. New onset or worsening is defined similarly as for the primary endpoint, by comparing symptoms occurring during the ARI episode to symptoms reported at the new baseline (instead of by comparing to Day 1). First occurrence of a considered endpoint during the second or third RSV season is defined as the first episode of the considered endpoint in a given RSV season (regardless A or B strain, unless otherwise specified).

  First occurrence of RT-PCR-confirmed RSV-mediated LRTD over 2 RSV seasons and over 3 RSV seasons according to each of the 3 case definitions

  This is defined similarly as the primary endpoint but taking into account events over the 2 or 3 seasons. The baseline assessment for the second RSV season is the Day 365 (Month 12) visit and for the third RSV season it is the Day 730 (Month 24) visit. New onset or worsening is defined similarly as for the primary endpoint, by comparing symptoms occurring during the ARI episode to symptoms reported at the new baseline (instead of comparing to Day 1). When evaluating the vaccine efficacy over 2 and 3 seasons, first occurrence of a considered endpoint over 2 or 3 seasons is defined as the first episode of the considered over the considered period (2 RSV seasons or 3 RSV seasons respectively, regardless A or B strain, unless otherwise specified).

  Other secondary or exploratory objectives that were assessed during the first RSV season (as defined in section 11.4.2 and below), might also be explored during the second and the third RSV season and over 2 and 3 RSV seasons. These endpoints are defined similarly as the corresponding endpoints during the first RSV season, but baseline, new onset or worsening, and first occurrence are defined in a similar way as for RT-PCR-confirmed RSV-mediated LRTD, during the second and the third RSV season and over 2 or 3 RSV seasons (see above).

- First occurrence of any RT-PCR-confirmed RSV disease caused by an RSV A or RSV B strain, respectively
- First occurrence of potential complications of respiratory disease (eg, pneumonia, new onset, worsening, or an exacerbation of CHF, asthma, and COPD) linked to any respiratory disease and linked to any RT-PCR confirmed RSV disease
- Efficacy of active study vaccine against other respiratory diseases
  Midturbinate nasal swabs may be tested for the presence of other respiratory pathogens
- First occurrence of hospitalization linked to any respiratory disease and linked to any RT-PCR confirmed RSV disease
- Determination of oxygen saturation during clinical assessment during ARI episodes
- First occurrence of RT-PCR-confirmed RSV-mediated LRTD according an ordinal case definition

The ordinal case definitions are provided in Table 12.

Table 12: Ordinal Case Definition

Ordinal Case definition	Ordinal variable	Participants fulfilling
≥3 symptoms of LRTI (new onset or worsening), in combination with confirmation of RSV by RT-PCR in one or more of the midturbinate nasal swabs, or in the sputum sample (when available)	4	Case Definition 1, 2 and 3
2 symptoms of LRTI (new onset or worsening), in combination with confirmation of RSV by RT-PCR in one or more of the midturbinate nasal swabs, or in the sputum sample (when available)	3	Case Definition 2 and 3 (not Case definition 1)
1 symptom of LRTI (new onset or worsening), in combination with confirmation of RSV by RT-PCR in one or more of the midturbinate nasal swabs, or in the sputum sample (when available)	2	Only Case Definition 3 (not Case definitions 1 and 2)
Other	1	No case definition

The CEC review will assess, independently and based on CRF/eDiary data, the location of the ARI (upper or lower respiratory tract infection) and the ARI severity. The CEC assessment, as well as other information based on MRU, presence of clinically relevant disease, use of therapeutic interventions, RiiQ, clinical assessment, Lawton-Brody IADL, and change in frailty will be used to evaluate the severity of the RSV-positive ARIs, and will be used to explore the relation with the case definitions.

11.4.3.1. Analysis

For endpoints that intend to explore VE, an exact Poisson regression model will be fitted in a similar way as for the primary endpoint. The 95% 2-sided CI for the VE (1-relative risk rate) will be calculated from the regression model described above.

For exploratory endpoints regarding only season 2 data, the follow-up time for cases in season 2 is defined as the time between the Day 365 (Month 12) visit and the occurrence of the first event (according to the considered endpoint) in the considered season, for non-cases in season 2, it is the time between the Day 365 visit and the end of the second season visit. However, for participants that discontinued before the end of the second season and had an event in Season 2 (according to the considered endpoint), the follow-up time is defined as the time between the Day 365 visit and the occurrence of the first event and for participants that discontinued before having an event in season 2, follow-up time is the time between the Day 365 visit and the date of last contact. Participants that discontinued prior to the Day 365 visit as well as participants that are part of Revaccination Subcohort A will be excluded from the analysis.

For exploratory endpoints regarding only Season 3 data, the follow-up time for cases in Season 3 is defined as the time between the Day 730 (Month 24) visit and the occurrence of the first event (according to the considered endpoint) in the considered season, for non-cases in Season 3, it is the time between the Day 730 visit and the end of the third season visit. However, for participants that discontinued before the end of the third season and had an event in Season 3 (according to the

considered endpoint), the follow-up time is defined as the time between the Day 730 visit and the occurrence of the first event and for participants that discontinued before having an event in Season 3, follow-up time is the time between the Day 730 visit and the date of last contact. Participants that discontinued prior to the Day 730 visit as well as participants that are part of Revaccination Subcohorts A and B will be excluded from the analysis.

For exploratory endpoints over 2 seasons (Season 1 and Season 2), the follow-up time is defined as the time between the Day 1 vaccination and the occurrence of the first event (according to the considered endpoint) in the first 2 seasons, for non-cases, it is the time between the Day 1 vaccination and the end of the second season visit. However, for participants that discontinued before the end of the second season and had an event (according to the considered endpoint), the follow-up time is defined as the time between the Day 1 vaccination and the occurrence of the first event and for participants that discontinued before having an event, follow-up time is the time between the Day 1 vaccination and the date of last contact. For Revaccination Subcohort A participants, only the first season is taken into account: for cases during the first season, the follow-up time is the time between the Day 1 vaccination and the occurrence of the first event (according to the considered endpoint), for non-cases it is the time between the Day 1 vaccination and end of first season visit.

For exploratory endpoints over 3 seasons (Season 1, 2 and 3), the follow-up time is defined similar as for endpoints over 2 seasons, but data up to the end of the third season are taken into account (instead only data up to the end of the second RSV season). For Revaccination Subcohort A participants, only the first season is taken into account and follow-up time is defined similar as explained above. For Revaccination Subcohort B participants only the first 2 seasons are taken into account: for cases during the first 2 seasons, the follow-up time is the time between the Day 1 vaccination and the occurrence of the first event (according to the considered endpoint), for non-cases it is the time between the Day 1 vaccination and the end of second season visit.

For continuous endpoints, actual values and changes from baseline (if meaningful) will be summarized descriptively. Categorical endpoints will be tabulated.

11.5. Patient-reported Outcomes

Daily symptom severity reported by participants using the RiiQ Symptom Scale, temperature log, and Patient Global Impression Scales from symptom onset to symptom resolution will be descriptively analyzed by group (active vaccine or placebo). Changes from baseline functioning associated with ARI collected using the RiiQ Impact Scales will also be analyzed.

Details on validation of the PRO questionnaires will be provided in a separate analysis plan.

11.5.1. Respiratory Infection Intensity and Impact Questionnaire (RiiQ™v2)

The RiiQ consists of 4 scales that are scored separately:

- RiiQ Symptom Scale (Question 1). Each symptom is rated on the following scale: 0 None, 1 Mild, 2 Moderate, and 3 Severe. The RiiQ Symptom scale can be scored as a mean of all

scores (Total Symptom Score) or 2 subscales scores, Respiratory Symptoms and Systemic Symptoms:

The RiiQ Respiratory Symptoms Subscale score is the mean of 6 symptoms, ie, 2 URTI symptoms (Nasal congestion and Sore throat) and 4 LRTI symptoms (Cough, Wheezing, Shortness of breath, and Coughing up phlegm/sputum)

The RiiQ Systemic Symptom subscale score is the mean of 7 systemic symptoms (Headache, Feeling feverish, Neck pain, Body aches and pain, Fatigue/tiredness, Interrupted sleep, and Loss of appetite).

- RiiQ Impact Scales (Questions 2 to 4):

  RiiQ Impact on Daily Activity scale (Question 2) consists of 7 activities. Ability to perform each activity item is rated on the following scale: 0 No difficulty, 1 Some difficulty, 2 Moderate Difficulty, and 3 Great difficulty. Scale scores are calculated as the mean of all 7 items (range 0-3).

  RiiQ Impact on Emotions scale (Question 3) consists of rating 4 negative emotions, rated on the following scale: 0 Not at all, 1 Somewhat, 2 Moderately, and 3 Extremely. Scale scores are calculated as the mean of all 4 items (range 0-3).

  RiiQ Impact on Relationships scale (Question 4) consists of 5 problems that a respiratory infection may cause in relationships with others, rated on the following scale: 0 Not at all concerned, 1 Somewhat concerned, 2 Moderately concerned, and 3 Extremely concerned) with scale scores calculated as the mean of all 5 items (range 0-3).

11.5.2. Patient Global Impression Scores

- Patient Global Impression of Health (PGI-H). Participants report their overall impression of their health status today on the following scale: 0 Very poor, 1 Poor, 2 Fair, 3 Good, 4 Very good.
- Patient Global Impression of Severity (PGI-S). Participants rate the severity of their respiratory illness on the following scale: 0 I feel fine (no respiratory illness), 1 I feel a little ill, 2 I feel very ill, 3 I feel extremely ill.
- Patient Global Impression of Change (PGI-C). Participants rate the amount of change in their health each day during an ARI episode on the following scale: -3 Very much better, -2 Much better, -1 A little better, 0 About the same/no change, 1 A little worse, 2 Much worse, 3 Very much worse
- Return to Usual Health. Participants are being asked whether they have returned to their usual health after developing symptoms suggesting an ARI.

11.6. Lawton-Brody Instrumental Activities of Daily Living (IADL) Scale

The Lawton-Brody IADL questionnaire (Attachment 8) covers 8 domains. Women are scored on all 8 domains; historically, for men, the domains of food preparation, housekeeping, and laundering are excluded from the analysis. Participants are scored according to their highest level of functioning in that category (either 0 or 1). A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women, and from 0 through 5 for men.

Change from baseline independence status associated with ARI collected using the Lawton-Brody IADL questionnaire will be descriptively analyzed.

11.7. Frailty Index Score

The frailty index score will be calculated from the medical conditions of interest, RiiQ, and the Lawton-Brody IADL. More details will be provided in the SAP.

The change from baseline in frailty index score will be determined. The following correlations will be explored (descriptively or graphically):

- the correlation between the baseline frailty index score and RSV infection incidence, severity (as determined from the RiiQ questionnaire) and duration.
- the correlation between the baseline frailty index score and the primary endpoints.
- the correlation between the change in frailty index score and presence of an RSV ARI.

11.8. Clinical Assessment

Symptoms from the clinical assessment will be scored on a 4-point scale (from 0 through 3), with higher scores indicating greater severity. The scores will be analyzed descriptively.

11.9. Immunogenicity Analyses

No formal statistical testing of the immunogenicity data is planned. All immunogenicity analyses will be performed on the PPI population. Key tables might be repeated for the FAS (including samples that are excluded from the PPI analysis).

11.9.1. Immuno Subset

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% CI for ELISA and RSV neutralization assay; median and quartiles for IFN-γ ELISpot and ICS) will be calculated for continuous immunologic parameters at all time points. For the humoral assays, geometric mean fold rises from baseline and corresponding 95% CIs might additionally be calculated. Baseline is considered as the last available assessment before the vaccination. Graphical representations of immunologic parameters will be made as applicable.

The impact of baseline factors on the humoral and cellular responses will be explored graphically or via descriptive statistics.

11.9.2. Revaccination Subcohorts

No formal hypothesis on immunogenicity will be tested for Revaccination Subcohorts. Descriptive statistics (geometric mean and 95% CI for ELISA and RSV neutralization assay, median and quartiles for IFN-γ ELISpot) will be calculated for continuous immunologic parameters at all time points. Geometric mean fold rises from baseline and corresponding 95% CIs might additionally be calculated. Geometric mean ratios and corresponding 95% CIs between Day 15 post first vaccination and Day 15 post second vaccination within the group receiving active study vaccine

on Day 1 and the day of the second vaccination depending on the Revaccination Subcohort will be calculated for the different assays.

In addition, the GMT ratios with corresponding 95% CIs of Day 15 post second vaccination for the group receiving active study vaccine twice versus the group receiving placebo first and active study vaccine 1, 2, or 3 years later will also be calculated for the different assays. Therefore, an analysis of variance (ANOVA) model will be fitted with the respective titers as dependent variable and group as independent variable. The estimate and CIs obtained as such will be back transformed (by exponentiation) to a GMT ratio and the corresponding CI. As a sensitivity analysis, different variances between the groups will be allowed, therefore the CIs will be calculated via Welsh's ANOVA.

For Revaccination Subcohorts 2A and 2B that get a third vaccination with Ad26.RSV.preF/RSV preF protein mixture or with the individual vaccine components, no formal hypothesis is tested; descriptive statistics over time after the third vaccination will be calculated.

Graphical representations of immunologic parameters will be made as applicable.

The impact of baseline factors on the humoral responses will be explored graphically or via descriptive statistics.

11.9.3. Correlates of Risk

If VE is demonstrated, correlates of risk will be explored. More details with appropriate methods will then be provided in a separate SAP.

11.10. Medical Resource Utilization Analyses

Medical resource utilization data will be descriptively summarized by intervention group.

11.11. Safety Analyses

No formal statistical testing of safety data is planned. Safety data by vaccination group and based on the FAS will be analyzed descriptively. The analysis of solicited and unsolicited AEs will be restricted to a subset of the FAS (ie, the Safety Subset). For SAEs, the complete FAS is considered. The impact of baseline factors (eg, being at increased risk for severe RSV disease) might be explored as well. Additionally, the analysis of solicited and unsolicited AEs and AESIs (if collected) will also be performed for each of the Revaccination Subcohorts and will be restricted to participants of the Revaccination Subcohorts that are part of the FAS.

Adverse Events (Solicited and Unsolicited)

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

Solicited local (at the injection site) and systemic AEs will be summarized descriptively. The overall frequencies per group as well as frequencies according to severity and duration will be calculated for solicited AEs.

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

Any ARI recorded as an (S)AE in the eCRF will be excluded from any AE analysis if the laboratory RT-PCR is subsequently found to be positive for RSV. ARIs arising from RSV infection will not be reported as (S)AEs in the Clinical Study Report as they are endpoints of the study and will be tabulated separately.

Vital Signs

A tabulation of the distribution of temperatures in the 7 days after vaccination, per half degree intervals, will be provided. For systolic and diastolic blood pressures, pulse rate and respiratory rate, the percentage of participants with values beyond clinically relevant limits will be summarized.

Physical Examination

Abnormalities resulting from a physical examination will be documented as medical history or as AE. Therefore, no physical examination specific tables or listings will be generated for Day 1. Abnormalities resulting from a physical examination on other timepoints will be listed.

11.12. Planned Analyses

Recruitment Completed in the Northern Hemisphere Only (Target Sample Size ≥5,500)

If participants are only enrolled in the NH and if by the end of the first NH RSV season (database cut-off of 15 May 2020) 18 or more RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed, the study will be unblinded for the sponsor and the primary analysis will be performed by the sponsor.

If, by the end of the first NH RSV season, less than 18 RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed, an IA will be performed by the IDMC. The IDMC will evaluate in an unblinded fashion if superiority is established for at least one of the primary endpoints.

- In the event of superiority, the sponsor will be notified. The database used for the IDMC analysis will be unblinded for the sponsor and the primary analysis will be performed by the sponsor.
- If superiority is not demonstrated, the IDMC will evaluate the conditional power to demonstrate proof of concept (under the original assumptions of incidence and VE) if 2,000 new participants are added to the study. If the conditional power is less than 60%, the database used for the IDMC analysis will be unblinded for the sponsor and the primary

analysis will be performed by the sponsor. If the conditional power is 60% or more, 2,000 new participants (Cohort 2) will be added to the study who will be followed up for one RSV season. The ongoing participants from Cohort 1 will be stopped at the end of RSV season or 6 months after vaccination whatever comes later.

Recruitment Spread Over the Northern and the Southern Hemisphere (Target Sample Size up to 5,800)

If the number of participants enrolled in the NH is less than 5,500 and less than 18 RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed in the NH before opening sites in the SH[a], additional participants will be enrolled in the SH up to a total sample size (NH and SH combined) of 5,800 participants. In that case, a single IA may be performed during the NH or SH RSV season. This "early" IA will be performed by the IDMC at one of 2 predetermined time points:

- The first time point will be at the end of the NH RSV season. The database cut-off for this analysis will be 15 May 2020.
- The second time point will be determined by operational and regulatory considerations to start Phase 3 the next year. The database cut-off for this analysis will be 15 August 2020.

The IA will be performed by the IDMC at the earliest of those 2 predetermined time points where at least 14 events (RT-PCR-confirmed RSV-mediated LRTD cases per Case Definition #2) are observed. If the early IA is performed, the IDMC will evaluate in an unblinded fashion if superiority is established for at least one of the primary endpoints. The IDMC will notify the sponsor of the outcome. In the event of superiority, the database used for the IDMC analysis will be unblinded for the sponsor and the primary analysis will be performed by the sponsor. If superiority is not shown at the IA or if the number of RT-PCR-confirmed RSV-mediated LRTD cases (using Case Definition #2) is less than 14 at the second time point, the primary analysis will be performed at the end of the SH RSV season (database cut-off of 30 October 2020) in a similar way as in a NH study only.

The IA plan is outlined in Figure 3 in case the study is performed in the NH only, and in Figure 4 in case the study is performed in the NH and SH.

Additional Analyses

If in a NH+SH study VE is demonstrated at the early IA, an additional analysis will be performed at the end of the RSV season. This will count as supportive information.

If VE is demonstrated at the end of the first NH RSV season, the study will continue and the ongoing participants from Cohort 1 will be followed up for a second RSV season. If this is the case, additional analyses will be performed at the end of the second RSV season to evaluate if

[a] If the number of participants enrolled in the NH is less than 5,500 and 18 or more RT-PCR-confirmed RSV-mediated LRTD events (using Case Definition #2) are observed in the NH before opening sites in the SH, no sites will be opened in the SH and the study will be performed as a NH study only.

there is a trend for durable efficacy. If analyses at the end of the second RSV season indicate a trend for durable efficacy or in case results on durability are inconclusive, the study will continue and the ongoing participants from Cohort 1 will be followed up for a third RSV season as indicated in the Schedule of Activities. If this is the case, additional analyses will be performed at the end of the third RSV season to further evaluate durability of efficacy.

Analysis 28 Days Post Second Vaccination in Revaccination Subcohorts A, B, and C

This analysis will be done for each Revaccination Subcohort (A, B, and C) and will include safety and immunogenicity data from the considered Revaccination Subcohort. The analysis will be performed on unblinded data. Data collected up to the time of the 28-day post second vaccination visit for the last participant in the considered Revaccination Subcohort will be included in the analysis.

The blind will be maintained at the participant/site level, with respect to the vaccination received on Day 1 until the database lock for the final analysis of the considered cohort, except for the participants in Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination prior to re-randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re-randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

End of Season 2 Analysis

This analysis will include all efficacy, safety, and immunogenicity data collected up to the time of the end of the second RSV season. If the number of RSV-positive cases observed during the second season is low, the efficacy analysis might be restricted to a listing of major efficacy endpoints in RSV-positive participants during the second RSV season. In case no RSV cases are reported, then the end of Season 2 analysis might be restricted to only safety and immunogenicity.

This analysis might be split in 2 parts given the availability of the data. The first part will include all efficacy, safety, and immunogenicity data collected until the end of the second RSV season and the second part will include additional safety data collected between the end of the second RSV season and the end of the SAE safety follow-up.

Analysis of Revaccination Subcohorts A and B, when Revaccination Subcohorts 2A and 2B have reached the 28 Days Post Third Vaccination Timepoint

This analysis will be done separately for each Revaccination Subcohort (A and B) and will include safety and immunogenicity data from the considered Revaccination Subcohort. The analysis will be performed on unblinded data. Data collected up to the time of the 28-day post third vaccination visit for the last participant in the considered Revaccination Subcohort will be included in the analysis.

The blind will be maintained at the participant/site level, with respect to the vaccination received on Day 1 until the database lock for the final analysis of the considered cohort, except for the participants in Revaccination Subcohorts A and B, who will be unblinded to the Day 1 vaccination

prior to re-randomization to the third vaccination: participants who received active vaccine on Day 1 will complete the study at that time, participants who received placebo on Day 1 will be re-randomized to receive either Ad26.RSV.preF/RSV preF protein mixture or the individual vaccine components in a blinded fashion.

End of Efficacy Study Analysis

This analysis will include all efficacy, safety, and immunogenicity data collected until the end of the third RSV season. Efficacy data collected up to the end of the third season visit for the last participant will be included in the analysis.

The end of efficacy study analysis will be performed on unblinded data.

Final Analysis of Revaccination Subcohorts (A, B, and C).

This analysis will be done for each Revaccination Subcohort (A, B, and C) and will include safety and immunogenicity data from the considered Revaccination Subcohort. The analysis will be performed on unblinded data. Data collected up to the last visit for the last participant in the considered Revaccination Subcohort will be included in the analysis.

Early Stop ARI Surveillance in 2020

Due to the increasing incidence of COVID-19 cases, it is becoming increasingly difficult to conduct ARI surveillance, without putting staff or study participants at risk. As the first RSV season is nearing a close, a decision has been made to stop ARI surveillance for the first RSV season under Amendment 2.

Unplanned Snapshot Interim Analysis

An unplanned snapshot IA may be performed to allow for early decision making on capacity planning for the Ad26 SARS-CoV2, which is being developed for the prophylactic immunization against SARS-CoV-2 infection, and Ad26.RSV.preF vaccines. This is especially important for the production capacity in 2020 and 2021. The results of this unplanned snapshot IA will only be shared with select members of upper management not involved in the conduct of the study. This will be described in more detail in a separate charter.

Since this unplanned snapshot IA will only be used for internal decision making, will not further affect the conduct of the study, and it is not expected that the number of events will drastically change for the primary analysis, no type I error adjustment will be applied. The success of the study will solely depend on the results of the primary analysis.

Validation of the PRO Questionnaires

Validation of PRO questionnaires will be performed in a blinded manner to ensure unbiased validation. More details will be provided in a separate analysis plan.

11.13. Independent Data Monitoring Committee

The study will be formally monitored by an IDMC. In general, the IDMC will monitor safety data on an ongoing basis to ensure the continuing safety of the participants. In addition, the IDMC will formally monitor the efficacy endpoints at the time points specified in Section 11.4. The IDMC will evaluate in an unblinded fashion whether superiority is established for at least one of the primary endpoints (at the early IA or at the end of the RSV season in the event that less than 18 RT-PCR-confirmed RSV-mediated LRTD events are observed) or whether futility (conditional power <60%) is shown for all 3 primary endpoints (at the end of the first RSV season in the event that less than 18 RT-PCR-confirmed RSV-mediated LRTD events are observed).

The details on the superiority and futility assessment of the IDMC are described in Section 11.12.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

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

Method of Detecting Adverse Events, AESIs, and Serious Adverse Events

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

Solicited Adverse Events

Solicited AEs are predefined local (at the vaccine injection sites) and systemic events for which the participant is specifically questioned and which are noted by participants in the Safety Subset in their eDiary (see Section 9.2.4, Safety Evaluations).

Unsolicited Adverse Events

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

AESIs

For details, refer to Section 12.3.4.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (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 for Harmonisation [ICH])

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

Refer to Section 12.3.1, All Adverse Events, for AEs collected in this study.

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.RSV.preF and RSV preF protein, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.[13,14]

Adverse Event Associated With the Use of the Intervention

An AE is considered associated with the use of the intervention if the attribution is related by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Every effort should be made by the investigator to explain any AE and assess its potential causal relationship, ie, to administration of study vaccine or to alternative causes (eg, natural history of the underlying diseases, concomitant therapy). This applies to all AEs, whether serious or non-serious.

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

Related: there is suspicion that there is a relationship between study vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that study vaccine contributed to the AE.

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

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

12.1.3. Severity Criteria

All AEs will be coded for severity using the revised FDA toxicity grading table in Attachment 2. For AEs not identified in the grading table, the following guidelines will be applied:

Mild (Grade 1): No interference with activity.

Moderate (Grade 2): Some interference with activity not requiring medical intervention.

Severe (Grade 3): Prevents daily activity and requires medical intervention.

Potentially life-threatening (Grade 4): Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

The severity of solicited AEs will be graded in the eDiary by the participant based on the severity assessment provided in the eDiary and then verified by the investigator using the FDA toxicity grading table in Attachment 2.

12.2. Special Reporting Situations

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

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

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

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated ICF is obtained onwards. All other AEs (unsolicited) will be reported from the time of vaccination through the following 28 days for Safety Subset participants, and from the time of revaccination through the following 28 days for the Revaccination Subcohort participants. AEs, including any that are ongoing at 28 days after vaccine administration, will be followed until clinical resolution or stabilization. Safety Subset participants will be contacted by telephone or telemedicine contact at 28 days (+3 days) after the first vaccination to collect information on unsolicited AEs and associated concomitant medications. For participants in the Revaccination Subcohorts, this information will be collected at the 28-day (+3 days) post-revaccination visit.

Solicited local (at the injection site) AEs and solicited systemic AEs will be recorded by each Safety Subset and Revaccination Subcohort participant in the eDiary beginning on the evening of the vaccine dosing day (Day 1 and Day 365 [Month 12]/Day 730 [Month 24]/Day 1,095 [Month 36], respectively) and on a daily basis for the following 7 days. Study-site personnel will review participant eDiary information and confirm the entries. If a solicited AE has not resolved 7 days post-vaccination, it will continue to be followed-up until the event has returned to baseline.

For all participants, SAEs will be collected from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later).[a]

[a] The windows for SAE collection in the Revaccination Subcohorts are described below.

For all participants, some subsets of SAEs will be collected for additional study periods[a]:

- ARIs and complications related to ARIs that classify as SAEs will be captured and will be reported as SAEs in the eCRF for the duration of the second RSV season, between the second and the third RSV season, and for the duration of the third RSV season.

- From the time of vaccination (Day 1) until the end of the study period for each participant, SAEs classified as related to the study vaccine, SAEs resulting in death, and (S)AEs leading to discontinuation from the study will be collected.

- During the entire study, (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be reported from the time a signed and dated informed consent form (ICF) is obtained onwards until the end of the study period for each participant.

The (S)AE listing in the eCRF will not be updated based on the RSV RT-PCR results and will remain listed on the eCRF as ARIs.

For Revaccination Subcohort A, all SAEs will be reported from administration of study vaccine on Day 1 until the end of the first RSV season (or 6 months after vaccination, whichever comes later), and from the time of revaccination at Month 12 until the end of the second RSV season, or until 6 months after revaccination, whichever comes later. For Revaccination Subcohort 2A, all SAEs and AESIs will also be collected from the time of revaccination on Day 730 until 6 months after revaccination. For Revaccination Subcohorts B and C, all SAEs and AESIs will be collected from the time of revaccination until 6 months thereafter. Collection of SAEs associated with ARIs and complications related to ARIs that classify as SAEs will stop at the end of the second RSV season for Subcohort A, on Day 730 (Month 24) for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C.

For all Revaccination Subcohorts, SAEs classified as related to the study vaccine, SAEs resulting in death, (S)AEs leading to discontinuation from the study, and (S)AEs and special reporting situations related to study procedures or to non-investigational (concomitant) Janssen products will be collected during the entire study for all participants. For the participants in the Revaccination Subcohort C, these (S)AEs will be collected retrospectively for the time period between the last end of the RSV season visit and the revaccination upon the day of revaccination.

From the time of local approval of protocol amendment 6 onwards, TTS is considered to be an AESI. Thrombotic events and/or thrombocytopenia (defined as platelet count below 150,000 cells/mm^3) are considered to be potential AESIs. All AESIs, including potential AESIs, will be reported to the sponsor from the moment of revaccination until 6 months after revaccination.

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

The investigator will monitor and check the AE data as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study vaccine. All AEs will be deemed related to study vaccine or not related to study vaccine, according to Section 12.1.2.

The investigator must review both post-injection reactogenicity and other AEs to insure the prompt and complete identification of all events that require expedited reporting as SAEs or are other serious and unexpected events.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

All AEs, regardless of seriousness, severity, or presumed relationship to study vaccine, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study vaccine. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

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

12.3.2. Serious Adverse Events

SAEs must be reported to the appropriate sponsor contact person by study-site personnel immediately, but no later than 24 hours of their knowledge of the event (Section 12.3.1).

Any ARI fulfilling the criteria of an SAE will be reported as such from vaccination on Day 1 and for the duration of the first RSV season (or 6 months after vaccination, whichever comes later), for the duration of the second RSV season, between the second and the third RSV season, and for the duration of the third RSV season. For participants in Revaccination Subcohorts, follow-up of ARIs will stop at the end of the second RSV season for Subcohort A, at the Day 730 (Month 24) visit for Subcohort B, and at the latest at the end of the third RSV season for Subcohort C. SAEs will not be updated after the RSV RT-PCR results become available and will remain listed on the eCRF as ARIs.

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 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax).

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

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

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

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

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

12.3.3. Pregnancy

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

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

12.3.4. Adverse Events of Special Interest

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 (including potential AESIs) will be carefully monitored during the study by the sponsor.

AESIs (including 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.

12.3.4.1. Thrombosis with Thrombocytopenia Syndrome

As described in Section 1.1, TTS has been observed very rarely following vaccination with the Janssen COVID-19 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.[1,4]

Because this syndrome is very rare and not completely understood, all cases of thrombosis and/or thrombocytopenia should be reported to the sponsor within 24 hours of awareness using the AESI form. Each potential AESI will be reviewed to identify a vaccine-induced immune thrombotic thrombocytopenia (VITT) case. Responsibilities and procedures for identification, review, and evaluation of potential TTS cases are outlined in 2 separate charters: the thrombosis with thrombocytopenia syndrome Adjudication Committee (TTSAC) Charter and the 'Process of Case Assessment for TTS in the RSV Vaccine Interventional Clinical Studies Charter'. A potential TTS case is defined as:

- Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Attachment 13,

  and/or

- Thrombocytopenia, defined as platelet count below 150,000 cells/mm^3

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 with a test for anti-PF4 and a coagulation profile should be provided as soon as possible upon the site becoming aware of the event. In case these results are not available at the time of the event report in the eCRF, the study site is recommended to obtain a complete blood count including platelet count and a coagulation profile (to be performed at the local laboratory). Repeat testing may be requested for confirmation upon sponsor discretion.

Aliquots of serum samples collected for immunogenicity tests can be reconverted for participant's safety purposes upon sponsor request (Table 13).

Table 13 provides non-exhaustive list(s) of laboratory tests that may be performed (upon sponsor request).

In addition, the sponsor may request additional laboratory tests on additional blood samples obtained as soon as possible after the potential AESI onset, either during an ad hoc unscheduled visit or the next scheduled visit, whichever comes first. Table 14 provides a non-exhaustive list of laboratory tests that may be requested by the sponsor in case of potential AESI reporting, for which additional samples may be needed.

Table 13: Laboratory Tests That May Be Performed Upon Sponsor Request on Immunogenicity Samples Collected on Days 1 and 15 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	• Days 1 and 15 visits (aliquots of serum samples collected for immunogenicity test can be reconverted for participant's safety purposes).

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

Table 14: Laboratory Tests That May Be Requested by the Sponsor to be Performed at the Central Laboratory After Potential AESI Reporting

Parameters	Timepoints
• Serum/plasma/whole blood samples for coagulation-related assays such as but not limited to: 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 upon sponsor request (during an ad hoc unscheduled visit or the next scheduled visit, whichever comes first).

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

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

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

If an event meets the criteria for an SAE (Section 12.1.1), 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 2022[1]; British Society of Haematology 2022[5]; CDC 2021[6]). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

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

13.1. Procedures

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

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY INTERVENTION INFORMATION

14.1. Physical Description of Study Vaccine(s)

Ad26.RSV.preF and RSV preF protein, manufactured and provided under the responsibility of the sponsor, will be assessed in this study:

Ad26.RSV.preF (JNJ-64400141)

Ad26.RSV.preF is a replication-incompetent Ad26 containing a DNA transgene that encodes the pre-fusion conformation-stabilized F protein derived from the RSV A2 strain.

For this study, Ad26.RSV.preF will be formulated as a solution for intramuscular injection and will be supplied as a frozen liquid to be thawed prior to use. Ad26.RSV.preF will be supplied in single-use vials (2×10^{11} vp/mL). Refer to the Investigational Product Preparation Instructions for details on dosing preparation.

Refer to the Investigator's Brochure for details of the components of Ad26.RSV.preF and a list of excipients.[13]

RSV preF protein (JNJ-64213175)

RSV preF protein is a pre-fusion conformation-stabilized F protein derived from the RSV A2 strain.

For this study, RSV preF protein will be formulated as a solution for intramuscular injection. RSV preF protein will be supplied in a single-use vial. Refer to the Investigational Product Preparation Instructions for details on dosing preparation.

Refer to the Investigator's Brochure for details of the components of RSV preF protein and a list of excipients.[13,14]

Note: RSV preF protein clinical trial material will be labelled as "RSV-F Vaccine".

14.2. Packaging and Labeling

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

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

Further details for study vaccine packaging and labeling can be found in the Site Investigational Product Procedures Manual.

14.3. Storage and Handling

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

An unblinded site pharmacist, or other qualified individual, who will have no other study function will prepare the syringe, labeled with the participant's identification number, and provide the syringes for Ad26.RSV.preF/RSV preF protein and placebo in a blinded manner to the blinded study vaccine administrator who will perform the injection. The unblinded pharmacist, or other qualified individual, may also perform vaccine administration, but will have no other study function following dosing.

Participants in Revaccination Subcohorts 2A and 2B will receive revaccination with Ad26.RSV.preF/RSV preF protein mixture or with the individual vaccine components.

Participants in the other Revaccination Subcohorts will receive revaccination with Ad26.RSV.preF/RSV preF protein mixture.

Further details for study vaccine storage, preparation, handling and stability can be found in the IPPI and in the Site Investigational Product Procedures Manual.

14.4. Vaccine Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the participant must be documented on the vaccine accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions.

Study vaccine must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study vaccine must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study vaccine will be documented on the Investigational Product Destruction Form. When the study site is an authorized destruction unit and study vaccine supplies are destroyed on-site, this must also be documented on the vaccine return form.

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

Study vaccine should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study vaccine will be supplied only to 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.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator’s Brochure for the Ad26/protein preF RSV vaccine[13,14]
- Site Investigational Product Procedures Manual
- Investigational Product Preparation Instruction (IPPI)
- Laboratory Manual
- IWRS Manual
- Electronic Data Capture (eDC) Manual/eCRF completion guidelines
- Sample ICF
- ePRO completion guides

- ePRO participant information sheets
- eDiaries and instructions for use
- Rulers (to measure diameter of any erythema and swelling)
- Thermometers
- Midturbinate nasal swab sample kits, including cooling bags
- Laboratory kits
- Contact information page(s)

16. ETHICAL ASPECTS

16.1. Study-specific 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.

Over the entire study, the total blood volume to be collected from each participant in the Immuno Subset will be approximately 220 mL when the study does not progress beyond the first year, and 330 mL or 440 mL when the study is continued beyond the first and second year, respectively. For all other participants in Cohort 1 who are not included in a Revaccination Subcohort, the total blood volume to be collected will 30 mL when the study does not progress beyond the first year, 45 mL when the study is continued beyond the first year, and 60 mL when the study is continued beyond the second year.

For participants in Cohort 2, the total blood volume to be collected will be 30 mL.

For participants in the Revaccination Subcohorts, the total blood volume to be collected from each participant will be: Revaccination Subcohort 1A and 2A: 120 mL and 490 mL, respectively; Revaccination Subcohort 1B and 2B: 430 mL and 755 mL, respectively; and Revaccination Subcohort 1C and 2C: 160 mL (360 mL in a subset of approximately 100 participants).

For each ARI episode, 40 mL additional blood will be sampled. This is considered to be an acceptable amount of blood to be collected over this time period from the population in this study.

Risks Related to Vaccination

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

Participants may exhibit general signs and symptoms associated with administration of a vaccine, or vaccination with placebo, including fatigue, headache, myalgia, arthralgia, chills and nausea. 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.

Participants may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, hives or even difficulty breathing. Severe reactions, including anaphylaxis, are rare but can occur with any vaccine. Medications must be available in the clinic to treat serious allergic reactions promptly. Participants with a known allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine components (including any of the constituents of the study vaccine) will be excluded from the study. Sites should have medical treatment available in case of severe allergic reactions following vaccine administration.

Risks Related to Adenoviral-vectored Vaccines

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

Local AEs (moderate injection site pain and tenderness, and moderate to severe redness at the injection site) and systemic AEs (headache, chills, joint pain, muscle pain, tiredness/generally not feeling well/fatigue and fever) have been reported after vaccination with Ad26-vectored vaccines. In a few participants, transient laboratory abnormalities have been seen, including changes in neutrophils. Laboratory changes including decreased hemoglobin, decreased platelets, and moderate elevations in liver transaminases were observed that were not associated with any clinical findings and appear to be transient based on no reported persistent abnormalities in any of the participants.

For further details on the safety profiles of other Ad26-vectored vaccine candidates, see the Investigator's Brochure.[13]

Risks Related to RSV preF Protein

RSV preF protein is being used for the first time in humans in the ongoing Study VAC18193RSV1004.

For further details, see the Investigator's Brochure.[13,14]

Risks from Collection of Midturbinate Nasal Swabs and Nasosorption Samples

Collection of a midturbinate nasal swab may cause a nosebleed.

Nasosorption sampling is more comfortable and less invasive than using a conventional swab.

Risks from Blood Draws

Blood drawing may cause pain/tenderness, bruising, bleeding, lightheadedness, dizziness, vasovagal response, and, rarely, infection at the site where the blood is taken.

Potential Benefits

Ad26.RSV.preF and RSV preF protein are under development for prophylaxis of RSV, however VE has not yet been investigated. There is no direct medical benefit to the participant for participation in this clinical study. Although study participants may benefit from clinical testing and physical examination, they may receive no direct benefit from participation. There could be a potential benefit from RSV vaccination in terms of immune response: vaccination could raise an immune response which might confer some additional protection against a future RSV infection. Others may benefit from knowledge gained in this study that may aid in the development of an RSV vaccine.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- Investigator's Brochure (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 Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- 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.

16.2.3. Informed Consent

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. Informed consent for additional study procedures will be requested from participants in the Immuno Subset and/or the Safety Subset. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

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

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

16.2.4. Privacy of Personal Data

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

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

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

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

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

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

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 10.2, Withdrawal from the Use of Samples in Future Research).

16.2.6. Country/Territory 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 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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.

17.2. 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) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

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

17.3. Regulatory Documentation

17.3.1. Regulatory Approval/Notification

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

17.3.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention 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

17.4. 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.

The investigator must also complete a participant screening log, which reports on all participants who were seen to determine eligibility for inclusion in the study.

17.5. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: 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 intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

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

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

The following participant (and investigator) completed assessments will be recorded directly into an electronic device and will be considered source data: solicited AEs after vaccination, body temperature, oxygen saturation, RiiQ, RiiQ Symptom Scale and RiiQ Impact on Daily Activities Scale, Clinical Assessment, Lawton-Brody IADL, and MRU questionnaire and ARI surveillance responses. Information from the participant eDiary will be reviewed by the investigator. The sponsor's preference is to enter the results of the clinical assessment directly in the site's eDevice, however, the results may be collected on paper first and transferred to the site's eDevice afterwards, on the same day as the assessments.

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

17.6. Case Report Form Completion

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

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

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

If necessary, queries will be generated in the eDC tool. If corrections to 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.

17.7. Data Quality Assurance/Quality Control

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

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

17.8. 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.

17.9. Monitoring

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

The sponsor or its designee will perform on-site monitoring visits or video site monitoring as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after

enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

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

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

17.10. Study Completion/Termination

17.10.1. Study Completion/End of Study

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

17.10.2. Study Termination

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

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

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

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

- Discontinuation of further study intervention development

17.11. On-Site Audits

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

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

17.12. Use of Information and Publication

All information, including but not limited to information regarding Ad26.RSV.preF and RSV 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.preF and RSV 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 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 substudy 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 study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

18. APPENDIX 1: GUIDANCE ON STUDY CONDUCT DURING A NATURAL DISASTER

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

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

GUIDANCE SPECIFIC TO THIS PROTOCOL:

- Depending on the ongoing incidence of COVID-19 infection and subject to availability of SARS-CoV-2 point-of-care testing, participants may receive COVID-19 screening at home or clinical visits.
- When site visits are not possible due to local/national guidelines, sites should collect the assessments via telephone or telemedicine contact or home-based visits, if the participant allows. The actual visit date and the type of visit (ie, telephone/telemedicine contact or home-based visit) should be captured in the eCRF according to the eCRF completion guidelines. Procedures that require an on-site visit, ie, clinical assessments, blood samples and nasosorption samples and physical examination) should be excluded.
- A revised ICF arising from this amendment needs to be signed by the participants during a site visit or home-based visit, if the participant allows. When a site or home-based visit is not possible due to local/national guidelines, the participant can sign the paper ICF and mail the signed document to the site.
- For participants with an ARI episode: midturbinate nasal swabs and a sputum sample (when available) still need to meet the case definition for RSV-mediated LRTD. The ARI Day 1-2 midturbinate swab is a self-swab collected at home by the participant, and the ARI Day 3-5 midturbinate swab and sputum sample (when available) may need to also be collected at home, when site visits may not be possible.

  In the setting that on-site visits are not possible, a courier service will need to be arranged to transport the samples to the site in a timely manner.
- Questionnaires that need to be completed at the Day 365 (Month 12), at the end of the second RSV season, and Day 730 (Month 24) visit, as applicable, and additionally for participants with ARI episode on ARI Days 3-5 and 29, could be completed by the participant in the eDiary or via a telephone/telemedicine interview with the participant, as applicable.

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Attachment 1: Definition of Acute Respiratory Infection

Acute respiratory infection (ARI) is defined as the occurrence of at least one respiratory symptom that the participant reports is different or worse than he or she usually experiences:

- Respiratory symptom: an upper respiratory tract infection (URTI) symptom (ie, nasal congestion, sore throat) or a lower respiratory tract infection (LRTI) symptom (ie, cough, short of breath, coughing up phlegm [sputum], wheezing) from the RiiQ™v2 Symptom Scale)

Resolution of an ARI episode is defined as 2 consecutive days with no symptoms listed on the RiiQ™v2 Symptom Scale or, for participants who have RiiQ™v2 symptoms present at baseline (assessed pre-vaccination for the first RSV season , at the Day 365 [Month 12] visit for the second RSV season [pre-vaccination if applicable], and at the Day 730 [Month 24] visit for the third RSV season), 2 consecutive days where all symptoms on the RiiQ™v2 Symptom Scale have returned to severity reported at baseline.

Attachment 2: **Toxicity Tables**

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

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

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Fever** (°C) Fever** (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	>40 >104
Tachycardia - beats per minute	101 – 115	116 – 130	>130	Hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	<45	Hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 160	>160	Hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	>100	Hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	<80	Hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	>25	Intubation

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

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.

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

Attachment 3: Clinical Assessment

CLINICAL QUESTIONNAIRE
Participant ID:

VITAL SIGNS	
Temperature (°C/°F)	
Blood pressure (SBP/DBP)	
Heart rate (bpm)	
Respiratory rate (breaths per minute)	
Oxygen saturation (SpO_2)	

PHYSICAL EXAMINATION SCORING				
Level	**0**	**1**	**2**	**3**
	No Symptoms	Just noticeable	Bothersome sometimes, not interfering with other activities	Bothersome most of the time, interfering with other activities
Cough	❑	❑	❑	❑
Sputum production	❑	❑	❑	❑
Shortness of breath	❑	❑	❑	❑
Malaise (tiredness)	❑	❑	❑	❑

UPPER RESPIRATORY				
Level	**0**	**1**	**2**	**3**
Nasal Discharge	None	Clear, serous: scant but slightly increased	Clear to white, obvious increased volume, + minor blood streaks on tissue	Frankly purulent (yellow or green), or gross blood
Pharyngitis	None	Mild and/or patchy erythema	Marked and/or confluent erythema	Erythema and purulent exudate
Sinus Tenderness	None		Mild tenderness	Severe tenderness or overlying erythema
LOWER RESPIRATORY				
Level	**0**	**1**	**2**	**3**
Dyspnea	None	May have brief episodes	May have increased episodes	May have severe episodes
Rales, rhonchi or other	None		Scattered wheezes or rhonchi	Widespread wheezes or rhonchi, rales, dyspnea, or signs of consolidation
Wheezing	None	Terminal expiration or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiration and expiration without stethoscope
Respiratory Effort	None	Mild chest wall retraction	Trachea tug with moderate chest wall retraction and nasal flare	Marked chest wall retraction with nasal flare

Attachment 4: ARI Surveillance Assessment

Since the last time you completed your eDiary, have you had any symptoms of a cold or respiratory infection such as a stuffy or runny nose (nasal congestion), a sore throat, a cough, coughing up phlegm (sputum), trouble breathing, or whistling sounds when you breathe (wheezing)?

If you usually have some of these symptoms even when you do not have a cold, please only answer "yes" if you have more symptoms than usual or your symptoms are worse than usual.

Responses:

No cold symptoms — *The participant will be referred to AE reminder screen (below)*

Yes, I had cold symptoms — *The participant completes ARI assessment as follows:*

1. Date ARI symptoms started or became worse than usual
2. RiiQ™v2 Symptom Scale

The ePRO system will compare reported symptoms/severity to values reported during the vaccination visit.

If symptoms are the same or less severe than the participant reported during the vaccination visit, the symptoms indicate no ARI has occurred according to protocol definition. Therefore, the remainder of the ARI assessment is not collected. The participant will be referred to AE reminder screen (below).

If symptoms are worse than baseline, the remaining ARI assessments are presented in the following order[a]:

3. RiiQ™v2 Impact on Daily Activities
4. PGI-H
5. PGI-S
6. PGI-C
   (Note that the PGI C will not be completed on ARI Day 1)
7. Return to Usual Health
   (Note that the Return to Usual Health question will not be completed on ARI Day 1)
8. Temperature Log

The participant will then be referred to AE reminder screen (below). A final screen reminds participants to collect a nasal swab and to contact site to schedule a site visit.

AE Reminder Screen:

Thank you for completing your eDiary.

If you are having any severe symptoms, health issues, or other concerns about your health, please contact your study doctor to discuss these.

[a] The RiiQ™v2 Impact on Daily Activities, PGI-H, PGI-S, PGI-C, Return to Usual Health, and temperature log assessments are part of the Combined Impact Assessment.

Attachment 5: Respiratory Infection Intensity and Impact Questionnaire (RiiQ™v2) – Symptom Scale

Please read each of the following questions and select the answer thinking about when you felt the worst in the past 24 hours.

During the past 24 hours, have you had the following symptoms?

	None	Mild	Moderate	Severe
a. Cough	☐	☐	☐	☐
b. Sore throat	☐	☐	☐	☐
c. Headache	☐	☐	☐	☐
d. Nasal congestion	☐	☐	☐	☐
e. Feeling feverish	☐	☐	☐	☐
f. Body aches and pains	☐	☐	☐	☐
g. Fatigue (tiredness)	☐	☐	☐	☐
h. Neck pain	☐	☐	☐	☐
i. Interrupted sleep	☐	☐	☐	☐
j. Wheezing	☐	☐	☐	☐
k. Coughing up phlegm (sputum)	☐	☐	☐	☐
l. Short of breath	☐	☐	☐	☐
m. Loss of appetite	☐	☐	☐	☐

Attachment 6: Respiratory Infection Intensity and Impact Questionnaire (RiiQ™v2)

Please read each of the following questions and select the answer thinking about when you felt the worst in the past 24 hours.

Symptoms

1. During the past 24 hours, have you had the following symptoms?

	None	Mild	Moderate	Severe
a. Cough	☐	☐	☐	☐
b. Sore throat	☐	☐	☐	☐
c. Headache	☐	☐	☐	☐
d. Nasal congestion	☐	☐	☐	☐
e. Feeling feverish	☐	☐	☐	☐
f. Body aches and pains	☐	☐	☐	☐
g. Fatigue (tiredness)	☐	☐	☐	☐
h. Neck pain	☐	☐	☐	☐
i. Interrupted sleep	☐	☐	☐	☐
j Wheezing	☐	☐	☐	☐
k. Coughing up phlegm (sputum)	☐	☐	☐	☐
l. Short of breath	☐	☐	☐	☐
m. Los of appetite	☐	☐	☐	☐

Impact of the Respiratory Infection

2. During the past 24 hours, how able were you to:

	No Difficulty	Some Difficulty	Moderate Difficulty	Great Difficulty
a. Get out of bed	☐	☐	☐	☐
b. Leave your home	☐	☐	☐	☐
c. Prepare meals / get your own food	☐	☐	☐	☐
d. Perform usual activities	☐	☐	☐	☐
e. Concentrate on tasks	☐	☐	☐	☐
f. Take care of yourself	☐	☐	☐	☐
g. Go out of the room you are in	☐	☐	☐	☐

3. During the past 24 hours, have you felt:

	Not at all	Somewhat	Moderately	Extremely
a. Irritable	☐	☐	☐	☐
b. Helpless	☐	☐	☐	☐
c. Worried	☐	☐	☐	☐
d. Frustrated	☐	☐	☐	☐

4. <u>Since this time yesterday</u>, have you been concerned about:

	Not at all concerned	Somewhat concerned	Moderately concerned	Extremely concerned
a. People worrying about you	☐	☐	☐	☐
b. Being a burden	☐	☐	☐	☐
c. People being annoyed with you	☐	☐	☐	☐
d. Needing to depend on people	☐	☐	☐	☐
e. People having to do extra things for you	☐	☐	☐	☐

(Variable recall Version. English. Administered under license by Janssen Pharmaceuticals).
(English – administration once daily)

Attachment 7: Patient Global Impression Scales

Patient Global Impression of Health (PGI-H)

Overall, how would you rate your health today? (select one)

- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

Patient Global Impression of Severity (PGI-S)

Overall, how would you rate your respiratory illness today? (select one)

- ☐ I feel fine (no respiratory illness)
- ☐ I feel a little bit ill
- ☐ I feel very ill
- ☐ I feel extremely ill

Patient Global Impression of Change (PGI-C)

How were your respiratory illness today compared to when you first entered this study (select one)

- ☐ Much better
- ☐ Somewhat better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Somewhat worse
- ☐ Much worse

Return to Usual Health

Have you returned to your usual health today? (select one)

- ☐ Yes
- ☐ No

Attachment 8: **Lawton-Brody Instrumental Activities of Daily Living (Lawton-Brody IADL Scale)**

LAWTON – BRODY INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (IADL)			
Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).			
A. Ability to Use Telephone		**E. Laundry**	
1. Operates telephone on own initiative-looks up and dials numbers, etc.	1	1. Does personal laundry completely	1
		2. Launders small items-rinses stockings, etc.	1
2. Dials a few well-known numbers	1	3. All laundry must be done by others	0
3. Answers telephone but does not dial	1		
4. Does not use telephone at all	0		
B. Shopping		**F. Mode of Transportation**	
1. Takes care of all shopping needs independently	1	1. Travels independently on public transportation or drives own car	1
2. Shops independently for small purchases	0		
3. Needs to be accompanied on any shopping trip	0	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
4. Completely unable to shop	0		
		3. Travels on public transportation when accompanied by another	1
		4. Travel limited to taxi or automobile with assistance of another	0
		5. Does not travel at all	0
C. Food Preparation		**G. Responsibility for Own Medications**	
1. Plans, prepares and serves adequate meals independently	1	1. Is responsible for taking medication in correct dosages at correct time	1
2. Prepares adequate meals if supplied with ingredients	0	2. Takes responsibility if medication is prepared in advance in separate dosage	0
3. Heats, serves and prepares meals, or prepares meals, or prepares meals but does not maintain adequate diet	0	3. Is not capable of dispensing own medication	0
4. Needs to have meals prepared and served	0		
D. Housekeeping		**H. Ability to Handle Finances**	
1. Maintains house alone or with occasional assistance (e.g. "heavy work domestic help")	1	1. Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank), collects and keeps track of income	1
2. Performs light daily tasks such as dish washing, bed making	1	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1	3. Incapable of handling money	0
4. Needs help with all home maintenance tasks	1		
5. Does not participate in any housekeeping tasks	0		
Score		**Score**	
		Total score	
A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women and 0 through 5 for men to avoid potential gender bias.			

Source:

Graf C. The Lawton instrumental activities of daily living scale. Am J Nurs. 2008;108(4):52-62.

Attachment 9: **Medical Resources Use Questionnaire – Baseline Version**

Participant ID:
Date (dd-mmm-yyyy):

1. Medical consultations

In the last month, how many times have you had medical consultations?

	No	Yes	If yes, specify the number of visits	Indicate a reason for each visit
General Practitioner				
Internal Medicine				
Pulmonologist				
Respiratory Physiotherapy				
Other (Please specify:)				

2. Professional home care

Please indicate the need for professional care at home in the last month.

	No	Yes	If yes, specify the number of visits	Indicate a reason for each type of professional care at home
General Practitioner				
Nurse				
Respiratory Physiotherapy				
Other (Please specify:)				

3. Hospital admissions

In the last month, did you visit the hospital?

Yes:
No:

	No	Yes	If yes, specify the number of visits/admissions	Reason for each hospital visit and length of stay (days)
Emergency Department*				
Hospitalization in general ward				
Hospitalization in critical care				

*Please count Emergency Department visits only if the visit did not result in a hospital admission.

4. Institutional care admission(s) other than hospital

Yes:
No:

Please indicate if there has been any need for admission for care in a long-term facility, in the last month.

	No	Yes	If yes, specify number of admissions	Reason for each institutional care admission and length of stay (days)
Long term facilities				
Rehabilitation facility				

Attachment 10: **Medical Resources Use Questionnaire**

Participant ID:
Date (dd-mmm-yyyy):

1. Medical consultations

Since onset of acute respiratory infection, how many times have you had medical consultations?

	No	Yes	If yes, specify the number of visits	Specify number of visits related to ARI or its complications	Indicate a reason for each visit
General Practitioner					
Internal Medicine					
Pulmonologist					
Respiratory Physiotherapy					
Other (Please specify:)					

2. Professional home care

Please indicate the need for professional care at home since onset of acute respiratory infection

	No	Yes	If yes, specify the number of visits	Specify number of visits related to ARI or its complications	Indicate a reason for each type of professional care at home
General Practitioner					
Nurse					
Respiratory Physiotherapy					
Other (Please specify:)					

3. Hospital admissions

Since onset of acute respiratory infection, did you visit the hospital?

Yes:
No:

	No	Yes	If yes, specify the number of visits/admissions	Specify number of visits/admissions related to ARI or its complications	Reason for each hospital visit and length of stay (days)
Emergency Department*					
Hospitalization in general ward					
Hospitalization in critical care					

*Please count Emergency Department visits only if the visit did not result in a hospital admission.

4. Institutional care admission(s) other than hospital

Please indicate if there has been any need for admission for care in a long-term facility, since onset of acute respiratory infection.

Yes:
No:

	No	Yes	If yes, specify number of admissions	Specify number of admissions related to ARI or its complications	Reason for each institutional care admission and length of stay (days)
Long term facilities					
Rehabilitation facility					

Attachment 11: Respiratory Infection Intensity and Impact Questionnaire (RiiQ™v2) – Impact on Daily Activity Scale

Please read the following question and select the answer thinking about when you felt the worst in the past 24 hours.

<u>During the past 24 hours,</u> how able were you to:

	No Difficulty	Some Difficulty	Moderate Difficulty	Great Difficulty
a. Get out of bed	□	□	□	□
b. Leave your home	□	□	□	□
c. Prepare meals / get your own food	□	□	□	□
d. Perform usual activities	□	□	□	□
e. Concentrate on tasks	□	□	□	□
f. Take care of yourself	□	□	□	□
g. Go out of the room you are in	□	□	□	□

Question 2 of the Respiratory Infection intensity and impact questionnaire (RiiQ™) ©RH Osborne (2006, 2018).
No part of the RiiQ™ may be copied or reproduced in any form without written permission from
RH Osborne PhD:measuredsolutions@bigpond.com
(Variable recall Version. English. Administered under license by Janssen Pharmaceuticals).
(English – administration once daily)

Attachment 12: **Medically Attended Acute Respiratory Infection (MA-ARI) Information Form**

Version 1.2 - 14 June 2019

Dear Health Care Provider,

A patient of yours, who is currently being seen or has recently been seen for symptoms of a respiratory tract infection, is taking part in a clinical trial sponsored by Janssen Vaccines and Prevention. This clinical trial studies the efficacy and safety of an experimental RSV vaccine, and more information can be found on clinicaltrials.gov (study reference: NCT03982199 - VAC18193RSV2001). Due to scientific nature of this trial, the sponsor kindly requests some information of the performed assessments, interventions and outcome. If you are seeing/saw this patient in an outpatient setting, please fill out only section 1 of the form. If you are seeing/saw this patient in the emergency department or during a hospitalization, please complete both sections 1 and section 2 of the form. If some assessments or interventions were not done, please leave these questions in the blank. Kindly complete as much information as is available and provide to your patient, who will return this form to the study site. If you received this form after the medical interaction by mail or fax, please return the completed form to the study site by fax or post in the provided postage-paid return envelope. If you have any questions, your patient can provide you with contact information for the study team, and/or please refer to the contact information provided by the study team.

Section 1: To be completed in all healthcare settings (e.g., family doctor, nurse practitioner, outpatient clinic, emergency department visits and hospitalizations).

Participant ID (will be completed by study staff):
Date of visit:
Name and role of healthcare professional completing form:
Optional contact details:

DIAGNOSIS/DIAGNOSES
Please list diagnosis or diagnoses made during clinical interaction here.

MEDICATIONS
Please list any new medications prescribed or changes in medication dosing.

VITAL SIGNS
Temperature (°C/°F): _____
Respiratory rate (breaths per minute): _____ **Does the measured respiratory rate support a diagnosis of lower respiratory tract disease (LRTD)?** □ **Yes** □ **No** *Below question only to be completed if patient has history of COPD or asthma.* **Does the measured respiratory rate support a diagnosis of a COPD or asthma exacerbation?** □ **COPD exacerbation** □ **asthma exacerbation** □ **No**
Oxygen saturation (SpO_2): _____ **Does the measured oxygen saturation support a diagnosis of lower respiratory tract disease (LRTD)?**

□ **Yes** □ **No** *Below question only to be completed if patient has history of COPD or asthma.* **Does the measured oxygen saturation support a diagnosis of a COPD or asthma exacerbation?** □ **COPD exacerbation** □ **asthma exacerbation** □ **No**
WERE ADDITIONAL DIAGNOSTIC TESTS PERFORMED? □ **Yes** □ **No** *If 'yes' selected, please fill out remaining questions in this section.*
Was a chest x-ray performed? □ **Yes** □ **No** **If yes, please indicate date performed: _____** **If yes, do the results support a diagnosis of lower respiratory tract disease (LRTD)?** □ **Yes** □ **No** **If LRTD diagnosis supported, further diagnosis by x-ray:** □ **Pneumonia** □ **Other LRTD**
Was a peak flow measurement made? □ **Yes** □ **No** **If yes, please indicate date performed: _____** **Peak flow (L/min): _____** **If yes, do the results support a diagnosis of LRTD?** □ **Yes** □ **No** *Below question only to be completed if patient has history of COPD or asthma.* **Do the results support a diagnosis of a COPD or asthma exacerbation?** □ **COPD exacerbation** □ **asthma exacerbation** □ **No**
Was spirometry performed? □ **Yes** □ **No** **If yes, please indicate date performed: _____** **Specify results:** *Only indicate results for measurements made.* **FEV1 (L): _____** **FEV6 (L): _____** **FVC (L): _____** **If yes, do the results support a diagnosis of LRTD?** □ **Yes** □ **No** *Below question only to be completed if patient has history of COPD or asthma.* **Do the results support a diagnosis of a COPD or asthma exacerbation?** □ **COPD exacerbation** □ **asthma exacerbation** □ **No**
Was another diagnostic method used? □ **Yes** □ **No** **If yes, please specify diagnostic method: _____** **Date performed: _____** **Specify results: _____** **Do the results support a diagnosis of LRTD?** □ **Yes** □ **No**
WAS ANY MANAGEMENT PRESCRIBED OTHER THAN MEDICATION? □ **Yes** □ **No** *(including nebulizer treatments, IV fluids, etc.)* *If 'yes' selected, please fill out remaining questions in this section.*
If yes, please specify: _____

Section 2: Additional questions only to be completed if patient seen in emergency department or is hospitalized.

WERE ADDITIONAL DIAGNOSTIC TESTS PERFORMED? □ Yes □ No
If 'yes' selected, please fill out remaining questions in this section.

Was a CT-scan performed? □ Yes □ No

If yes, please indicate date performed: _____
If yes, do the results support a diagnosis of LRTD? □ Yes □ No
If LRTD diagnosis supported, further diagnosis by CT: □ Pneumonia □ Other LRTD

Was an MRI performed? □ Yes □ No

If yes, please indicate date performed: _____
If yes, do the results support a diagnosis of LRTD? □ Yes □ No
If LRTD diagnosis supported, further diagnosis by MRI: □ Pneumonia □ Other LRTD

Was bronchoscopy performed? □ Yes □ No

If yes, please indicate date performed: _____
Specify results: _____
If yes, do the results support a diagnosis of LRTD? □ Yes □ No

Was an arterial blood gas measured? □ Yes □ No

If yes, please indicate date performed: _____

Specify results: pH: _____, **pCO_2 (mmHg):** _____, **pO_2 (mmHg):** _____, **HCO_3 (mEq/L):** _____, **O_2 saturation (%):** _____
If yes, do the results support a diagnosis of LRTD? □ Yes □ No

Below question only to be completed if patient has history of COPD or asthma.
Do the results support a diagnosis of a COPD or asthma exacerbation?
□ COPD exacerbation □ asthma exacerbation □ No

Was another diagnostic method used? □ Yes □ No

If yes, please specify diagnostic method: _____

Date performed: _____

Specify results: _____
Do the results support a diagnosis of LRTD? □ Yes □ No

SUPPLEMENTAL OXYGEN

Was supplemental oxygen administered? □ Yes □ No
If 'yes' selected, please fill out remaining questions in this section.

Type of supplemental oxygen administration:
□ Invasive Mechanical Ventilation
□ Non-Invasive Mechanical Ventilation
□ Nasal Cannula
□ Nonrebreathing Face Mask with Reservoir and One-Way Valve
□ Venturi Mask
□ Simple Face Mask
□ Reservoir Cannulas

□ Other: _____

If invasive mechanical ventilation, specify:
□ Through endotracheal tube □ Through tracheostomy tube

If non-invasive mechanical ventilation, specify:
□ Continuous positive airway pressure □ Bilevel positive airway pressure

Oxygen concentration and units: _____

Start date and time: _____

End date and time (if applicable): _____

Has supplemental oxygen administration returned to that level provided prior to the current respiratory illness?
□ **Yes** □ **No**

Below question only to be completed if patient has history of COPD or asthma.
If applicable, does requirement for oxygen supplementation or increased oxygen supplementation support a diagnosis of a COPD or asthma exacerbation?

□ **COPD exacerbation** □ **asthma exacerbation** □ **No**

*****

ADDITIONAL COMMENTS

Attachment 13: Thrombotic Events to be Reported as Potential AESIs

At the time of protocol amendment 6 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

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	16-Feb-2023 19:59:01 (GMT)	Document Approval